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ORIGINAL ARTICLE

# Emotional repression in patients with chronic inflammatory rheumatism

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Abstract:

**Background:** A person's psychological background may support and direct the inflammatory evolution of a disease toward a specific type of chronic inflammatory rheumatism (CIR).
**Aim:** This study aimed to identify a particular emotional profile of patients with CIR, particularly rheumatoid arthritis (RA) and spondyloarthritis (SpA), based on psychological profile assessments between patients with and without CIR. Emotional repression, that is, a tendency to inhibit the expression of negative feelings and/or unpleasant thoughts, was particularly studied.
**Methods:** This monocentric observational pilot study included patients from the rheumatology department of a university hospital. These patients were systematically assessed for different psychological parameters by an experienced psychiatrist, and their clinical and biological characteristics were collected accordingly. Data analysis was performed using the Chi-squared test or Fisher's exact test.
**Results:** Fifty-nine patients were assessed: 47 patients with CIR (i.e., 27 with RA and 20 with SpA) (CIR group) and 12 non-CIR patients (i.e., nine with osteoarthritis, one with viral disease, one with osteoporosis, and one with osteomalacia) (control group). Severe emotional repression and early life events were both significantly higher in the CIR group than in the control group ($P = 0.02$). In contrast, severe psychological and somatic complaints were significantly higher in the control group than in the CIR group ($P < 0.01$ and $P = 0.01$, respectively).
**Conclusion:** Our findings suggested that emotional repression from traumatic life events could aggravate the etiology and/or course of CIR. Therefore, appropriate psychological care should have a relevant place within the current therapeutic options for the clinical management of CIR.
**Relevance for Patients:** The management of CIR should include psychological support as learning coping mechanisms can facilitate the recovery of CIR patients.

## 1. Introduction

The development of chronic inflammatory rheumatism (CIR) is multi-factorial (e.g., genetic, environmental, hormonal, infectious, and/or psychological), and the degree of implication of these different factors in CIR onset has not been determined [1,2]. Several studies on traumatic life events and stressful situations have suggested that such situations could be implicated in triggering CIR onset and its symptomatic progression [3,4].

Non-pharmacological interventions have recently been used more frequently for disease management, especially regular physical activity, educational therapeutic workshops with support groups, and mindfulness meditation, among others. In addition, self-reported evaluation and patient-reported outcomes have become increasingly important for the assessment of diseases, suggesting that the patients' psychological well-being is essential in routine practice for rheumatologists to evaluate the efficacy of disease management

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with better precision [5]. Likewise, psychological support is increasingly integrated into the management of patients with CIR as they are more prone to mental and overall health disorders.

Emotional repression refers to the tendency to inhibit the expression of negative feelings and/or unpleasant thoughts and is a common manifestation in CIR patients. Hence, an assessment of the patients' emotional profile could provide a more relevant and effective approach to managing emotional repression and treating CIR. In this regard, we hypothesized that a particular psychological profile, namely, emotional repression, could be associated with autoimmune deregulation.

Herein, this preliminary and exploratory study primarily investigated the emotional function of CIR patients by assessing their psychological profiles to explore a possible association between autoimmunity and emotional regulation. In addition, we further evaluated the emotional profiles for potential associations with other conditions (i.e., rheumatoid arthritis [RA] and spondyloarthritis [SpA]) and different rheumatological characteristics (i.e., biological inflammatory syndrome, sacroiliitis, structural involvement (i.e., osteoarticular destruction of the joint due to the inflammatory activity of rheumatism), and positive rheumatoid factor [RF], anti-citrullinated peptide antibody [ACPA], and human leukocyte antigen *[HLA]-B27* allele).

## 2. Methods

### *2.1. Population and study design*

This monocentric cross-sectional observational pilot study was conducted in the rheumatology department of a university hospital. During a routine follow-up, the CIR patients were offered an evaluation based on the global CIR management framework, which included dermatological, dental, and gynecological consultations, as well as rheumatologist-requested psychiatric assessments (anxiety disorders, depressive disorders, sleep disorders, conjugal violence, and childhood traumas). None of the recruited 59 patients refused to participate in the evaluation. The exclusion criteria were: age <18 or >65 years old, cognitive disorders, substance dependence, or acute somatic or any psychiatric disorders requiring emergency hospitalization.

The participating patients were accompanied to the rheumatology department by seven different rheumatologists. CIR patients were classified as having RA (based on the 2010 classification by the American College of Rheumatology/European League Against Rheumatism) SpA (based on the 2009 criteria by the Assessment of SpA International Society), or psoriatic arthritis (based on the ClASsification criteria for Psoriatic ARthritis [CASPAR]). We identified 12 patients with ankylosing SpA and eight with psoriatic arthritis, and these patients were categorized under SpA to facilitate statistical analyses. Although their clinical characteristics might differ slightly, their pathologies share common pathophysiological mechanisms and genetic backgrounds, such as the presence of *HLA-B27*.

Non-CIR patients constituted the control group, and these patients were in the rheumatology department for other rheumatological diseases.

### *2.2. Psychological assessment tools*

An experienced psychiatrist collected information during a semi-structured, semi-directed interview lasting 1.5 – 2 h. The psychological parameters assessed were (i) depressive symptoms and their severity (based on the Montgomery-Asberg Depression Rating Scale) [6]; (ii) history of major depression episodes; (iii) anxiety symptoms using a 21-question multiple-choice self-report inventory (i.e., the Beck Anxiety Inventory) [7]; (iv) alexithymia, a behavioral trait of individuals who are unable to identify and describe their interior feelings, have limited imaginative capacity, and tend to focus their thoughts externally rather than resorting to introspection [8,9], and its severity using the 20-item Toronto Alexithymia Scale [10]; (v) social desirability intensity, that is, the tendency to seek approval of others and preserve one's self-image, using the Marlowe-Crowne Social Desirability scale (MCSD), a 33-item self-report questionnaire [11]; (vi) the severity of emotional repression, that is, the tendency to inhibit the expression of negative feelings or disagreeable thoughts, in accordance with the Weinberger classification; and (vii) the combination of State-Trait Anxiety Inventory (STAI) [12] and MCSD as emotionally repressed individuals typically have a low STAI score and high MCSD.

The psychiatrist used a Likert-type scale to assess the severity of the psychological parameters in a specific questionnaire, which assessed (i) the severity of somatic and psychological complaints (i.e., severe complaints referred to personalized responses to most of the questions); (ii) emotional-expressivity intensity (i.e., graded as "mild" when the patient had several emotional moments without excessive reactions, "moderate" when the patient's facial expressions were accompanied by fluctuating emotions as the discussion progressed, or "severe" when the patient had a tendency for hyper-expressivity throughout the interview); (iii) life events (i.e., type 1 for events occurring before 15 years old and type 2 for events occurring within 3 years preceding the rheumatological disease onset) and their intensities (i.e., classified as "mild" when stressful events were non-existent or mild, "moderate" when stressful events did not incur traumatic stress [e.g., emotional deprivation concerning socio-economic difficulties, severe or disabling diseases of close friends/relatives], or "severe" for a traumatic event [e.g., sudden death of a person caring for a child, physical or sexual assault, patient witnessed a death, or thought he/she would die]); (iv) somatic escalation (i.e., the occurrence of a series of several somatic disorders or another chronic pathology before disease onset); (v) actual stress level; (vi) impact of the rheumatological disease on the patient's professional activities, corresponding to the occupational repercussions experienced (i.e., classified as "mild" for minor impact, "moderate" for notable impact, or "severe" for a painful experience [e.g., loss of professional environment and activity, feeling of injustice, or elevated fear of losing one's job]); (vii) manual labor; and (viii) physical activity enjoyment before and after disease onset.

For the different psychological parameters, we combined the "mild" and "moderate" intensities for comparison against the "severe" intensity. The mild-to-moderate psychological disorders

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were easily identified in patients exhibiting severe anxiety or depressive comorbidities and emotional experiences (often affected by chronic pain), but retaining the "severe" intensity enabled a more significant difference. In addition, this approach accounted for the population recruitment bias.

During the same hospitalization, various patient characteristics, mostly rheumatological, were collected from the electronic medical files using the *DxCare* (medical information and prescription software) program. The collected data included: (i) Biological inflammatory syndrome, defined as an erythrocyte sedimentation rate ≥30 mm/1st h and/or C-reactive protein ≥5 mg/L; (ii) positive ACPA, defined as 7 U/mL by enzyme-linked immunosorbent assay (ELISA); (iii) RF >15 IU/mL by ELISA; (iv) magnetic resonance imaging (MRI) detection of grade-2 bilateral or grade-3 unilateral sacroiliitis, with active inflammatory (edema) or chronic (erosion, bone condensation, bone bridges, and fat conversion) lesions.

### 2.3. Statistical analysis

Continuous variables were expressed as median (first quartile [Q1] – third quartile [Q3]). Categorical variables were expressed as number (percentages), where the percentages were calculated after excluding missing data, and were compared by Chi-squared test or Fisher's exact test accordingly. Missing data were not replaced. For all analyses, $P < 0.05$ was considered statistically significant. Type I error was not adjusted for multiplicity because of the exploratory character of the comparisons. All statistical analyses were performed with SAS release 9.4 (SAS Institute Inc, USA).

## 3. Results

### 3.1. Patient characteristics

The study population comprised 59 patients: 47 (79.7 %) CIR patients and 12 (20.3%) non-CIR patients. The patients' characteristics according to their disease are summarized in Table 1.

The control group consisted of 12 women with a median age of 65.0 years [55.0 – 72.0] (nine with osteoarthritis, one with viral disease, one with osteoporosis, and one with osteomalacia). In addition, the nine women with osteoarthritis had structural involvement.

Among the 47 CIR patients (72.3% women and 27.7% men; median age 55.0 years [39.0 – 60.0]), 27 (57.4%) had RA and 20 (42.6%) had SpA. Among the 27 RA patients (81.5% women median age 57 years [52 – 63]), most were RF-positive, ACPA-positive, and had structural involvement. In addition, 10 of the RA patients had biological inflammatory syndrome. Among the 20 SpA patients (60.0% women; median age 41.5 years [34.5 – 53.0]), six of them had a biological inflammatory syndrome, nine of them were *HLA-B27*-positive, and 11 of them had MRI-detected sacroiliitis.

### 3.2. Psychological assessments

A comparison between the CIR and control groups displayed significant differences in emotional repression, somatic complaints, psychological complaints, type-1 life-event severity, manual labor, or physical activity enjoyment before disease diagnosis (Table 2).

A comparison of the RA and SpA groups revealed significant differences in prior depressive episodes, professional impact, and manual labor (Table 3).

A comparison between patients with and without biological inflammatory syndromes revealed significant differences in emotional repression (Table 4).

A comparison between patients with and without structural involvement revealed significant differences in somatic complaints, emotional expressivity, professional impact, and physical activity enjoyment before disease onset (Table 5).

In addition, none of the psychological parameters were significantly associated with ACPA. Likewise, the number of patients who were *HLA-B27*-positive or had sacroiliitis was too low for analysis. Hence, their significance and association could not be established.

## 4. Discussion

The objective of this study was to assess the relevance of psychological support for patients with CIR. CIR patients, compared to those with other rheumatological pathologies, presented significantly more frequent severe emotional repression, whereas those with other pathologies had significantly more frequent severe psychological and somatic complaints, potentially attesting to their strong emotional repression.

**Table 1.** Patients' characteristics according to their disease (*n*=59)

| Characteristics | RA (*n*=27) | SpA (*n*=20) | CIR (*n*=47) | Other diseases (*n*=12) |
|---|---|---|---|---|
| Median age [Q1 – Q3] (yr) | 57.0 [52.0 – 63.0] | 41.5 [34.5 – 53.0] | 55.0 [39.0 – 60.0] | 65.0 [55.0 – 72.0] |
| F/M sex ratio | 22/5 | 12/8 | 34/13 | 12/0 |
| Rheumatoid factor+, *n* (%) | 18 (66.7) | 1 (12.5) | 19 (54.3) | 0 (0) |
| ACPA+, *n* (%) | 17 (63) | 1 (12.5) | 18 (51.4) | 0 (0) |
| Elevated ESR and/or CRP, *n* (%) | 10 (37.0) | 6 (30) | 16 (34.0) | 0 (0) |
| *HLA-B27*+, *n* (%) | 0 (0) | 9 (47.4) | 9 (42.9) | 0 (0) |
| Sacroiliitis, *n* (%) | 0 (0) | 10 (55.6) | 10 (50) | 0 (0%) |
| Structural involvement, *n* (%) | 14 (51.9) | 0 (0) | 14 (35) | 9 (81.8) |

Note: CIR refers to the combination of RA and SpA.

Abbreviation: +: Positive; ACPA: Anti-citrullinated peptide antibody; CIR: Chronic inflammatory rheumatism; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; F/M: Female-to-male; *HLA-B27*: Human leukocyte antigen B27; Q1: First quartile; Q3: Third quartile; RA: Rheumatoid arthritis; SpA: Spondyloarthritis; yr: Year.

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**Table 2.** Psychological assessments of patients with CIR versus other diseases

| Psychological parameters | CIR (*n*=47) | Other diseases (*n*=12) | *P*-value |
|---|---|---|---|
| Depression | 38 (80.9%) | 11 (91.7%) | 0.67 |
| Depression intensity | | | 0.4 |
| Mild/moderate | 32 (84.2%) | 8 (72.7%) | |
| Severe | 6 (15.8%) | 3 (27.3%) | |
| Previous depression | 37 (78.7%) | 11 (91.7%) | 0.431 |
| Anxiety | 47 (100%) | 12 (100%) | NA |
| Anxiety intensity | | | 0.174 |
| Mild/moderate | 21 (44.7%) | 8 (66.7%) | |
| Severe | 26 (55.3%) | 4 (33.3%) | |
| Alexithymia | 46 (97.9%) | 11 (91.7%) | 0.368 |
| Alexithymia intensity | | | 1 |
| Mild/moderate | 20 (43.5%) | 5 (45.5%) | |
| Severe | 26 (56.5%) | 6 (54.5%) | |
| Social desirability | | | 0.431 |
| Mild/moderate | 37 (78.7%) | 11 (91.7%) | |
| Severe | 10 (21.3%) | 1 (8.3%) | |
| Emotional repression | | | 0.019* |
| Mild/moderate | 25 (53.2%) | 11 (91.7%) | |
| Severe | 22 (46.8%) | 1 (8.3%) | |
| Conflict-management style | | | 0.716 |
| Avoidance | 37 (78.7%) | 9 (75%) | |
| Intermediate | 10 (21.3%) | 3 (25%) | |
| Tendency to cede responsibility to others | | | 0.501 |
| Mild/moderate | 45 (95.7%) | 11 (91.7%) | |
| Severe | 2 (4.3%) | 1 (8.3%) | |
| Persecution complex | 14 (29.8%) | 1 (8.3%) | 0.16 |
| Somatic complaints | | | 0.01* |
| Mild/moderate | 32 (68.1%) | 3 (25%) | |
| Severe | 15 (31.9%) | 9 (75%) | |
| Psychological complaints | | | 0.002* |
| Mild/moderate | 33 (70.2%) | 2 (16.7%) | |
| Severe | 14 (29.8%) | 10 (83.3%) | |
| Emotional expressivity intensity | | | 1 |
| Mild/moderate | 32 (68.1%) | 8 (66.7%) | |
| Severe | 15 (31.9%) | 4 (33.3%) | |
| Life event 1 | 29 (65.9%) | 8 (72.7%) | 1 |
| Life event 1 intensity | | | 0.015* |
| Mild/moderate | 15 (51.7%) | 8 (100%) | |
| Severe | 14 (48.3%) | 0 (0%) | |
| Life event 2 | 44 (93.6%) | 11 (91.7%) | 1 |
| Life event 2 intensity | | | 1 |
| Mild/moderate | 30 (68.2%) | 8 (72.7%) | |
| Severe | 14 (31.8%) | 3 (27.3%) | |
| Heavy conflictual load over the last 3 years | 40 (85.1%) | 9 (75.0%) | 0.409 |
| Somatic escalade | 14 (29.8%) | 7 (58.3%) | 0.093 |
| Actual stress level | | | 1 |
| Mild/moderate | 44 (93.6%) | 12 (100%) | |
| Severe | 3 (6.4%) | 0 (0%) | |
| Professional impact | | | 0.064 |
| Mild/moderate | 22 (50%) | 7 (87.5%) | |
| Severe | 22 (50%) | 1 (12.5%) | |
| Manual labor | 28 (59.6%) | 2 (16.7%) | 0.008* |
| Physical activity enjoyment pre-diagnosis | 23 (48.9%) | 2 (16.7%) | 0.043* |
| Physical activity enjoyment post-diagnosis | 8 (17%) | 1 (8.3%) | 0.67 |

Note: Data are expressed as *n* (%) and compared using the Chi-squared test or Fisher's exact test accordingly; *$P<0.05$.
Abbreviations: NA: Not applicable; CIR: Chronic inflammatory rheumatism.

Temoshok [13] previously described the personality profile of RA patients as type C, characterized by submissive behavior, conciliatory approach, repression of hostility, self-effacement of personal needs, and depressive vulnerability. Grossarth-Maticek *et al.* [14,15] made similar observations in cancer patients. Bayle *et al.* [16] devised a psychological vulnerability score and obtained converging results close to the type C personality, and the scores were significantly higher for patients with secondary Raynaud's syndrome than a control group with idiopathic or primary Raynaud's syndrome.

Nagano *et al.* [17] demonstrated that rational and anti-emotional behaviors by RA patients, characterized by an extreme tendency to squelch emotional behaviors and rationalize negative experiences, were associated with poorer prognoses. Ishii *et al.* [18] found that RA patients, who were easily brought to tears in response to stress, had better responses to treatment and better overall prognoses.

Collectively, previous studies and our present findings highlight the importance of emotional dysregulation, especially emotional repression, on CIR etiology and prognosis. However, the present study should not be generalized as biased toward CIR or propose a secondary coping strategy for CIR. Emotional repression has also been considered a consequence of the CIR diagnosis instead of CIR itself [19,20].

The intensity of key early life events was significantly more severe for CIR patients than for those with other diseases. Cutolo and Straub [21,22] reported that stressful events preceded RA onset for 86% of their patients.

Several studies have associated severe life events with CIR onset or flares, whereas other studies have associated CIR with minor life events and daily stress. In contrast, we found no significant difference in the actual stress level presented by CIR and other diseases, probably because of a lack of statistical power. Rimón and Laasko [23] described that higher stress at RA onset predicted a poorer prognosis for the disease. O'Donovan *et al.* [24] also found that veterans experiencing trauma and

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**Table 3.** Psychological assessments of patients with RA versus SpA

| Psychological parameters | RA (*n*=27) | SpA (*n*=20) | *P*-value |
|---|---|---|---|
| Depression | 21 (77.8%) | 17 (85%) | 0.713 |
| Depression intensity | | | 0.197 |
| Mild/moderate | 16 (76.2%) | 16 (94.1%) | |
| Severe | 5 (23.8%) | 1 (5.9%) | |
| Previous depression | 26 (96.3%) | 11 (55%) | <0.001* |
| Anxiety | 27 (100%) | 20 (100%) | NA |
| Anxiety intensity | | | 0.069 |
| Mild/moderate | 9 (33.3%) | 12 (60.0%) | |
| Severe | 18 (66.7%) | 8 (40.0%) | |
| Alexithymia | 27 (100%) | 19 (95%) | 0.426 |
| Alexithymia intensity | | | 0.172 |
| Mild/moderate | 14 (51.9%) | 6 (31.6%) | |
| Severe | 13 (48.1%) | 13 (68.4%) | |
| Social desirability | | | 0.481 |
| Mild/moderate | 20 (74.1%) | 17 (85%) | |
| Severe | 7 (25.9%) | 3 (15%) | |
| Emotional repression | | | 0.333 |
| Mild/moderate | 16 (59.3%) | 9 (45%) | |
| Severe | 11 (40.7%) | 11 (55%) | |
| Conflict-management style | | | 0.481 |
| Avoidance | 20 (74.1%) | 17 (85%) | |
| Intermediate | 7 (25.9%) | 3 (15%) | |
| Tendency to cede responsibility to others | | | 0.5 |
| Mild/moderate | 25 (92.6%) | 20 (100%) | |
| Severe | 2 (7.4%) | 0 (0%) | |
| Persecution complex | 10 (37%) | 4 (20%) | 0.207 |
| Somatic complaints | | | 0.381 |
| Mild/moderate | 17 (63%) | 15 (75%) | |
| Severe | 10 (37%) | 5 (25%) | |
| Psychological complaints | | | 0.207 |
| Mild/moderate | 17 (63%) | 16 (80%) | |
| Severe | 10 (37%) | 4 (20%) | |
| Emotional expressivity intensity | | | 0.132 |
| Mild/moderate | 16 (59.3%) | 16 (80%) | |
| Severe | 11 (40.7%) | 4 (20%) | |
| Life event 1 | 16 (66.7%) | 13 (65%) | 0.908 |
| Life event 1 intensity | | | 0.837 |
| Mild/moderate | 8 (50%) | 7 (53.8%) | |
| Severe | 8 (50%) | 6 (46.2%) | |
| Life event 2 | 24 (88.9%) | 20 (100%) | 0.251 |
| Life event 2 intensity | | | 0.375 |
| Mild/moderate | 15 (62.5%) | 15 (75%) | |
| Severe | 9 (37.5%) | 5 (25%) | |
| Heavy conflictual load over the last three years | 22 (81.5%) | 18 (90%) | 0.682 |
| Somatic escalade | 6 (22.2%) | 8 (40%) | 0.188 |
| Actual stress level | | | 0.251 |
| Mild/moderate | 24 (88.9%) | 20 (100%) | |
| Severe | 3 (11.1%) | 0 (0%) | |
| Professional impact | | | 0.006* |
| Mild/moderate | 17 (68%) | 5 (26.3%) | |
| Severe | 8 (32%) | 14 (73.7%) | |
| Manual labor | 12 (44.4%) | 16 (80%) | 0.014* |
| Physical activity enjoyment pre-diagnosis | 10 (37%) | 13 (65%) | 0.058 |
| Physical activity enjoyment post-diagnosis | 5 (18.5%) | 3 (15%) | 1 |

*(Cont'd...)*

**Table 3.** *(Continued)*

Note: Data are expressed as *n* (%) and compared using the Chi-squared test or Fisher's exact test accordingly; *$P<0.05$.

Abbreviations: NA: Not applicable; RA: Rheumatoid arthritis; SpA: spondyloarthritis.

developing post-traumatic stress disorder (PTSD) could enhance the risk of developing autoimmune diseases, including RA. Based on their study of Vietnam veterans, Boscarino *et al.* [25] reported that those with RA had more PTSD symptoms compared to those without RA.

The results of those studies are in agreement with a biopsychosocial model linking psychological stress and stressful life events with the etiology of autoimmune diseases. The impact of stress, resulting from an intense life event and aggravated by conditions like emotional repression, would increase vulnerability to autoimmune diseases due to dysregulated immunity [26-30] and enhanced inflammation.

Herein, no significant difference was found between CIR and non-CIR patients regarding the frequency of depression disorders, depression severity, history of prior depressive episode(s), or anxiety symptoms.

Depressive and anxiety disorders are described as the most frequent comorbidities for CIR patients. Reynier-Legarçon *et al.* [31] found that patients with autoimmune diseases (systemic lupus erythematosus, systemic scleroderma, or primary Sjögren syndrome) presented more severe depressive and anxiety symptoms than the general population. Baerwald *et al.* [32] found that depressive disorders were significantly more common in RA patients than in the general population.

Recently, Kang [33] investigated the effect of arthritis on mental health using the 12-item version of the general health survey (GHQ-12) and reported a total of three factors of GHQ-12, that is, GHQ-12A (social dysfunction and anhedonia; six items), GHQ-12B (depression and anxiety; four items), and GHQ-12C (loss of confidence; two items), suggesting that both the global mental health and dimensions of mental health are negatively affected by arthritis. We were not able to replicate those findings, probably because of a lack of statistical power. In contrast, the homogeneity of our patients, in terms of depressive and anxiety symptoms, attenuated any potential bias linked to their emotional dysregulation associated with these psychological comorbidities.

Moreover, no significant differences were found between the RA and SpA groups for the frequency of depression and depression severity. However, RA patients reported significantly more frequent prior depressive episodes than SpA patients, a finding of which has never been reported previously. Nonetheless,

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**Table 4.** Psychological assessments of patients with versus without BIS

| Psychological parameters | With BIS (*n*=16) | Without BIS (*n*=31) | *P*-value |
|---|---|---|---|
| Depression | 13 (81.3%) | 25 (80.6%) | 1 |
| Depression intensity | | | 1 |
| Mild/moderate | 11 (84.6%) | 21 (84.0%) | |
| Severe | 2 (15.4%) | 4 (16.0%) | |
| Previous depression | 14 (87.5%) | 23 (74.2%) | 0.457 |
| Anxiety | 16 (100%) | 31 (100%) | NA |
| Anxiety intensity | | | 0.252 |
| Mild/moderate | 9 (56.3%) | 12 (38.7%) | |
| Severe | 7 (43.8%) | 19 (61.3%) | |
| Alexithymia | 16 (100%) | 30 (96.8%) | 1 |
| Alexithymia intensity | | | 0.222 |
| Mild/moderate | 5 (31.3%) | 15 (50%) | |
| Severe | 11 (68.8%) | 15 (50%) | |
| Social desirability | | | 0.716 |
| Mild/moderate | 12 (75.0%) | 25 (80.6%) | |
| Severe | 4 (25.0%) | 6 (19.4%) | |
| Emotional repression | | | 0.031* |
| Mild/moderate | 12 (75.0%) | 13 (41.9%) | |
| Severe | 4 (25.0%) | 18 (58.1%) | |
| Conflict-management style | | | **0**.02* |
| Avoidance | 9 (56.3%) | 28 (90.3%) | |
| Intermediate | 7 (43.8%) | 3 (9.7%) | |
| Tendency to cede responsibility to others | | | 0.541 |
| Mild/moderate | 16 (100%) | 29 (93.5%) | |
| Severe | 0 (0%) | 2 (6.5%) | |
| Persecution complex | 3 (18.8%) | 11 (35.5%) | 0.321 |
| Somatic complaints | | | 0.555 |
| Mild/moderate | 10 (62.5%) | 22 (71.0%) | |
| Severe | 6 (37.5%) | 9 (29.0%) | |
| Psychological complaints | | | 1 |
| Mild/moderate | 11 (68.8%) | 22 (71.0%) | |
| Severe | 5 (31.3%) | 9 (29.0%) | |
| Emotional expressivity intensity | | | 0.211 |
| Mild/moderate | 9 (56.3%) | 23 (74.2%) | |
| Severe | 7 (43.8%) | 8 (25.8%) | |
| Life event 1 | 11 (78.6%) | 18 (60.0%) | 0.314 |
| Life event 1 intensity | | | 0.812 |
| Mild/moderate | 6 (54.4%) | 9 (50.0%) | |
| Severe | 5 (45.5%) | 9 (50.0%) | |
| Life event 2 | 15 (93.8%) | 29 (93.5%) | 1 |
| Life event 2 intensity | | | 1 |
| Mild/moderate | 10 (66.7%) | 20 (69.0%) | |
| Severe | 5 (33.3%) | 9 (31.0%) | |
| Heavy conflictual load over the last three years | 14 (87.5%) | 26 (83.9%) | 1 |
| Somatic escalade | 7 (43.8%) | 7 (22.6%) | 0.182 |
| Actual stress level | | | 0.541 |
| Mild/moderate | 16 (100%) | 28 (90.3%) | |
| Severe | 0 (0%) | 3 (9.7%) | |
| Professional impact | | | 0.75 |
| Mild/moderate | 8 (53.3%) | 14 (48.3%) | |
| Severe | 7 (46.7%) | 15 (51.7%) | |
| Manual labor | 8 (50%) | 20 (64.5%) | 0.337 |
| Physical activity enjoyment pre-diagnosis | 7 (43.8%) | 16 (51.6%) | 0.609 |
| Physical activity enjoyment post-diagnosis | 3 (18.8%) | 5 (16.1%) | 1 |

Note: Data are expressed as *n* (%) and compared using the Chi-squared test or Fisher's exact test accordingly; *$P<0.05$.
Abbreviations: BIS: Biological inflammatory syndrome; NA: Not applicable.

some findings indicated that anxiety symptoms, depression, and perception of the disease impacted the physical quality of life differently for SpA and RA patients. Some authors noted that RA patients had more physical quality-of-life difficulties, while those with psoriatic arthritis and ankylosing SpA had more mental quality-of-life issues [33-36]. Hyphantis *et al*. [37] reported that SpA patients' quality of life was associated with anxiety and not depressive symptoms, which were associated with RA patients. Our results, consistent with earlier findings, suggest a link between depression and RA patients.

Together, these results suggest that CIR (RA or SpA) patients would probably benefit from emotional management from psychotherapists and antidepressants for symptomatic depressive episodes. Moreover, these symptoms can contribute to a poorer prognosis for their respective rheumatological disease [37]. Bijsterbosch *et al.* [38] demonstrated that arthrosis patients' perceptions of their disease were predictive of the functional disability and that cognitive-behavioral therapy could modify the representations of the disease and obtain a better functional result.

A biological inflammatory syndrome was significantly associated with a low disorder of emotional regulation (mild/moderate emotional repression). However, earlier studies have reported a stronger association between emotional disorders and a biological inflammatory syndrome.

Smoak *et al.* [39] found increased nuclear factor-$\kappa$B activity in patients with PTSD, resulting from childhood violence, compared to healthy controls. Howren *et al.* [40] reported that patients with depression had significantly higher interleukin-1 and -6, tumor necrosis factor-$\alpha$, and C-reactive protein levels. Goldsmith *et al.* [41] also observed from a meta-analysis of 68 studies, that patients with schizophrenia, bipolar disorder, or major depressive episodes had increased levels of inflammatory cytokines. In addition, depressive symptoms were more frequent in patients with autoimmune diseases and taking anti-inflammatory drugs. Gobin *et al.* [42] found that antidepressants lowered the production of inflammatory cytokines, for example, interleukins-1$\beta$ and -6 and tumor necrosis factor-$\alpha$.

Several monoclonal antibodies targeting relevant inflammatory pathways for the treatment of CIR were associated with neuropsychiatric adverse events, notably depression, or suicidal

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**Table 5.** Psychological assessments of patients with versus without articular structural involvement

| Psychological parameters | With ASI (*n*=14) | Without ASI (*n*=26) | *P*-value |
|---|---|---|---|
| Depression | 11 (78.6%) | 20 (76.9%) | 1 |
| Depression intensity | | | 1 |
| Mild/moderate | 9 (81.8%) | 17 (85.0%) | |
| Severe | 2 (18.2%) | 3 (15.0%) | |
| Previous depression | 14 (100%) | 19 (73.1%) | 0.075 |
| Anxiety | 14 (100%) | 26 (100%) | 1 |
| Anxiety intensity | | | 0.079 |
| Mild/moderate | 4 (28.6%) | 15 (57.7%) | |
| Severe | 10 (71.4%) | 11 (42.3%) | |
| Alexithymia | 14 (100%) | 25 (96.2%) | 1 |
| Alexithymia intensity | | | 0.584 |
| Mild/moderate | 6 (42.9%) | 13 (52.0%) | |
| Severe | 8 (57.1%) | 12 (48.0%) | |
| Social desirability | | | 0.222 |
| Mild/moderate | 13 (92.9%) | 19 (73.1%) | |
| Severe | 1 (7.1%) | 7 (26.9%) | |
| Emotional repression | | | 0.191 |
| Mild/moderate | 10 (71.4%) | 13 (50.0%) | |
| Severe | 4 (28.6%) | 13 (50.0%) | |
| Conflict-management style | | | 0.102 |
| Avoidance | 9 (64.3%) | 23 (88.5%) | |
| Intermediate | 5 (35.7%) | 3 (11.5%) | |
| Tendency to cede responsibility to others | | | 0.533 |
| Mild/moderate | 14 (100%) | 24 (92.3%) | |
| Severe | 0 (0%) | 2 (7.7%) | |
| Persecution complex | 5 (35.7%) | 8 (30.8%) | 1 |
| Somatic complaints | | | 0.031* |
| Mild/moderate | 6 (42.9%) | 21 (80.8%) | |
| Severe | 8 (57.1%) | 5 (19.2%) | |
| Psychological complaints | | | 0.48 |
| Mild/moderate | 8 (57.1%) | 19 (73.1%) | |
| Severe | 6 (42.9%) | 7 (26.9%) | |
| Emotional expressivity intensity | | | 0.007* |
| Mild/moderate | 5 (35.7%) | 21 (80.8%) | |
| Severe | 9 (64.3%) | 5 (19.2%) | |
| Life event 1 | 9 (69.2%) | 14 (58.3%) | 0.724 |
| Life event 1 intensity | | | 1 |
| Mild/moderate | 5 (55.6%) | 7 (50.0%) | |
| Severe | 4 (44.4%) | 7 (50.0%) | |
| Life event 2 | 12 (85.7%) | 25 (96.2%) | 0.276 |
| Life event 2 intensity | | | 1 |
| Mild/moderate | 8 (66.7%) | 16 (64.0%) | |
| Severe | 4 (33.3%) | 9 (36.0%) | |
| Heavy conflictual load over the last three years | 11 (78.6%) | 23 (88.5%) | 0.646 |
| Somatic escalade | 6 (42.9%) | 4 (15.4%) | 0.123 |
| Actual stress level | | | 0.539 |
| Mild/moderate | 14 (100%) | 23 (88.5%) | |
| Severe147 | 0 (0%) | 3 (11.5%) | |
| Professional impact | | | 0.009* |
| Mild/moderate | 11 (84.6%) | 10 (40.0%) | |
| Severe | 2 (15.4%) | 15 (60.0%) | |
| Manual labor | 7 (50%) | 15 (57.7%) | 0.641 |
| Physical activity enjoyment pre-diagnosis | 3 (21.4%) | 15 (57.7%) | 0.028* |
| Physical activity enjoyment post-diagnosis | 2 (14.3%) | 4 (15.4%) | 1 |

Note: Data are expressed as *n* (%) and compared using the Chi-squared test or Fisher's exact test accordingly; *$P<0.05$.
Abbreviations: ASI: Articular structural involvement; NA: Not applicable.

ideation or behavior [43]. The development of brodalumab, a molecule targeting interleukin-17, was stopped after suicidal behaviors were observed during clinical trials [44,45].

Our results, consistent with the previous studies, suggested a bidirectional relationship between depressive syndrome and biological inflammatory syndrome, but this finding should be validated in a longitudinal study. It remains to be determined whether systemic inflammation could induce emotional symptoms through neuronal cells or whether these emotional disorders are considered biological inflammatory syndrome that subsequently trigger the onset of CIR.

One of the main limitations of this preliminary study was the lack of statistical power due to a small sample size. However, this pilot study investigated potential associations between CIR and biopsychosocial factors, and its findings are indicative of areas that should be examined in greater depth in future studies. In addition, because this was an observational study, no conclusions could be drawn about any association with causality. As this was a cross-sectional investigation, it was not possible to determine whether the primary emotional regulation disorders, possibly contributing to the rheumatological disease onset or secondary disorders, should be interpreted as adaptive or coping modalities to handle a functional handicap or limiting pain caused by the disease. Our study suffered from two selection biases: (i) it was a monocentric study recruiting patients at a university hospital, representing a particular sociodemographic status; and (ii) most patients were assessed in a day for severe pathologies and comorbidities. Furthermore, the clinical psychological parameters chosen for assessment, although not subjected to consensual agreement, corresponded to clinical entities. Nonetheless, participants in this study benefited from combined psychiatric and rheumatological assessments during a day of hospitalization, which is considered novel, enabling the evaluation of a large number of psychological factors and comparing them to concomitant rheumatological findings.

## 5. Conclusion

Our study established an association between emotional repression, intense life events, and the etiology and development

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of CIR. Moreover, RA patients had significantly more depressive episodes than SpA patients. Our observations suggested that targeted psychotherapy could complement the clinical management of CIR.

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None.

## Conflict of Interest

The authors declare that they have no competing interests.

## Ethics Approval and Consent to Participate

All patients were informed about the study's objectives and agreed to the anonymous use of the collected data. The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the Department of Clinical Research and Innovation of the Amiens-Picardie University Hospital. The authors have obtained the written and signed informed consent of the participants before their participation.

## Consent for Publication

The authors have obtained the written and signed informed consent of the patients for releasing their data in this paper.

## Availability of Data

Data are available from the corresponding author on reasonable request.

## References

[1] Pretorius E, Akeredolu OO, Soma P, Kell DB. Major Involvement of Bacterial Components in Rheumatoid Arthritis and Its Accompanying Oxidative Stress, Systemic Inflammation and Hypercoagulability. Exp Biol Med (Maywood) 2017;242:355-73.
doi: 10.1177/1535370216681549

[2] Dougados M, Baeten D. Spondyloarthritis. Lancet 2011;377:212737.
doi: 10.1016/S0140-6736(11)60071-8

[3] Halliday JL. Psychological Aspects of Rheumatoid Arthritis. Proc R Soc Med 1942;35:4557.

[4] Moos RH. Personality Factors Associated with Rheumatoid Arthritis: A review. J Chronic Dis 1964;17:4155.
doi: 10.1016/0021-9681(64)90038-4

[5] Söderlin MK, Bergsten U, Svensson B, BARFOT Study Group. Patient-Reported Events Preceding the Onset of Rheumatoid Arthritis: Possible Clues to Aetiology. Musculoskeletal Care 2011;9:2531.
doi: 10.1002/msc.193

[6] Montgomery SA, Asberg M. A New Depression Scale Designed to be Sensitive to Change. Br J Psychiatry 1979;134:3829.
doi: 10.1192/bjp.134.4.382

[7] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An Inventory for Measuring Depression. Arch Gen Psychiatry 1961;4:56171.
doi: 10.1001/archpsyc.1961.01710120031004

[8] Sifneos PE. Alexithymia: Past and present. Am J Psychiatry 1996;153:13742.
doi: 10.1176/ajp.153.7.137

[9] Sifneos PE. The Prevalence of 'alexithymic'Characteristics in Psychosomatic Patients. Psychother Psychosom 1973;22:25562.
doi: 10.1159/000286529

[10] Bagby RM, Taylor GJ, Parker JD. Construct Validity of the Toronto Alexithymia Scale. Psychother Psychosom 1988;50:2934.
doi: 10.1159/000288097

[11] Crowne DP, Marlowe D. A New Scale of Social Desirability Independent of Psychopathology. J Consult Psychol 1960;349-354.
doi: 10.1037/h0047358

[12] Gaudry E, Vagg P, Spielberger CD. Validation of the State-Trait Distinction in Anxiety Research. Multivar Behav Res 1975;10:33141.
doi: 10.1207/s15327906mbr1003_6

[13] Temoshok L. Personality, Coping Style, Emotion and cancer: Towards an Integrative Model. Cancer Surv 1987;6:54567.

[14] Grossarth-Maticek R, Vetter H, Frentzel-Beyme R, Heller WD. Precursor Lesions of the GI Tract and Psychosocial Risk Factors for Prediction and Prevention of Gastric Cancer. Cancer Detect Prev 1988;13:239.

[15] Grossarth-Maticek R, Eysenck HJ, Boyle GJ, Heep J, Costa SD, Diel IJ, *et al*. Interaction of Psychosocial and Physical Risk Factors in the Causation of Mammary Cancer, and Its Prevention through Psychological Methods of Treatment. J Clin Psychol 2000;56:3350.
doi: 10.1002/(sici)1097-4679(200001)56:1<33::aid-jclp4>3.0.co;2-2

[16] Bayle O, Consoli SM, Baudin M, Vayssairat M, Fiessinger JN, Housset E. Idiopathic and Secondary Raynaud's Phenomenon. A Comparative Psychosomatic Approach. Presse Med 1990;19:7415.

[17] Nagano J, Morita T, Taneichi K, Nagaoka S, Katsube S, Asai T, *et al*. Rational/Antiemotional Behaviors in Interpersonal Relationships and the Functional Prognosis of Patients with Rheumatoid Arthritis: A Japanese Multicenter, Longitudinal Study. Biopsychosoc Med 2014;8:8.

doi: 10.1186/1751-0759-8-8

[18] Ishii H, Nagashima M, Tanno M, Nakajima A, Yoshino S. Does Being Easily Moved to Tears as a Response to Psychological Stress Reflect Response to Treatment and the General Prognosis in Patients with Rheumatoid Arthritis? Clin Exp Rheumatol 2003;21:6116.

[19] Butow PN, Hiller JE, Price MA, Thackway SV, Kricker A, Tennant CC. Epidemiological Evidence for a Relationship Between Life Events, Coping Style, and Personality Factors in the Development of Breast Cancer. J Psychosom Res 2000;49:16981.
doi: 10.1016/s0022-3999(00)00156-2

[20] Zachariae R, Jensen AB, Pedersen C, Jørgensen MM, Christensen S, Lassesen B, *et al*. Repressive Coping Before and After Diagnosis of Breast Cancer. Psychooncology 2004;13:54761.
doi: 10.1002/pon.772.

[21] Cutolo M, Straub RH. Stress as a Risk Factor in the Pathogenesis of Rheumatoid Arthritis. Neuroimmunomodulation 2006;13:27782
doi: 10.1159/000104855

[22] Straub RH, Cutolo M. Does Stress Influence the Course of Rheumatic Diseases? Clin Exp Rheumatol 2006;24:2258.

[23] Rimón R, Laakso RL. Life Stress and Rheumatoid Arthritis. A 15-Year Follow-Up Study. Psychother Psychosom 1985;43:3843.
doi: 10.1159/000287856.

[24] O'Donovan A, Cohen BE, Seal KH, Bertenthal D, Margaretten M, Nishimi K, *et al*. Elevated Risk for Autoimmune Disorders in Iraq and Afghanistan Veterans with Posttraumatic Stress Disorder. Biol Psychiatry 2015;77:36574.
doi: 10.1016/j.biopsych.2014.06.015

[25] Boscarino JA, Forsberg CW, Goldberg J. A Twin Study of the Association between PTSD Symptoms and Rheumatoid Arthritis. Psychosom Med 2010;72:4816
doi: 10.1097/PSY.0b013e3181d9a80c

[26] Webster Marketon JI, Glaser R. Stress Hormones and Immune Function. Cell Immunol 2008;252(1-2):1626.
doi: 10.1016/j.cellimm.2007.09.006

[27] Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, *et al*. Vagus Nerve Stimulation Attenuates the Systemic Inflammatory Response to endotoxin. Nature 2000;405:45862.
doi: 10.1038/35013070

[28] Levite M. Neuropeptides, by Direct Interaction with T Cells, Induce Cytokine Secretion and Break the Commitment to a Distinct T Helper Phenotype. Proc Natl Acad Sci U S A 1998;95:125449.
doi: 10.1073/pnas.95.21.12544

[29] Carpenter LL, Gawuga CE, Tyrka AR, Lee JK, Anderson GM, Price LH. Association Between Plasma IL-6 Response to Acute Stress and Early-Life Adversity in Healthy Adults. Neuropsychopharmacol 2010;35:261723.
doi: 10.1038/npp.2010.159

[30] Janusek LW, Tell D, Gaylord-Harden N, Mathews HL. Relationship of Childhood Adversity and Neighborhood Violence to a Proinflammatory Phenotype in Emerging adult African American men: An Epigenetic Link. Brain Behav Immun 2017;60:12635.
doi: 10.1016/j.bbi.2016.10.006

[31] Reynier-Legarçon E, Clément JP, Calvet B, Bézananary H, Liozon E, Gondran G, *et al*. Personnalité et Maladies Auto-Immunes Systémiques. Rev Méd Internet 2016;37:38.
doi: 10.1016/j.revmed.2016.04.238

[32] Baerwald C, Manger B, Hueber A. Depression as Comorbidity of Rheumatoid arthritis. Z Rheumatol 2019;78:2438.
doi: 10.1007/s00393-018-0568-5

[33] Kang W. Global and Dimensions of Mental Health in Arthritis Patients. Healthcare (Basel) 2023;11:195.
doi: 10.3390/healthcare11020195

[34] Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, *et al*. Classification Criteria for Psoriatic Arthritis: Development of New Criteria from a Large International Study. Arthritis Rheum 2006;54:266573.
doi: 10.1002/art.21972

[35] Salaffi F, Carotti M, Gasparini S, Intorcia M, Grassi W. The Health-Related Quality of life in Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis: A Comparison with a Selected Sample of Healthy People. Health Qual Life Outcomes 2009;7:25.
doi: 10.1186/1477-7525-7-25

[36] Dagfinrud H, Mengshoel AM, Hagen KB, Loge JH, Kvien TK. Health Status of Patients with Ankylosing Spondylitis: A Comparison with the General Population. Ann Rheum Dis 2004;63:160510.
doi: 10.1136/ard.2003.019224

[37] Hyphantis T, Kotsis K, Tsifetaki N, Creed F, Drosos AA, Carvalho AF, *et al*. The Relationship Between Depressive Symptoms, Illness Perceptions and Quality of Life in Ankylosing Spondylitis in Comparison to Rheumatoid Arthritis. Clin Rheumatol 2013;32:63544.
doi: 10.1007/s10067-012-2162-6

[38] Michelsen B, Kristianslund EK, Sexton J, Hammer HB, Fagerli KM, Lie E, *et al*. Do Depression and Anxiety Reduce the Likelihood of Remission in Rheumatoid Arthritis and Psoriatic Arthritis? Data from the Prospective Multicentre NOR-DMARD Study. Ann Rheum Dis 2017;76:190610.
doi: 10.1136/annrheumdis-2017-211284

[39] Bijsterbosch J, Scharloo M, Visser AW, Watt I, Meulenbelt I,

Huizinga TW, *et al*. Illness Perceptions in Patients with Osteoarthritis: Change Over Time and Association with Disability. Arthritis Rheum 2009;61:105461.
doi: 10.1002/art.24674

[40] Smoak KA, Cidlowski JA. Mechanisms of Glucocorticoid Receptor Signaling During Inflammation. Mech Ageing Dev 2004;125:697706.
doi: 10.1016/j.mad.2004.06.010

[41] Howren MB, Lamkin DM, Suls J. Associations of Depression with C-Reactive Protein, IL-1, and IL-6: A Meta-Analysis. Psychosom Med 2009;71:17186.
doi: 10.1097/PSY.0b013e3181907c1b

[42] Goldsmith DR, Rapaport MH, Miller BJ. A Meta-Analysis of Blood Cytokine Network Alterations in Psychiatric Patients: Comparisons between Schizophrenia, Bipolar Disorder and Depression. Mol Psychiatry 2016;21:1696709.
doi: 10.1038/mp.2016.3

[43] Gobin V, Van Steendam K, Denys D, Deforce D. Selective Serotonin Reuptake Inhibitors as a Novel Class of Immunosuppressants. Int Immunopharmacol 2014;20:14856.
doi: 10.1016/j.intimp.2014.02.030

[44] Minnema LA, Giezen TJ, Souverein PC, Egberts TC, Leufkens HG, Gardarsdottir H. Exploring the Association between Monoclonal Antibodies and Depression and Suicidal Ideation and Behavior: A vigibase study. Drug Saf 2019;42:887-95.
doi: 10.1007/s40264-018-00789-9

[45] Lebwohl MG, Papp KA, Marangell LB, Koo J, Blauvelt A, Gooderham M, *et al*. Psychiatric Adverse Events During Treatment with Brodalumab: Analysis of Psoriasis Clinical Trials. J Am Acad Dermatol 2018;78:81-9.e5.
doi: 10.1016/j.jaad.2017.08.024



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