Elevated prolactin levels in patients with rheumatoid arthritis: association with disease activity and structural damage

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Abstract

Objectives

Prolactin (PRL) is a hormone with cytokine-like activities that has been demonstrated to be involved in immune responses. However, there are inconsistent results related to the role of PRL in rheumatoid arthritis (RA). Therefore, the aim of this study was to evaluate the levels of PRL in serum and synovial fluid in patients with RA and osteoarthritis (OA) and examine whether PRL might be associated with laboratory and clinical disease activity of RA.

Methods

A total of 29 patients with RA and 26 patients with OA were included in the study. The concentration of PRL in the serum and synovial fluid was measured by immunoradiometric assays, and the levels of serum anti-citrullinated protein/peptide autoantibodies (ACPA) and IgM rheumatoid factor (IgM-RF) were analysed by ELISA. Disease activity score (DAS 28) and radiological (Larsen) score were assessed.

Results

The levels of PRL in serum (299.55±27.28 vs. 230.59±16.61mIU/l, p=0.041) as well as in synovial fluid (338.85± 33.49 vs. 245.97±21.88mIU/l, p=0.024) were significantly higher in patients with RA than in patients with OA. A moderate correlation was found between disease activity of RA and levels of PRL in synovial fluid (r=0.485, p=0.010) and the serum PRL levels correlated significantly with the total Larsen score (r=0.484, p=0.014)

Conclusion

The findings of increased prolactin levels in patients with RA lead to the assumption that prolactin may play a role in disease severity and the process of joint damage in RA.

Key words

prolactin, rheumatoid arthritis, disease activity, hormones

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by the accumulation of immune cells and activation of synovial fibroblasts within the synovial membrane, which subsequently results in cartilage destruction and erosion of the adjacent bone (1-3). To date, the aetiology of RA is unknown, and its pathogenesis remains incompletely understood. However, sex hormones have been suggested to modulate both onset as well as progression of the disease (4). Females are affected more frequently than males, and there is evidence that during pregnancy RA usually improves, which is in contrast to the characteristic exacerbation after delivery, a period when both cortisol and oestrogens rapidly decline and prolactin (PRL) remains significantly increased (4, 5).

In addition to its unique roles in reproduction and lactation, PRL acts as a potent immunomodulator (6, 7). The immune capability of PRL is generally stimulatory, while oestrogens and cortisol support the anti-inflammatory Th2 immune response. PRL maintains immune homeostasis, and its receptors have been detected on several immune cells, synovial fibroblasts and chondrocytes (6, 8, 9). In immune cells, PRL up-regulates transcription of the interferon regulatory factor IRF-1 gene and modulates expression of pro-inflammatory cytokines interleukin (IL)-12, interferon (IFN)-γ and tumour necrosis factor (TNF)-α (10, 11). Moreover, PRL exhibits anti-apoptotic activities, leading to increased survival of both autoreactive T-cells and B-cells (10, 12).

Several hormones, including PRL, have been observed in the synovial fluid of patients with RA (13), and elevated serum PRL levels have been detected in children suffering from antinuclear antibody (ANA)-positive juvenile idiopathic arthritis (14). In addition, serum PRL levels have been shown to correlate with disease activity of systemic lupus erythematosus (15, 16). However, in the case of RA there have been found inconsistent results varying from lower (17), equal (18) to higher PRL serum levels (19, 20). Nevertheless, in an experimental model, PRL was shown to aggravate arthritis in hypophysectomised rats (21) and in humans PRL serum levels correlated with proinflammatory chemokine MIP-1α (22), active disease (22) and worse Steinbrocker functional stage (20). Moreover, RA patients with increased serum PRL levels required strenuous therapy with glucocorticoids (23).

The aim of our study was to determine the levels of PRL in serum and synovial fluid of patients with RA and osteoarthritis (OA) and to characterise its potential association with the disease activity and joint damage.

Methods

Patients

Twenty-nine patients fulfilling the American College of Rheumatology (ACR) revised criteria for RA (24) were included in this study. The control group consisted of 26 patients with knee OA who met the ACR criteria for OA of the knee (25). Detailed characteristics of both groups are shown in Table I. The study was approved by the Ethical Committee of the Institute of Rheumatology in Prague, and all patients agreed on participation by signing the informed consent.

Synovial fluid was collected under standard conditions from the knee joint during therapeutic arthrocentesis. As the PRL serum levels show physiological diurnal variation, the blood samples were taken 1-5 days thereafter in the morning hours (at least 1 hour after waking up) and after at least 20 minutes at rest before sampling. Patients suffering from hypothyreosis, those that were pregnant or using drugs affecting PRL secretion were not included in this study.

Functional disability questionnaires (Czech validated versions) and disease activity were assessed at the time of arthrocentesis. The Western Ontario and McMaster Universities Index (WOMAC) was used for patients with OA. For patients with RA, the disease activity score (DAS) and health assessment questionnaire (HAQ) were examined. The DAS28 was calculated using the formula: $0.56\sqrt{}$ (number of tender joints)+$0.28\sqrt{}$ (number of swollen joints)+0.7Ln (erythrocyte

Table I. Baseline characteristics of patients.

	RA (n=29)	OA (n=26)	*p*-value
Age (years)	62.21 ± 2.52	66.20 ± 2.15	0.246
Gender (female/male)	22/7	15/11	0.249
Female: pre/postmenopausal	2/22	0/15	0.504
Disease duration (years)	7.86 ± 1.85	8.07 ± 1.68	0.594
Disease activity (DAS 28)	4.83 ± 0.29	NA	–
Mean Larsen score (index)	26.12	–	–
Glucocorticoids (n)	21	–	–
DMARDs (n) MTX/HCQ/SAS/LEF	29 17/3/5/4	–	–
Biological agents:			
TNF inhibitors/tocilizumab	8 7/1	–	–
CRP (mg/l)	21.65 ± 5.16	5.10 ± 1.62	0.007
ESR (mm/ 1st h)	26.34 ± 5.62	11.5 ± 1.74	0.010
ACPA (IU/ml)	275.21 ± 100.3	NA	–
RF IgM (U/ml)	17.28 ± 4.11	NA	–

DAS, disease activity score; DMARDs, Disease modifying antirheumatic drugs; MTX: Methotrexate; HCQ: Hydroxycloroquine; SAS: Sulphasalazine; LEF: Leflunomide; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ACPA: Anti-citrullinated peptide autoantibodies; RF: rheumatoid factor.

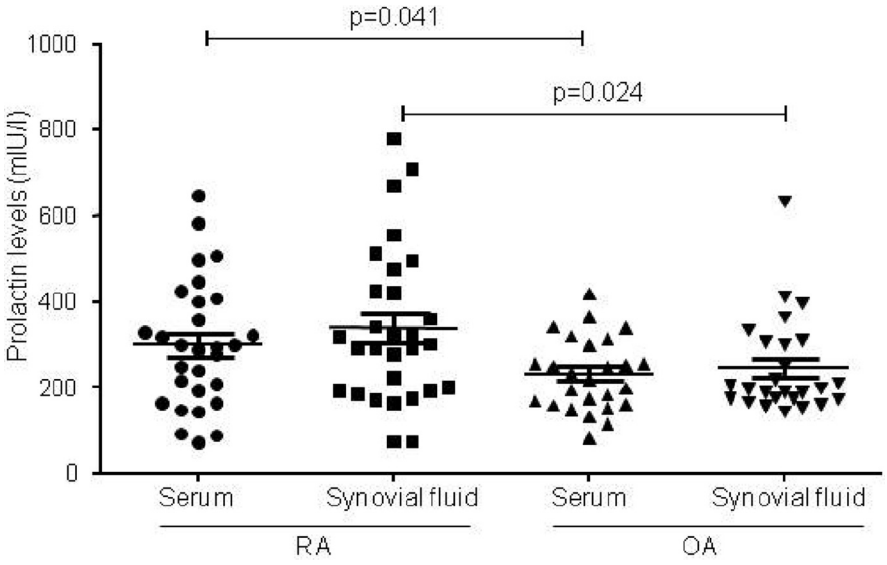

Fig. 1. Serum and synovial fluid levels of prolactin in patients with rheumatoid arthritis (RA) and osteoarthritis (OA).

sedimentation rate) +0.014 (patient's assessment of disease activity). RA patients were stratified according to the DAS28 into three groups with low (DAS28 <3.2), moderate (DAS28 3.2-5.1) and high disease activity (DAS28>5.1). Radiographs of hands, wrists and feet in frontal projection were taken from all patients at baseline. Radiographs were evaluated for joint space narrowing and erosions using modification of Larsen score (26). The total radiographic (Larsen) score was calculated by the grading from 0 (intact bony outlines and normal joint space) to 5 (mutilating changes) in 32 joint regions (26).

Laboratory analysis

The concentration of PRL in serum and synovial fluid was measured in duplicate using an immunoradiometric assay (IRMA, Immunotech, Prague). Samples (50µl) were incubated with ^{125} I-labelled antibody (150000cpm/500µl) in tubes pre-coated with mice monoclonal antibody for one hour at room temperature by continuous shaking. The contents of tubes were then aspirated. The tubes were washed twice with 2ml of wash solution, and the radioactivity bound to the tubes was measured using a gamma counter. The standards supplied with the kits were calibrated using the international standard WHO 84/500 (1ng/ml=30.3mIU/l). The limit of sensitivity of the assay was 30mIU/l. The intra-and inter-assay coefficients of variation were determined with the use of pooled patients' serum samples and were 4.5 and 8.8%, respectively. In the test there was no cross reactivity to other human hormones (hLH, hFSH, hTSH, hCG, hGH and HPL) as well as to rheumatoid factor. The levels of anti-citrullinated protein/peptide autoantibodies (ACPA) and IgM rheumatoid factor (IgM-RF) were analysed by ELISA (Test Line s.r.o., Czech Republic). C-reactive protein (CRP) was determined by nephelometry.

Statistical analysis

The IBM statistics software SPSS version 17 (http://www.spss.com) was used for statistical analysis. The levels of PRL were normally distributed, and therefore the student's *t*-test was used to analyse the difference between the two groups. *Pearson's* correlation coefficient was used for correlations between PRL and selected variables. Data are presented as the mean±standard deviation. A *p*-value less than 0.05 was considered statistically significant. Chi-square test and Student's *t*-test were used for the analysis of the variables of the demographic data.

Results

Increased prolactin levels in patients with rheumatoid arthritis

The mean serum PRL levels in patients with RA were significantly higher than those in patients with OA (299.55±27.28 *vs*. 230.59±16.61mIU/l, p=0.041). Similarly, the levels of PRL in synovial fluid were significantly higher in patients with RA than in patients with OA (338.85± 33.49 *vs*. 245.97±21.88mIU/l, p=0.024) (Fig. 1). The levels of PRL in synovial fluid were insignificantly increased compared to PRL levels in the serum in both groups; synovial fluid and serum levels significantly correlated with each other in patients with RA (r=0.546, p=0.002) as well as in patients with OA (r=0.528, p=0.006), see Figure 2. The levels of PRL in serum and synovial fluid in both groups were not affected

by disease duration or treatment with non-steroidal antirheumatic drugs or low dose glucocorticoids. The levels of PRL were also not affected by disease modifying anti-rheumatic drugs or biologics (data not shown).

When we stratified the subjects according to hormonal status, serum levels of PRL were significantly higher in postmenopausal, female RA patients (n=20) in comparison with the same group of OA patients (n=15) (323.1±40.90 *vs*. 221±22.71mIU/l, p=0.037). However, in the synovial fluid, there was no difference between postmenopausal females with RA and OA (329.1±31.28 *vs*. 268.80±33.26mIU/l, p=0.297). No differences were observed in serum as well as synovial fluid PRL levels between RA and OA males (data not shown). In the group of RA patients, PRL levels in synovial fluid, but not serum, were significantly higher in postmenopausal females in comparison to RA males (329.1±31.28 *vs*. 207.6±45.51mIU/l, p=0.040). However, in the OA patients, there were no differences in serum (221±22.71 *vs*. 243.7±24.8mIU/l; p=0.507) and synovial fluid (268.8±33.26 *vs*. 214.7±23.42mIU/l; p=0.929) PRL levels between postmenopausal females and males.

Association between prolactin, disease activity and morphological changes in patients with rheumatoid arthritis

Increased synovial fluid PRL levels were found in RA patients suffering from active disease (DAS28>5.1; n=11) in comparison with patients with moderate and low disease activity (433.0±62.5 *vs*. 318.3±42.6 mIU/l, p=0.045). Altogether, synovial fluid PRL levels significantly correlated with DAS28 in patients with RA (r=0.485, p=0.010; Fig. 3). In contrast, we only found a trend for the association between disease activity and serum PRL levels in patients with RA (r=0.345, p=0.078). On the other hand, the total radiographic (Larsen) score correlated significantly with the serum PRL levels (r=0.484, p=0.014), but not with that in synovial fluid (r=0.154, p=0.460; Fig. 4). The levels of PRL in both serum and synovial fluid did not correlate with functional status of the disease assessed by HAQ or by WOMAC in RA and OA patients, respectively (data not shown). The levels of PRL in the serum as well as in the synovial fluid were not associated with either the levels of serum CRP or with the serum autoantibodies such as IgM-RF or ACPA (data not shown).

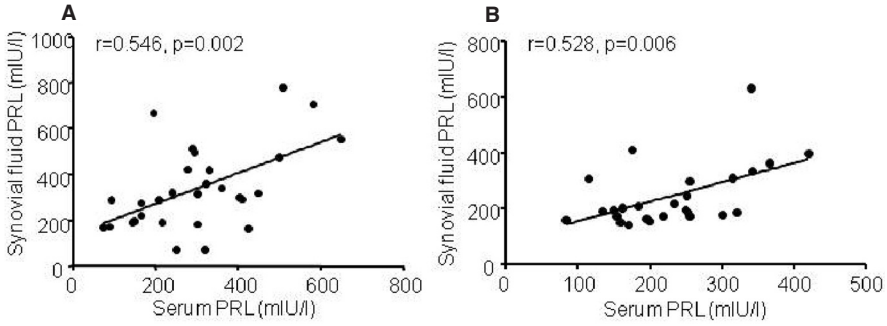

Fig. 2. Correlation between the levels of prolactin (PRL) in the serum and synovial fluid of patients with (**A**) rheumatoid arthritis (RA) and (**B**) osteoarthritis (OA).

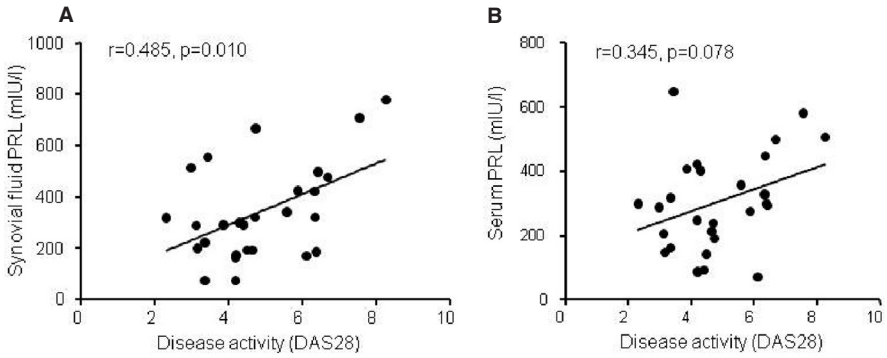

Fig. 3. Association between the levels of prolactin (PRL) in the synovial fluid (**A**) and serum (**B**) and disease activity in patients with rheumatoid arthritis (RA).

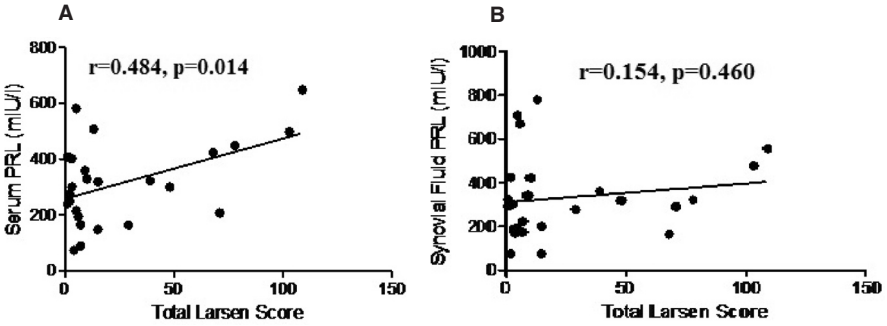

Fig. 4. Correlation between the levels of prolactin (PRL) in the (**A**) serum and (**B**) synovial fluid and Total Larsen score in patients with rheumatoid arthritis (RA).

Discussion

In this study, we found increased levels of PRL in both the serum and synovial fluid of patients with RA in comparison to patients with OA. Furthermore, the levels of synovial fluid PRL correlated significantly with the disease activity and the levels of systemic PRL correlated with the total radiographic score in patients with RA. Our results suggest that the inflammatory course of the disease may contribute to increased PRL levels, which may reflect structural damage in patients with RA.

The levels of serum PRL and its relationship with disease activity and severity have been demonstrated in several autoimmune diseases including systemic lupus erythematosus (15, 16), systemic sclerosis (27) and celiac disease (28). However, previous data

studying serum levels of PRL in RA patients have been inconsistent. The levels of serum PRL have been reported from lower (17), equal (18, 29) to higher (19, 20) in comparison to healthy individuals, and association between the levels of PRL and disease activity have not yet been shown. Similar to the latter data (19, 20), we showed increased PRL levels in serum and in the synovial fluid of patients with RA, which supports the association between the levels of PRL in the serum and synovial fluid (30). Furthermore, the levels of PRL in the synovial fluid significantly correlated with the disease activity of RA, while systemic levels of PRL showed only a tendency for this association and reflected rather the morphologic joint changes of active long-standing RA. Whether PRL could represent a surrogate marker with predictive value for further radiographic progression of the disease or even contribute to structural changes itself has not yet been shown.

Some authors have suggested that PRL in synovial fluid is derived from the plasma (13, 31). However, under inflammatory conditions, PRL may be also produced locally in immune cells and resident tissue cells of the joint, including synovial fibroblasts and chondrocytes expressing also PRL receptor (8, 9). There is evidence that PRL serves as a potent immunostimulatory cytokine and may be involved in inflammation and synovial hyperplasia (8, 10-12). PRL is suggested to have dual functions locally in the joint tissues. While in chondrocytes PRL prevents their apoptosis due to activation of antiapoptotic genes (32), it stimulates synovial cell proliferation and increases the synthesis of matrix metalloproteinase (MMP)-3, IL-6 and IL-8 (8). We therefore suggest that the increased levels of PRL produced either locally or derived from the blood circulation may contribute to structural changes associated with the development of RA.

In contrast to local sites, the systemic levels of PRL in our study showed only a tendency for association with the actual disease activity. However, we did not perform analysis of free serum prolactin and macroprolactin because only three RA patients had moderate hyperprolactinemia. In future studies, it might be interesting to determine whether the disease activity of RA correlates with levels of the free serum PRL as was previously demonstrated in patients with SLE (16). The regulation of PRL synthesis is negatively controlled by dopamine and is positively regulated by stress, exercise, circadian rhythms, the levels of oestrogens and proinflammatory cytokines such as TNF-α and IL-6 (33, 34). In postmenopausal females, the levels of serum PRL should be similar to that in males, which is what we saw in this study. Increased levels of serum PRL in postmenopausal, female RA patients compared to those in postmenopausal, female OA patients may be due to increased inflammatory activity of the autoimmune disease compared with the non-inflammatory nature of OA. On the other hand, we observed comparable PRL levels between RA and OA male patients. This observation could be explained by the very small number of male patients included in our study, while others have demonstrated increased serum PRL levels in male RA patients compared to OA male patients (20, 35), which supports chronic inflammation as the cause of elevated PRL levels. On the other hand, two works demonstrated that serum levels of PRL were not altered in the beginning of the RA (29, 36). Recently has been found that patients with active RA have decreased PRL response to hypoglycaemia-induced stress, although the response recovered following treatment with disease modifying antirheumatic drugs (DMARDs) (29). Our study is cross-sectional; therefore we are unable to evaluate the effect of anti-inflammatory treatment on the levels of PRL in patients with RA. However, we did not detect any differences in the levels of PRL in patients treated with DMARDs and biologic agents.

In summary, this study shows increased PRL levels in the serum and mainly in the synovial fluid of patients with RA in comparison to control OA subjects. This study shows the correlation between disease activity, structural damage and the levels of PRL in patients with RA. Our data support the hypothesis that PRL may play a role in the pathology of RA.

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