Elevated Levels of Eotaxin-2 in Serum of Fibromyalgia Patients

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Fibromyalgia syndrome (FMS) is a highly prevalent chronic pain syndrome characterized by widespread pain and other somatic symptoms, including fatigue, sleep disturbances, cognitive dysfunction, and depression [1]. The diagnosis of FMS is based on clinical grounds [2], and despite many attempts to identify objective biomarkers for FMS, no such well-validated biochemical marker for either diagnosis or severity has emerged. While the pathogenesis of FMS remains incompletely understood, one leading paradigm is that of pain centralization, an increase of the processing of pain within the central nervous system (CNS) [3].

Recent studies suggest that cytokines may play a role in the pathogenesis of FMS, in particular, chemotactic cytokines referred as chemokines [4]. Chemokines are a family of small (8–10 kDa) proteins that induce chemotaxis of inflammatory cells. Emerging evidence reveals that chemokines play a role in the physiology of the nervous system, including neuronal migration, cell proliferation, and synaptic activity [5]. Chemokines and their receptors are among the key players responsible for communication between neurons and inflammatory cells, and this crosstalk is crucial for normal neurological functioning [5]. Furthermore, chemokines seem to contribute to a reciprocal interaction between neurons, glia, and microglia in a so-called “gliopathy,” that is, activation of glial cells and neuroglial interactions as a basis for chronic pain [6–8]. Chemokines participate in synaptic transmission and in the formation of second-messenger systems in neurons and glial cells, favoring the noxious process. Chemokines enhance sensitivity to pain by direct action on chemokine receptors expressed in the entire pain pathway, from peripheral nerves to the dorsal ganglia and spinal cord. Simultaneously, they regulate the inflammatory response by acting on elements of the nervous system [5].

Since pain is the salient symptom of FMS, one may consider that, as modulators of nociception, certain chemokines may be involved in the pathophysiology of this
syndrome. Increased levels of inflammatory cytokines and chemokines in serum [4, 9, 10] and cerebral spinal fluid [11] have been recently reported in cross-sectional studies in FMS cohorts. Subsequently, a prospective study by Wang et al. has not only confirmed the finding of increased circulating levels of cytokines in FMS, but also suggested a potential cytokine response to a therapeutic intervention [12, 13]. After 6 months of multidisciplinary pain therapy, baseline serum level of interleukin-8 (IL-8) reduced nearly to the normal range in correlation with a reduction in pain intensity. Ang et al. have further demonstrated that the level of pain in FMS corresponds to circulating chemokines levels, with up-trending levels of monocyte chemotactic protein-1 (MCP-1) and IL-8 in parallel with increasing pain severity over time [14]. Nonetheless, the relationship between the chemokine-cytokine network and FMS has yet to be clarified. Eotaxin-2 (CCL24), a member of the CC chemokine family, is a potent chemoattractant for eosinophils, basophils, and lymphocytes, distributed in a variety of tissues, including human brain [15]. To our best knowledge, no studies previously examined the eotaxin-2 profile in FMS patients. Thus, we conducted a case-control study to determine levels of circulating eotaxin-2 and high-sensitive C-reactive protein (hs-CRP) in FMS patients compared to healthy controls (HC). We further examined the relationship between these potential biomarkers and FMS severity.

2. Methods

50 patients suffering from primary FMS were consecutively recruited through the Rheumatology Clinic at the Tel Aviv Sourasky Medical Center. 15 healthy subjects were recruited as healthy controls (HC). Upon recruitment, patients were examined by a physician to verify the diagnosis of FMS and screened for alternative diagnoses such as inflammatory joint disease. Patients with a known diagnosis of inflammatory joint disease/chronic kidney disease/chronic liver disease/heart failure/diabetes mellitus/active malignancy were excluded from the study. Patients currently treated with immune-suppressive medications, including steroids, were excluded from the study. The diagnosis of FMS was verified according to the American College of Rheumatology (ACR) updated diagnostic criteria [2]. Patients subsequently filled out questionnaires to assess and document the severity of FMS symptoms. Questionnaires included basic demographic data (age, sex, smoking status, weight, height, use of medications, comorbidities, and previous medical history), widespread pain index (WPI), documenting extent of widespread pain, symptoms severity score (SSS), documenting severity of associated symptoms, Fibromyalgia Impact Questionnaire (FIQ), and Beck Depression Inventory (BDI) for evaluation of depression. Blood specimens for Eotaxin-2 and hs-CRP were drawn, separated, aliquoted, and stored frozen at −20°C until analysis. Eotaxin-2 was measured using ELISA. The study was approved by the Institutional Review Board of the Hospital, and all patients provided written informed consent.

3. Statistical Analysis and Data Processing

Data were statistically analyzed with SPSS (version 20; IBM, Armonk, New York, NY, USA). Before analysis, residuals were tested for normal distribution (Shapiro–Wilk test) and equality of variance (Levene’s test). Nonparametric tests were used where appropriate. Group comparisons were calculated using Student’s independent t-test (parametric), Kruskal–Wallis test (nonparametric) or Pearson’s chi test for categorical variables. According to the underlying hypotheses, a two-tailed test was performed. The significance level was set to \( p = 0.05 \). Values are given as means ± standard deviations (SD).

4. Results

Fifty-four patients suffering from FMS and 15 HC were enrolled in the study. Four patients were excluded due to impaired glucose tolerance treated pharmacologically (\( n = 2 \)) or due to missing data (\( n = 2 \)). The FMS cohort included predominantly females (84%) of 49 ± 14.6 years of age, body mass index (BMI) of 26.8 ± 5.1, and disease duration of 6 ± 5.5 years. Thirty percent of FMS patients were smokers. Half of the patients were unemployed. Thirty-two percent of patients stated incapability to work due to FMS. HC cohort included subjects of 37.5 ± 12.6 years of age, with a similar gender representation (53% females and 47% males) and BMI 22.6 (± 3.3).

The levels of the mediators along with indices of disease activity in FMS are summarized in Table 1. FMS patients exhibited significantly higher eotaxin-2 levels as compared to healthy controls, 833 (± 384) versus 622 (± 149), \( p = 0.04 \), respectively, as presented in Figure 1. No significant gender-based difference was found in the mediators’ levels or disease severity indices.

When examining the correlation between FMS severity indices and levels of eotaxin-2, no significant correlation was found. There was also no significant correlation between the parameters of FMS severity and hs-CRP. The lack of correlation between eotaxin-2 and hs-CRP is noteworthy. The majority of FMS patients had normal range of hs-CRP levels; however, the average level of hs-CRP was slightly elevated in FMS patients (4.81 mg/l). As expected, a positive correlation was found between hs-CRP and BMI (\( r = 0.44, p = 0.02 \)), but not for eotaxin-2 levels and BMI (\( r = 0.06, p = 0.8 \)). Smoking was not found to correlate neither with eotaxin-2/hs-CRP levels nor with disease severity indices.

5. Discussion

The present pilot study is the first one to report significantly increased circulating levels of eotaxin-2 in serum of FMS patients, compared with healthy controls, with no direct association between eotaxin-2 levels and FMS severity indices. This finding is consistent with the accumulating evidence regarding a distinct cytokine profile in FMS patients, further supporting the hypothesis of cytokines playing an important role in FMS pathophysiology [4, 10, 12–14].
Eotaxins are C-C motif chemokines first identified as potent eosinophil chemoattractants. They facilitate eosinophil recruitment to sites of inflammation in response to parasitic infections, as well as in allergic and autoimmune diseases such as asthma, atopic dermatitis, and inflammatory bowel disease [16]. The eotaxin family currently includes diseases such as asthma, atopic dermatitis, and inflammatory parasitic infections, as well as in allergic and autoimmune paradigms. They facilitate eosinophil recruitment to sites of inflammation in response to parasitic infections, as well as in allergic and autoimmune diseases such as asthma, atopic dermatitis, and inflammatory bowel disease [16]. The eotaxin family currently includes diseases such as asthma, atopic dermatitis, and inflammatory parasitic infections, as well as in allergic and autoimmune diseases such as asthma, atopic dermatitis, and inflammatory bowel disease [16]. 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interruption and fatigue intensity may be of interest. Further studies of additional cytokines and especially chemokines are indicated in order to pinpoint a biochemical marker for FMS disease severity, while additional research is also necessary in order to uncover a possible pathogenetic role of eotaxin-2 in FMS and in order to evaluate its potential role as a therapeutic target.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**Authors' Contributions**

Victoria Furer and Eyal Hazan equally contributed to this work.

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