Serum Oxytocin Levels in Patients with Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis and their Association with Disease Activity

Serumoxytocinspiegel bei Patienten mit ankylosierender Spondylitis und nicht radiologische axiale Spondyloarthritis und deren Zusammenhang mit der Krankheitsaktivität

Authors
Ozkan Yukselmis[1], Pelin Oktayoğlu[2], Mehmet Caglayan[2], Nuriye Mete[3]

Affiliations
1 Department of Physical Therapy and Rehabilitation, TC Saglik Bakanligi Diyarbakir Devlet Hastanesi, Diyarbakir, Turkey
2 Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Division of Rheumatology, Dicle University, Diyarbakir, Turkey
3 Department of Biochemistry, Dicle University, Diyarbakir, Turkey

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Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Dr. Pelin Oktayoğlu
Faculty of Medicine
Department of Physical Medicine and Rehabilitation
Division of Rheumatology
Dicle University
Dicle University Faculty of Medicine Department of PRM
Diyarbakir 21280
Turkey
Tel.: 904122488001, Fax : 904122488001
plnftr@hotmail.com

ABSTRACT

Objectives Spondyloarthritis refers to a group of chronic inflammatory diseases that particularly involve the sacroiliac joints and spine but may also have an influence on extra-articular involvement in some patients. Oxytocin is a peptide hormone released from the hypothalamus and stored in the pituitary gland. It is known to have anti-inflammatory effects. The aim of this study was to investigate the serum levels of oxytocin and their potential association with disease activity and spinal mobility in patients with ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nrAxSpA).

Material and Methods Seventy-one patients with nrAxSpA, 38 patients with AS and 67 healthy control subjects were included in this study. Disease activity was assessed by the Bath Ankylosing Spondylitis Disease Activity Index, and spinal mobility by the Bath Ankylosing Spondylitis Metrologic Index. Laboratory examinations included complete blood count, ESR, CRP and oxytocin tests.

Results There was no significant difference in serum levels of oxytocin among the 3 groups ($p = 0.973$). However, serum levels of oxytocin correlated negatively with both ESR ($r = -0.359$, $p = 0.027$), CRP ($r = -0.316$, $p = 0.056$) and BASDAI scores ($r = -0{,}448$, $p = 0.005$) in patients with AS. On the other hand, serum levels of oxytocin had a negative correlation only with ESR in patients with nrAxSpA ($r = -0.321$ $p = 0.009$).

Conclusion This study lays the foundation for further studies that may aim to investigate how addition of oxytocin to the treatment regimen impacts on disease activity in patients with AS who exhibit particularly low levels of oxytocin during the active disease period.

ZUSAMMENFASSUNG

Zielsetzung Spondylarthritiden sind chronisch entzündliche Erkrankungen, bei denen insbesondere die Iliosakralgelenke und die Wirbelsäule betroffen sind. Bei einigen Patienten besteht daneben auch eine extraartikuläre Manifestation. Oxytocin ist ein Peptidhormon, das aus dem Hypothalamus freigesetzt und in der Hypophyse gespeichert wird. Es ist bekannt, dass Oxy-

tocin entzündungshemmende Wirkungen hat. Das Ziel dieser Studie war es, die Oxytocin-Serumspiegel und ihren möglichen Zusammenhang mit der Krankheitsaktivität, der Beweglichkeit der Wirbelsäule bei Patienten mit ankylosierender Spondylitis (AS) und nicht radiologischer axialer Spondyloathritis (nrAxSpA) zu untersuchen.

Patienten und Methoden 71 Patienten mit nrAxSpA und 38 Patienten mit AS sowie 67 gesunde Kontrollpersonen wurden in diese Studie eingeschlossen. Die Krankheitsaktivität wurde durch den Bath Ankylosing Spondylitis Disease Activity Index und die Wirbelsäulenmobilität durch den Bath Ankylosing Spondylitis Metrologic Index bewertet. Die Laboruntersuchungen umfassten vollständige Blutbild-, ESR-, CRP- und Oxytocin-Tests.

Ergebnisse Es gab keinen signifikanten Unterschied in den Serumspiegeln von Oxytocin zwischen den drei Gruppen (p = 0,973). Die Serumspiegel von Oxytocin korrelierten jedoch sowohl mit ESR- (r = − 0,359, p = 0,027) als auch CRP- (r = − 0,316, p = 0,056) und BASDAI-Werten (r = − 0,448, p = 0,005) bei Patienten mit AS negativ . Andererseits hatten die Oxytocin-Serumspiegel nur bei den Patienten mit nrAxSpA eine negative Korrelation mit der ESR (r = − 0,321 p = 0,009).

Schlussfolgerung Diese Studie bildet die Grundlage für weitere Studien, die untersuchen sollen, wie sich die Zugabe von Oxytocin zum Behandlungsschema auf die Krankheitsaktivität bei Patienten mit AS auswirkt, die während der aktiven Krankheitsperiode besonders niedrige Oxytocinspiegel aufweisen.

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease which includes 2 subtypes within the same disease spectrum [1]. Patients with axial spondyloarthritis (axSpA) include those with radiographic axSpA (also termed ankylosing spondylitis [AS]), which indicates radiographic evidence of sacroiliitis according to the modified New York criteria [2], and those with nonradiographic axial spondyloarthritis (nr-axSpA) [3], who have similar signs and symptoms without radiographic changes.

Oxytocin (OXY) is a particularly abundant neuropeptide exerting a wide spectrum of central and peripheral effects as a neurohormone, neurotransmitter or neuromodulator. In the central nervous system, the OXY gene is predominantly expressed in magnocellular neurons in the hypothalamic paraventricular and supraoptic nuclei [4]. It has been known for years that OXY has anti-inflammatory effects. These effects were demonstrated in experimental models of ulcer and colitis in rats and ginea pigs. OXY is also known to protect against sepsis-induced multiple organ failure [5, 6]. Administration of OXY prior to hepatic ischemia-reperfusion injury prevents a potential elevation in levels of transaminase and TNF-alpha in systemic circulation [6]. It also inhibits a potential increase in levels of inflammatory cytokine induced by bacterial lipopolysaccharides (ACTH, cortisol, TNF-alpha, IL-1, IL-4, IL-6, MCP-1 and VEGF) [7]. In light of this information, we aimed at exploring OXY levels in sera of patients with AS and nr-axSpA as well as a potential association between these levels and the disease activity.

Material and Method

Patients presenting to rheumatology polyclinic of Faculty of Medicine of Dicle University between March 2017 and October 2017, who met the Modified New York Criteria [2] for AS and patients who met the Assessment of SpondyloArthritis international Society (ASAS) classification criteria [3] for axSpA but not the modified New York radiographic criteria [2] for ankylosing spondylitis were included in this study. A total of 67 individuals who presented to the physiotherapy polyclinic of the same center because of any mechanical non-rheumatic pain were included in the control group. One of the inclusion criteria was age between 18–65 years.

The exclusion criteria included the following: therapy with more than 7.5 mg/day of cortico-steroids, history of malignancies, psoriasis, overlap syndrome, pregnancy or lactation, autoimmune or other auto-inflammatory diseases, diabetes mellitus, acute infections, thyroidal dysfunction, metabolic syndrome and stage 3–4 heart failure. Data on date of diagnosis, medications patients used in the last 6 months, age, gender, height, weight, body mass index (BMI), comorbidities, smoking status and alcohol consumption were noted down. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores were used to define the disease activity [8, 9] and Bath Ankylosing Spondylitis Metrological Index (BASMI) scores were used to define spinal mobility [10]. Results were noted down separately for each individual patient. Patients underwent a laboratory analysis for evaluation of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and hemogram, and the results were duly written down. Blood samples collected for the purpose of OXY testing were stored in eppendorf tubes at − 80 ° until analysis. Samples stored for OXY testing were analyzed using the ELISA (Enzyme-Linked ImmunoSorbent Assay) method in accordance with the suggested procedures (Elabscience Elisa Kit). Prior to the study, an approval was obtained from the ethics board of the Faculty of Medicine of Dicle University. All the study was carried out according to the Helsinki declaration. Patients gave their informed consent to the study both in written and oral form.

Statistical Analysis

Statistical analysis of data was conducted using SPSS version 18.0 (Statistical Package for Social Sciences) and Microsoft Office Excel 2010. Percentages, arithmetic means, standard deviations and minimum and maximum values were calculated. Kolmogorov-Smirnov test was used to determine whether the data followed a normal distribution or not. Means and frequency distributions were calculated. Upon confirmation of normal distribution of data, Chi Square test was performed for comparison of categorical data, as well as Student t test and one-way analysis of variance for comparison of numerical data. On the other hand, non parametric variables were compared using Mann Whitney U test. As to the correlation analysis, Pearson and Spearman tests were used, as suitable.

Simple regression analysis method was used for the assessment of relationship between relevant variables. For all the tests, a p-value smaller than 0.05 was considered statistically significant.

Results

A total of 71 patients with nr-axSpA (41 males and 30 females) and 38 patients with AS (33 males and 5 females) were included in the present study. On the other hand, the control group consisted of 43 males and 24 females, totaling 67 individuals. Although there was no statistically significant difference in gender between the nr-axSpA and the control group (p = 0.439), the AS patients differed significantly from both the control group (p = 0.013) and the nr-axSpA patients (p = 0.002) in gender. Patients with AS were labeled as Group 1 whereas patients with nr-axSpA were labeled as Group 2, and the control subjects as Group 3. The mean age of the patients was 38.66 ± 7.31, 32.73 ± 8.05 and 33.31 ± 7.28 respectively in Group 1, Group 2 and Group 3. There was a statistically significant age difference between Group 1 and Group 3 (p = 001) whereas such difference was non-existent between Group 2 and Group 3 (p = 0.656). Group 1 differed significantly also from Group 2 in the parameter of age (p = 0.001). The mean BMI was found to be 25.62 ± 4.99 25.64 ± 3.93 and 24.95 ± 4.18 respectively in Group 1, Group 2 and Group 3. Of 38 AS patients, 25 were on biological agents whereas 13 were on sulfasalazine and/or non-steroidal anti-inflammatory (NSAI) drugs. In Group 2, on the other hand, 40 patients were on biological agents whereas 31 were on sulfasalazine and/or NSAI drugs. No statistically significant difference was found between the 3 groups when it comes to BMI (p = 0.595). In Group 1, 35 of 38 patients underwent HLA B27 testing. Of them all, 21 patients tested positive (%60) whereas 14 patients tested negative (%40). In Group 2, on the other hand, 15 patients (%25.4) tested positive for HLA B27 whereas 44 patients (%74.6) tested negative. The rest of the patients could not receive the test because of technical reasons. ▶ **Table 1** shows the clinical and laboratory parameters in all 3 groups.

No significant difference was found between Group 1 and Group 2 in mean duration of disease (p = 0.001) or BASDAI scores (p = 0.191). The mean BASMI score was higher in Group 1 than in Group 2 (0.001). There was no statistically significant difference between Group 1 and Group 2 in mean ESR (p = 0.641), CRP (p = 0.575) or OXY levels (p = 0.982).

As to the ESR and CRP levels, Group 1 had significantly higher levels of ESR (p = 0.001) and CRP (p = 0.006) than Group 3. On the other hand, Group 1 did not differ significantly from Group 3 in serum OXY levels (p = 0.848).

▶ **Figure 1** shows serum OXY levels in all 3 groups.

On the other hand, Group 2 had significantly higher levels of CRP (p = 0.001) and ESR (p = 0.001) than Group 3, with no significant difference between the 2 groups in serum OXY levels (p = 0.843).

Patients with a BASDAI score equal or higher than 4 were considered active patients whereas those with a BASDAI score lower than 4 were considered inactive patients. This way, Group 1 had 19 active patients as opposed to 22 inactive patients. The active and inactive patients had the following serum OXY levels respectively: 486.82 ± 86.65 and 541.28 ± 86.42, with no statistically significant difference between them 2 (p = 0.101). On the other hand, active AS patients had a mean ESR level of 13.44 ± 12.19 and CRP level of 1.90 ± 2.93 as opposed to the ESR and CRP levels of 6.05 ± 4.96) and 0.54 ± 0.50 in inactive AS patients. In this respect, active and inactive patients differed significantly from one another in levels of ESR and CRP (p = 0.008 and p = 0.028, respectively).

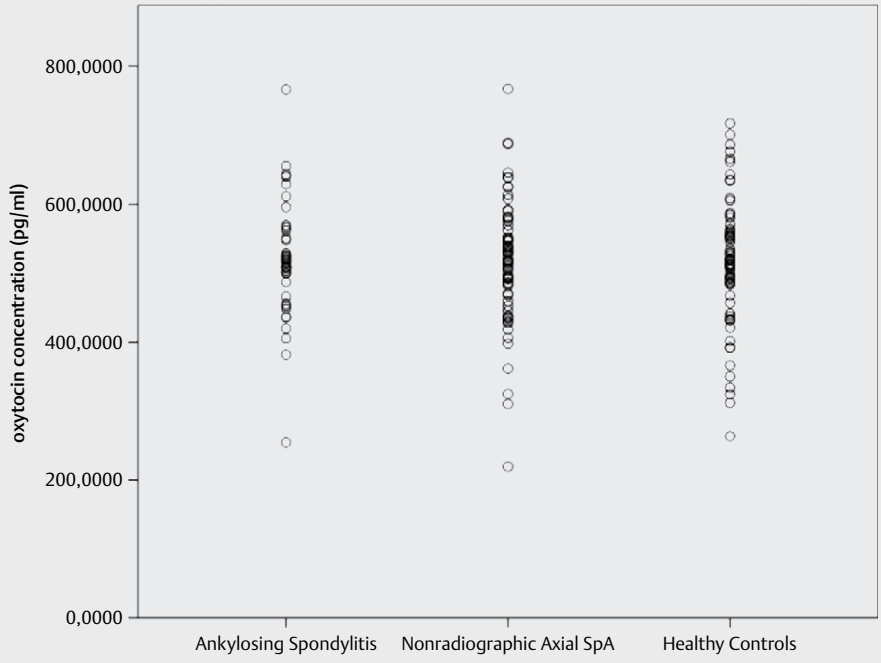
When it comes to active and inactive patients in Group 2, active patients had a mean OXY level of 521.47 ± 95.77 whereas inactive patients exhibited a mean OXY level of 516.17 ± 89.13. In this respect, active and inactive patients of Group 2 did not differ significantly from one another in serum OXY levels (p = 0.615). ESR levels were 8.24 ± 6.49 and 8.50 ± 7.02 respectively in active and inactive patients, with no statistically significant difference between them 2 (p = 0.974). In addition, there was no significant difference between active and inactive patients of Group 2 in CRP levels as active patients had a mean CRP level of 0.84 ± 1.04 and inactive patients of 0.98 ± 1.31 (▶ **Table 2**).

As to the correlation between serum OXY levels and the parameters of age, BMI, duration of disease, BASDAI, BASMI, ESR and CRP in Group 1, serum OXY levels had a negative correlation with the parameters of ESR (r = − 0.359, p = 0.027), BASDAI (r = − 0.448, p = 0.005) and a weak negative correlation with CRP (r = − 0.316, p = 0.056). When the potential correlation between the same parameters was examined in Group 2, serum OXY levels was found to have a negative correlation only with ESR this time (r = − 0.321, p = 0.005).

Simple regression analysis method was used to clarify the relationship between oxytocin and BASDAI, ESR and CRP in patients with AS. In the analysis, oxytocin was considered as an independent variable whereas BASDAI, ESR and CRP were considered separately as dependent variables, in this group. Results of the analysis showed that oxytocin was an independent variable which had impacts on BASDAI (β = − 0.448, t = − 3.004, p = 0.005), ESR (β = − 0.359, t = − 2.311, p = 0.027) and CRP (β = − 0.316, t = − 2.001, p = 0.053). Same analysis method was also used in group 2. Oxytocin was considered as an independent variable while ESR was considered as dependent variable. Oxytocin was indicated to have a significant effect on ESR (β = − 0.321, t = − 2.668 p = 0.009)

▶ **Table 1** Clinical and laboratory parameters in all groups.

	Duration of disease	BASMI	BASDAI	ESR	CRP	OXY (pg/ml)
AS (mean ± SD)	11.16 ± 6.91	7.87 ± 2.12	3.57 ± 1.77	9.16 ± 9.37	1.12 ± 2.02	518.35 ± 88.42
Nr-axSpA (mean ± SD	6.05 ± 4.90	5.41 ± 0.57	3.18 ± 1.30	8.42 ± 6.82	0.94 ± 1.23	517.94 ± 90.69
Healthy controls (mean ± SD)	-	-	-	4.48 ± 3.63	0.42 ± 0.23	514.75 ± 94.55



▶ **Fig. 1** Serum oxytocin levels in 3 groups.

▶ **Table 2** Comparison of laboratory parameters according to the activity of disease in-group analysis.

	ESR Median (%25–75 IQR)	CRP Median (%25–75 IQR)	OXY Median (%25–75 IQR)
Ankylosing spondylitis (BASDAI ≥ 4)	10 (5.50–15.50)	0.80 (0.34–1.95)	503.72 (449.59–525.57)
Ankylosing spondylitis (BASDAI < 4)	5 (2.00–9.25)	0.34 (0.34–0.54)	521.38 (502.83–599.72)
Non-radiographic axial SpA (BASDAI ≥ 4)	7 (2.5–12.50)	0.35 (0.34–1.11)	503.02 (466.54–588.84)
Non-radiographic axial SpA (BASDAI < 4)	5.50 (3–11.75)	0.34 (0.34–1.00)	530.58 (474.67–567.76)

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, IQR: interquartile range.

Discussion

Oxytocin (OXY), which is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus, is a neurohypophysial nonapeptide hormone that carries out a variety of actions through the OXY receptor, a G-protein coupled receptor [11]. The bulk of evidence points out the possibility that OXY may have anti-inflammatory and antioxidant features and regulate the immune and anti-inflammatory response [12]. In the present study, we examined the serum OXY levels in both AS and nr-axSpA patients and found that none of these groups of patients differed significantly from the control group in OXY levels. On the other hand, we spotted a negative correlation between OXY levels and the inflammatory markers of ESR and CRP as well as the disease activity marker of BASDAI in patients with AS. In nr-axSpA patients, on the other hand, OXY levels had a negative correlation only with ESR.

Assessment of Spondylo-Arthritis International Society (ASAS) has published a new set of classification criteria for axial SpA [3]. Development of a new set of criteria was necessary because the former modified New York criteria for AS [2] were not permissive for identification of axial SpA patients early in the course of disease in the absence of radiographic changes in sacroiliac joints, which can take years to become visible. This situation might offer an explanation for the significant age difference between the AS and nr-axSpA patients. The significant gender difference between the AS and nr-axSpA patients, on the other hand, is attributable to a predominance of male patients among all AS patients. Approximate male to female ratio is 2–3 in fact initial studies showed male/female ratio of 10/1 for the patients with AS [13–15]. On the other hand, an equal gender distribution is observed among the nr-axSpA patients [16]. In the present study, duration of disease was significantly longer in patients with AS compared to patients with nr-axSpA, which may be attributable to the delayed true diagnosis patients with AS usually get [17–19]. This happens partially due to the lack of diagnostic laboratory testing such as autoantibodies in

collagen diseases as well as to the fact that radiological signs in sacroiliac joints, which are crucial for diagnosis of AS when using the modified New York criteria, may take years to show in radiographic evaluations because of the slow progression of the underlying inflammatory process [2, 20, 21].

In the present study, we found that serum OXY levels had a negative correlation with the parameters of ESR, CRP and BASDAI in patients with AS. There is evidence that both CRP and ESR are acute phase reactants which are in correlation with disease activity in patients with AS. CRP is known to be the first detected inflammatory acute phase reaction protein, with its concentration closely associated with the degree of inflammation in AS [22]. Patients with AS were previously shown to have increased serum levels of IL6 and TNF alpha than healthy subjects [23]. Another previous study showed that oxidative stress and lipid peroxidation were particularly accelerated in untreated patients with an active AS. The bulk of evidence points out the possibility that OXY may have anti-inflammatory and antioxidant features and regulate the immune and anti-inflammatory response via inhibiting LPS-stimulated secretion of pro-inflammatory cytokines such as TNF-alpha, interleukin (IL)-6, IL-1b, glutamate, Nitric Oxide (NO), and reactive oxygen species [24, 25]. It was demonstrated in vitro that OXY exerts antioxidant and anti-inflammatory effects on vascular cells and THP-1 macrophages. OXY receptors were found in all cell types that were examined, and OXY was shown to cause a reduction in NADPH dependent superoxide production and IL-6 secretion in these cells [24]. One mechanism by which OXY exerts its anti-inflammatory functions is through weakening the transition of macrophages, by acting on its receptors, into a proinflammatory mode, which results in an inhibition of NF-κB signaling [26]. NF-κB, a transcription factor for a proinflammatory immune response, is inhibited with OXY treatment, which leads to a decreased release of TNF-α [27].

The negative correlation between serum OXY levels and ESR, CRP and BASDAI indicates that serum OXY level goes down as the disease activity goes up. This finding may lead us to consider the addition of OXY to treatment regimen when the disease activity increases in patients with AS. Based on this, we may as well suggest conduction of further studies that can expand on this finding. The same approach can also be adopted for patients with nr-axSpA, who also demonstrated a negative correlation between serum OXY levels and ESR. Previous studies showed that OXY treatment modulates immune and anti-inflammatory response in wound healing and experimental sepsis [24, 28–31]. The involvement of OXY and the oxytocin receptor (OTR) in immune reaction is consistent with their presence in regulatory T cells [32], which take a critical part in suppression of autoimmune reactivity and cessation of the inflammatory response. Furthermore, the inflammatory process modulates the OTR gene by means of acute phase reactants and interleukins [33, 34].

Anderberg and Moberg found a negative correlation between the scored symptoms of depression and anxiety and OXY concentration as well as a positive correlation between the item of happiness and OXY concentration in patients with FM [35]. On the other hand, Miva et al. found no significant difference between rheumatoid arthritis patients with and without depression when it comes to serum OXY levels; however, they claimed that mean OXY concentration was lower in RA patients than in healthy individuals, who had been subject to a separate previous study [36, 37].

Welch et al. suggested that OXY and OXY receptor signalling could be regarded as a brake on intestinal motility, causes a reduction in mucosal activation of enteric neurons and helps with enteric neuronal development. They also suggested that OXY acts as a regulatory agent for proliferation of crypt cells and mucosal permeability, and OXY/OTR signalling protects against inflammation [38]. Iseri et al. also demonstrated that OXY treatment decreases the severity of colitis with simultaneous reductions in serum TNF alpha response and oxidative injury of the colon, indicating that OXY exerts a strong anti-inflammatory effect on the oxidative injury of the colon [29]. Praet et al. found microscopic gut inflammation in 46.2 % of the patients with spondyloarthritis and suggested the presence of an association between BASDAI and gut inflammation [39]. Mielants et al. found inflammatory gut lesions in 57 % of the patients with AS [40]. The association between the gut inflammation and spondyloarthritis and the correlation between BASDAI and gut inflammation, as shown by microscopic findings [39, 40], and the finding that OXY ameliorates the severity of colitis [29] are all in consistency with the finding of the present study that a reduction in OXY levels occurs simultaneously with an increase in disease activity. In a recent study about the COVID 19 treatment, it was shown that oxytocin analog has the ability to lower IL-6, IL 1β, NF-KB and anti TNF and the authors suggested that OXY is a potential anti-inflammatory candidate for COVID-19 infectious disease [41].

On the other hand, there is still a need for conduction of further studies which can explore if the addition of OXY to treatment of AS and nr-axSpA leads to a reduction in disease activity.

To the best of our knowledge, this is the first and the only study to explore serum OXY levels in patients with AS and nr-axSpA. The present study found that the 2 study groups, namely AS and nr-axSpA groups, did not differ significantly from the control group in serum OXY levels, which suggests that OXY may not be playing an essential role in the pathogenesis of the 2 diseases. The limitation of the study was the fact that some patients were on biological agents.

Moreover, the present study found an inverse correlation between serum OXY levels and the markers of disease activity in both AS and nr-axSpA patients, which may lead us to consider the addition of OXY to treatment regimen when the disease activity begins to increase. This finding also lays the ground for further studies that can expand on this area of research.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet 2017; 390: 73–84

[2] van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: a proposal for modification of the New York criteria. Arthritis Rheum 1984; 27: 361–368

[3] Rudwaleit M, van der Heijde D, Landewé R et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009; 68: 777–783

[4] Kiss A, Mikkelsen JD. Oxytocin – anatomy and functional assignments: a minireview. Endocr Regul 2005; 39: 97–105

[5] Iseri SO, Sener G, Saglam B et al. Oxytocin protects against sepsis-induced multiple organ damage: Role of neutrophils. J Surg Res 2005; 126: 73–81

[6] Dusunceli F, Iseri SO, Ercan F et al. Oxytocin alleviates hepatic ischemia-reperfusion injury in rats. Peptides 2008; 29: 1216–1222

[7] Clodi M, Vila G, Geyeregger R et al. Oxytocin alleviates the neuroendocrine and cytokine response to bacterial endotoxin in healthy men. Am J Physiol Endocrinol Metab 2008; 295: 686–691

[8] Garrett S, Jenkinson T, Kennedy LG et al. A new approach to defining disease status in ankylosing spondylitis: the bath ankylosing spondylitis disease activity index. J Rheumatol 1994; 21: 2286Y2291

[9] Akkoc Y, Karatepe AG, Akar S et al. A Turkish version of the Bath ankylosing spondylitis disease activity index: reliability and validity. Rheumatol Int 2005; 25: 280Y284

[10] Jenkinson TR, Mallorie P, Whitelock HC et al Defining spinal mobility in ankylosing spondylitis (AS): the Bath AS Metrological Index (BASMI). J Rheumatol 1994; 21: 1694–1698

[11] Barberis C, Mouillac B, Durroux T. Structural bases of vasopressin/oxytocin receptor function. J Endocrinol 1998; 156: 223–229

[12] Wu Y, Wu T, Xu B et al. Oxytocin prevents cartilage matrix destruction via regulating matrix metalloproteinases. Biochem Biophys Res Commun 2017; 6 486: 601–606

[13] West HF. Aetiology of ankylosing spondylitis. Ann Rheum Dis 1949; 8: 143–148

[14] Polley HF, Slocumb CH. Rheumatoid spondylitis; a study of 1035 cases. Ann Rheum Dis 1947; 6: 95–98

[15] Moll JM, Haslock I, Macrae IF et al. Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behcet's syndrome. Medicine (Baltimore) 1974; 53: 343–364

[16] van Tubergen A. The changing clinical picture and epidemiology of spondyloarthritis. Nat Rev Rheumatol 2015; 11: 110–118

[17] Rudwaleit M, Sieper J. Referral strategies for early diagnosis of axial spondyloarthritis. Nat Rev Rheumatol 2012; 8: 262–268

[18] Slobodin G, Reyhan I, Avshovich N et al. Recently diagnosed axial spondyloarthritis: gender differences and factors related to delay in diagnosis. Clin Rheumatol 2011; 30: 1075–1080

[19] Lin Z, Xu H, Gu J et al. Investigation and analysis on the delayed diagnosis in patients with ankylosing spondylitis in a Chinese population. Clin Exp Rheumatol 2008; 26: 1163

[20] Feldtkeller E, Khan MA, van der Heijde D et al. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. Rheumatol Int 2003; 23: 61–66

[21] Nakashima Y, Ohishi M, Okazaki K et al. Delayed diagnosis of ankylosing spondylitis in a Japanese population. Mod Rheumatol 2016; 26: 421–425

[22] Ruof J, Stucki G. Validity aspects of erythrocyte sedimentation rate and C-reactive protein in ankylosing spondylitis: a literature review. J Rheumatol 1999; 26: 966–970

[23] Bal A, Unlu E, Bahar G et al. Comparison of serum IL-1 beta, sIL-2R, IL-6, and TNF-alpha levels with disease activity parameters in ankylosing spondylitis. Clin Rheumatol 2007; 26: 211–215

[24] Szeto DA, Nation AJ, Mendez J et al. Oxytocin attenuates NADPH-dependent superoxide activity and IL-6 secretion in macrophages and vascular cells. Am J Physiol Endocrinol Metab; 2008; 295: E1495–E1501

[25] Yuan L, Liu S, Bai X et al. Oxytocin inhibits lipopolysaccharide-induced inflammation in microglial cells and attenuates microglial activation in lipopolysaccharide-treated mice. J Neuroinflammation 2016; 13: 77

[26] Tang Y, Shi Y, Gao Y et al. Oxytocin system alleviates intestinal inflammation by regulating macrophages polarization in experimental colitis. Clin Sci (Lond) 2019; 133: 1977–1992

[27] Garrido-Urbani S, Deblon N, Poher AL et al. Inhibitory role of oxytocin on TNF_ expression assessed in vitro and in vivo. Diabetes Metab 2018; 44: 292–295

[28] Biyikli NK, Tugtepe H, Sener G et al. Oxytocin alleviates oxidative renal injury in pyelonephritic rats via a neutrophil-dependent mechanism. Peptides 2006; 27: 2249–2257

[29] Iseri SO, Sener G, Saglam B et al. Oxytocin ameliorates oxidative colonic inflammation by a neutrophil-dependent mechanism. Peptides 2005; 26: 483–491

[30] Petersson M, Lundeberg T, Sohlstrom A et al. Oxytocin increases the survival of musculocutaneous flaps. Naunyn Schmiedebergs Arch Pharmacol 1998; 357: 701–704

[31] Petersson M, Wiberg U, Lundeberg T et al. Oxytocin decreases carrageenan induced inflammation in rats. Peptides 2001; 22: 1479–1484

[32] Elands J, Resink A, de Kloet ER. Neurohypophyseal hormone receptors in the rat thymus, spleen, and lymphocytes. Endocrinology. 1990; 126: 2703–2710

[33] Schmid B, Wong S, Mitchell BF. Transcriptional regulation of oxytocin receptor by interleukin-1beta and interleukin-6. Endocrinology 2001; 142: 1380–1385

[34] Jankowski M, Bissonauth V, Gao L et al Anti-inflammatory effect of oxytocin in rat myocardial infarction. Basic Res Cardiol 2010; 105: 205–218

[35] Anderberg UM, Uvnas-Moberg K. Plasma oxytocin levels in female fibromyalgia syndrome patients. Z Rheumatol 2000; 59: 373–379

[36] Miwa Y, Furuya H, Yanai R et al. The Relationship between the Serum Oxytocin Levels, Disease Activity, the ADLs and the QOL in Patients with Rheumatoid Arthritis. Intern Med 2017; 56: 3167–3172

[37] Kutake Y, Imamura Y, Mizogushi Y et al. In female mild cognitive impairment and Alzheimer type dementia, peripheral oxytocin concentration is lower than healthy elderly. Jpn J Psychiatr Neurol 2016; 528

[38] Welch MG, Margolis KG, Li Z et al. Oxytocin regulates gastrointestinal motility, inflammation, macromolecular permeability, and mucosal maintenance in mice. Am J Physiol Gastrointest Liver Physiol 2014; 307: G848–G862

[39] Van Praet L, Van den Bosch FE, Jacques P et al. Microscopic gut inflammation in axial spondyloarthritis: a multiparametric predictive model. Ann Rheum Dis 2013; 72: 414–417

[40] Mielants H, Veys EM, Cuvelier C et al. Ileocolonoscopic findings in seronegative spondylarthropathies. Br J Rheumatol 1988; 27: 95–105

[41] Imami AS, O'Donovan SM, Creeden JF et al. Oxytocin's anti-inflammatory and proimmune functions in COVID-19: a transciptomic signature based approach. Physiol Genomics 2020; 52: 401–407

Hinweis

Dieser Artikel wurde gemäß des Erratums vom 25.8.2021 geändert.

Erratum

Im oben genannten Artikel wurde der deutsche Titel und die deutsche Zusammenfassung korrigiert.