

Concentration of cytokines in patients with osteoarthritis of the knee and fibromyalgia

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Introduction: Fibromyalgia and osteoarthritis may present a relationship with the concentration of cytokines. The aim of this study was to compare the serum concentrations of IL-12p70, tumor necrosis factor, IL-10, IL-6, IL-1 β , and IL-8 in patients with knee osteoarthritis and fibromyalgia.

Materials and methods: The study included 53 women (71.2 \pm 7.6 years old) diagnosed with knee osteoarthritis with moderate-to-severe pain (visual analog scale >4) for at least 3 months. Sixty women (54.1 \pm 8.1 years old) diagnosed with fibromyalgia according to the American College of Rheumatology criteria and with moderate-to-severe pain (visual analog scale >4) also participated in this study. For the dosage of cytokines, blood was collected in the morning: 5 mL from the cubital vein. The material was centrifuged at 4°C, separated into 100 μ L aliquots and stored at -80°C until processing. Serum concentrations of the studied cytokines were assessed using the BD Cytometric Bead Array method. Data were analyzed with Student's *t*-test and the Mann-Whitney *U* test.

Results: We found higher levels of IL-6, IL-10, and IL-1 β in fibromyalgia patients. After adjustment of age as a covariate, there was no statistically significant difference in the concentration of any cytokine between fibromyalgia and knee osteoarthritis patients.

Conclusion: Patients with knee osteoarthritis and fibromyalgia with the same duration and intensity of pain demonstrate similar concentrations of cytokines. Aging may play a role in cytokine profile, a finding not so extensively addressed in the literature and one that should be further investigated.

Keywords: cytokines, osteoarthritis, fibromyalgia, aging

Introduction

With regard to rheumatic diseases, osteoarthritis (OA) is the most common joint disease in the world,¹ and symptoms in the knee joint occur in 10% of women and 13% of men aged 60 years or older.^{2,3} Another rheumatic disease, fibromyalgia (FM), is characterized by diffused chronic pain that causes many other symptoms, also worth mentioning due to its high annual cost (direct and indirect) of US\$5,945 per person.⁴ FM negatively impacts quality of life, particularly of women between 45 and 64 years old,⁵⁻⁷ which could be aggravated by the aging population, also taking into consideration the fact that this chronic disease has no consensus about its pathogenesis.⁸ Chronic pain is associated with aging and the inflammatory response.⁹ For this reason, we investigated the inflammatory process in two different chronic healthy conditions by assessing serum cytokine levels and profile. Cytokines are a large group of small proteins and polypeptides that are molecules that act on cells involved in immune and inflammatory responses.¹⁰ Some authors claim that serum levels of certain cytokines may be correlated with such symptoms as pain, depression, and fatigue.¹¹ For FM, for example, it is known that loss of balance between proinflammatory and anti-inflammatory serum

cytokines plays a role in the maintenance of chronic pain, depression, and fatigue.¹¹

Although not a specific issue characterizing FM,³ there may be a relationship between symptoms and cytokines.^{8,12–16} With regard to OA, these cytokines can also play a major role in the immune response, due to the inflammatory process at the lesion site.^{17,18} We identified several studies on the levels of serum cytokines IL-6, IL-8, IL-10, IL-1, IL-12p70, and TNF α , both on FM and knee OA patients. However, no studies compared both entities using the same data-collection and methodological assessments. Therefore the objective of this study was to compare the concentrations of cytokines in patients with FM and knee OA. We hypothesized that serum levels would be higher in FM patients and that the cytokine profile would be different between both studied groups. Knowledge of the possible role of inflammatory components in both FM and knee OA may improve treatment of these conditions. Therefore, comparing the behavior of cytokines in these two chronic diseases can provide interesting data on the symptomatology and prospects of future treatments.

Materials and methods

This study was approved by the Ethics Committee for Analysis of Research Projects of Hospital of Clinics, University of São Paulo Medical School, São Paulo, Brazil (CAPPesq 0131/10 and 1176/09). All participants were informed about the study procedure and signed a consent to participate in this study. We recruited women aged 30–65 years with moderate-to-severe pain (visual analog scale [VAS] ≥ 4)¹⁹ diagnosed with FM according to the American College of Rheumatology.²⁰

Excluded from this group were patients diagnosed with psychiatric disease, such as severe depression or schizophrenia, with neurological alterations and/or sequelae, heart disease, coagulopathy, chronic illness, pregnancy, or who had any other rheumatologic disorders, or autoimmune or immunologic diseases. The recruitment of patients/participants was done through referrals from various departments of the University of São Paulo Medical School, through personal contacts, and family members who volunteered to participate.

Knee OA admission criteria included women ≥ 60 years diagnosed with OA of the knee by the American College of Rheumatology criteria and Kellgren–Lawrence scale grades of 2–4,^{21,22} experiencing moderate-to-severe pain (VAS ≥ 4),¹⁹ as general averaged level of pain experienced during the day for the past month, lasting ≥ 3 months. Those who had other rheumatic disease, chronic pain, history of

malignancy, previous knee surgery, autoimmune diseases, or active infectious diseases were excluded from the study.

For dosage of the concentrations of serum cytokines, a blood sample (5 mL) was taken from the cubital vein between 8 am and 11 am and immediately placed in a Vacutainer[®] (BD, Franklin Lakes, NJ, USA) tube. No addition anticoagulant was added in order to obtain serum after centrifugation at 500 g and 4°C. The sera samples were aliquoted in Eppendorf (Hamburg, Germany) Cryotubes and stored at -80°C until use. A human inflammatory cytokines kit (Cytometric Bead Array [CBA]; BD Biosciences, San Jose, CA, USA) was used to quantitatively measure serum concentrations of IL-6, IL-8, TNF α , IL-1 β , IL-10, and IL-12p70 according to the manufacturer's instructions. Individual cytokine concentrations (pg/mL) were computed using the standard reference curve of CellQuest[™] (BD Biosciences) and CBA software. The reading of the serum samples was performed by the FACSCalibur[™] cytometer (BD Biosciences) of the Laboratory of Medical Investigation – LIM 56, Hospital of Clinics, School of Medicine, University of São Paulo.

Statistical analysis

The Kolmogorov–Smirnov adjustment test for a normal distribution for all study variables was used. Quantitative characteristics of the patients were described in the two groups with the use of summary measures (mean, standard deviation, median, minimum, and maximum).

Statistical comparisons of the serum levels of IL-6, IL-8, IL-10, IL-1, TNF α , and IL-12p70 were made between patients with knee OA and FM. Comparisons between the two groups were made by Student's *t*-test if data were normally distributed, and by Mann–Whitney *U* test where data were not normally distributed.²³ We used age as a covariate. Data analysis was done by SPSS 15.0 software (SPSS, Chicago, IL, USA). Statistical significance was set at $P < 0.05$, two tailed.

Results

The study included 53 patients with OA of the knee (71.2 ± 7.6 years old) and 60 patients with FM (54.1 ± 8.1 years old). Table 1 shows that patients with OA of the knee were on average statistically older than patients with FM ($P < 0.001$). Other baseline characteristics did not differ statistically between groups ($P > 0.05$). When no statistical adjustment for age was performed, IL-12p70 was significantly higher in patients with OA ($P < 0.001$). Likewise, IL-10 and IL-1 β were significantly higher in FM patients ($P = 0.001$ and $P < 0.001$, respectively). After adjustment for age, there was

Table 1 General characteristics of groups: results of Mann–Whitney *U* test

Variable	Group	Mean	SD	Median	Min	Max	n	P-value
Age (years)	Knee osteoarthritis	71.2	7.6	71.0	56.0	90.0	53	<0.001*
	Fibromyalgia	54.1	8.1	55.0	31.0	66.0	60	
BMI (kg/m ²)	Knee osteoarthritis	27.9	5.9	26.9	20.0	52.7	52	0.124*
	Fibromyalgia	29.7	5.9	28.4	20.4	45.4	59	
Duration of pain (months)	Knee osteoarthritis	114.6	87.0	120.0	3.00	360.0	53	0.382
	Fibromyalgia	123.4	75.6	120.0	12.0	360.0	58	
VAS	Knee osteoarthritis	7.4	1.9	7.8	1.8	9.9	53	0.439
	Fibromyalgia	7.7	1.8	8.0	2.5	10.0	60	

Note: *Results of Student's *t*-test.

Abbreviations: SD, standard deviation; Min, minimum; Max, maximum; BMI, body mass index; VAS, visual analog scale.

no difference between the cytokine concentrations between the two groups (Table 2).

Discussion

Previous studies have shown that in comparison to healthy individuals, OA and FM patients show a significant difference in their concentrations of inflammatory cytokines.^{12,15,18} However, the results of this study indicate that individuals with OA of the knee and FM with similar pain duration and intensity of pain had similar concentrations of cytokines.

Increased levels of proinflammatory cytokines are related to the development and progression of OA due to alteration of gene expression, stimulation of reactive oxygen species production, altered metabolism of articular components, and bone resorption.^{24–26} Some authors have related the loss of functioning to higher levels of serum levels of proinflammatory cytokines.^{24,27–29} A study¹⁸ where muscle biopsy was performed, which verified muscle strength in individuals with knee OA and a controlled group, found that the first group had lower muscle strength and higher levels of protein/receptor levels of IL-6 compared to healthy subjects; IL-1 was slightly elevated, although not statistically significant, as was IL-8.

Although it is not considered an inflammatory disease, FM can be associated with the presence of inflammatory symptoms with various cytokines, as these are related to the modulation of hyperalgesia, fatigue, sleep disturbances, and pain, among others. The literature suggests that in subjects with FM, there is a lack of regulation of cytokines IL-1, IL-6, and IL-8.^{13,30} When comparing a control group and patients with FM, Wallace et al¹² found that the latter had higher serum levels of IL-8 compared to the controls, and the authors also added that IL-6 may be responsible for many symptoms of FM, such as hyperalgesia, fatigue, and depression. Other authors¹⁴ also observed an increase in IL serum levels of IL-10, IL-8 and TNF α in patients with FM compared with control subjects. Another study suggests that the serum level of IL-8 in patients with FM contributes to increased pain intensity.¹⁵

To our knowledge, there are no studies comparing cytokines in patients with rheumatic diseases, specifically between FM and OA, the two major rheumatic diseases. Therefore, it is difficult to compare data from our study. Our study presented three factors – body composition, duration, and intensity of pain – that could have interfered with the results,

Table 2 Comparison of results of serum cytokine concentration between fibromyalgia and knee osteoarthritis patients

Variable	Group	Mean	SD	Median	Min	Max	n	P-value*	P-value#
IL-12p70 (pg/mL)	Knee osteoarthritis	11.4	37.36	0.0	0.0	178.3	53	<0.001	0.156
	Fibromyalgia	7.7	26.17	2.6	0.0	171.5	60		
TNF α (pg/mL)	Knee osteoarthritis	2.2	4.52	1.2	0.0	24.2	53	0.128	0.630
	Fibromyalgia	2.0	2.08	2.0	0.0	11.7	60		
IL-10 (pg/mL)	Knee osteoarthritis	1.6	2.36	1.2	0.0	15.7	53	0.001	0.949
	Fibromyalgia	2.0	1.13	2.0	0.0	7.8	60		
IL-6 (pg/mL)	Knee osteoarthritis	4.4	4.61	2.8	1.2	19.3	53	0.488	0.395
	Fibromyalgia	3.5	1.86	3.3	0.0	12.3	60		
IL-1 β (pg/mL)	Knee osteoarthritis	1.9	3.30	1.1	0.0	17.0	53	<0.001	0.143
	Fibromyalgia	3.4	2.27	2.7	0.0	14.0	60		
IL-8 (pg/mL)	Knee osteoarthritis	10.6	8.50	8.7	0.0	53.5	53	0.434	0.688
	Fibromyalgia	10.5	8.67	7.2	0.0	45.5	60		

Notes: *Results of Mann–Whitney *U* test; #results of test adjusted for age.

Abbreviations: SD, standard deviation; Min, minimum; Max, maximum; IL, interleukin; TNF, tumor necrosis factor.

but as these were similar between groups, it is believed that the results related to the concentration of cytokines were due to the condition of the disease itself.

When results without adjusting for age were checked, the OA group showed a higher concentration of proinflammatory IL-12p70 cytokines in relation to the FM group. The FM group had higher concentrations of one proinflammatory (IL-1) and one immunomodulatory cytokine (IL-10) compared to the OA group. However, these differences did not remain when adjustment for age was done.

Aging may influence cytokine profile, and should always be taken into consideration. Noncommunicable chronic conditions/diseases and the aging process are global conditions that currently have an increased prevalence. Both conditions are now a public health priority. Better understanding of the influence and impact of aging in the pathophysiology of common health conditions is urgently needed.³¹ Studies have indicated that patients with FM present shortened telomere length, a measure of biological age, when compared to a control group of individuals, also indicating that when pain and depression are associated with this type of patient and there might be a consistent difference of approximately 6 years in chronological aging.⁹ Therefore, it is believed that these chronic diseases, often present in middle-aged and elderly women with FM and also elderly individuals with OA, can accelerate the process of aging.

Another factor that should be considered is that besides the pathogenesis of these chronic diseases (FM and OA) being dependent on the combination of genetic, psychological, and environmental factors,³² there is also the factor of hypersensitivity within the diffuse neural networks of the central nervous system involved in nociception. This explains the fact that the treatment for this type of disease should not be focused only on reducing pain but also on the improvement of abnormalities in peripheral sensitization/neuroendocrine abnormalities and the central/autonomic nervous system.³³ As stated by Staud,³³ educational programs, exercise, and cognitive therapies should also be associated with treatment.

Ortega et al³⁴ describe an indirect way of controlling cytokines by the practice of regular exercise. Physical exercise in patients with rheumatic diseases should aim to improve local symptoms and overall health.³⁵ Exercise is important, since disuse and the aging process are associated with increased inflammation.¹⁸

Ortega et al³⁴ reported that after an exercise program carried out in an indoor swimming pool, FM volunteers showed a significant decrease in serum levels of IL-8, interferon

and C-reactive protein with decreased concentration of circulating cortisol and noradrenaline levels.¹⁵ Wang et al¹⁵ reported that after 6 months of multidisciplinary therapy against pain, there was decreased serum concentration of IL-8 in women with FM. Another important issue is the increase in markers of muscle inflammation often present in both FM and OA related with reduced muscle strength,¹⁸ and exercise can cause an increase in the concentration of intra-articular and perisynovial fluid of protein/receptor levels of IL-10 in women, suggesting that exercise beneficially acts on chondroprotective anti-inflammatory cytokines in patients with OA.³⁶ As for IL-1 β concentration, which is among the most important mediators involved with inflammatory response,³⁷ a higher concentration was observed within patients with FM (when age was not adjusted). However, it is believed that this type of cytokine is also important in patients with OA, because its expression is also associated with the loss of muscle mass due to aging,³⁸ a very common event in patients with OA. It is important to recommend patients with these chronic diseases for physical exercise, because of loss of muscle mass, and also because exercise can positively affect muscle pH and blood flow.³⁹

We must not forget about ideal body weight in patients with chronic diseases, since adipose tissue increases the synthesis of pro-inflammatory cytokines, such as IL-6, IL-1, IL-8, TNF α , and IL-18, and decreases the regulatory cytokines, such as IL-10.⁴⁰ In the present study, although the two groups were similar with respect to this factor, both showed high values of body composition in relation to patterns of normality.⁴¹

Our study had some limitations. First, we did not measure all existing cytokines, eg, IL-17 or IL-18. Before starting the study, we performed an extensive literature search on existing information regarding serum levels of cytokines in patients diagnosed with knee OA. We decided to analyze the cytokines in our study that could be compared with previously published papers. Further studies should explore the role of other cytokines in these patients. Second, we did not include a control group of healthy volunteers, due to budgetary restrictions. Finally, age was significantly different between the two groups. We therefore adjusted the statistical analyses using age as a covariate. In fact, our results demonstrate higher levels of IL-6, IL-10, and IL-1 β in FM patients. However, when adjusted for age, these differences were no longer present. This indicates that aging may play a role in the cytokine profile, a finding not so extensively addressed in the literature and one that should be further investigated.

Future study should focus on the detection of cytokines in the skin, which could indicate the presence of the focus of inflammation that may occur in about 30% of patients of FM.⁴² We believe that the investigation of pressure pain threshold on points that present less tolerance to pressure in patients with OA and FM could lead to interesting results.

We conclude that patients with OA and FM with the same duration and intensity of pain have similar values for the concentration of cytokines, showing that there is no difference in the level of cytokine concentrations between these two chronic rheumatic diseases that affect middle-aged and elderly people.

Disclosure

The authors report no conflicts of interest in this work.

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