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Prolactin Hormone and Vasoinhibin in Rheumatoid Arthritis Patients

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Abstract

Rheumatoid Arthritis (RA) is a chronic autoimmune disease affecting synovial joints causing joint destruction, deformity that may lead to disability. There are many risk factors affecting RA including hormones as prolactin (PRL) and its proteolytic cleavage product known as vasoinhibin. This study was case control study conducted in Al-Azhar Rheumatology and Rehabilitation, clinical pathology departments for girls to assess levels of prolactin and vasoinhibin in serum of 60 rheumatoid arthritis patients versus 30 controls. Also, to assess the correlation of serum prolactin and vasoinhibin levels with laboratory and clinical parameters of rheumatoid arthritis patients. Our study revealed high positive statistically significant increase in PRL and vasoinhibin in patients than control. Prolactin showed positive significant correlation with number of tender joints and number of swollen joints, vasoinhibin, ESR, CRP, CDAI, DAS-28 with P-value<0.05. serum Vasoinhibin showed positive high statistical significance correlation with number of tender joints, number of swollen joints, patient and physician global assessments, ESR, DAS-28, CDAI with P-value <0.001, while with prolactin, VAS with P-value<0.05.

Keywords: Rheumatoid arthritis**, PRL:** prolactin**, ACR\EULAR**: American College of Rheumatology\European League against Rheumatism, **ESR**: erythrocyte sedimentation rate, **DAS**: Disease Activity Score, **CDAI**: Clinical disease activity index, **VAS**: Visual Analogue Scale**, HAQ:** Health assessment Questionnaire**, CRP:** C-Reactive Protein, **RF**: rheumatoid factor.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by symmetrical inflammation of synovial joints. RA may be associated with extra-articular manifestations, such as skin, heart, eyes, kidneys, and lungs. It is associated

not only with long-term sequelae of bone and cartilage destruction but also tendons and ligaments laxity Lee et al. [1]. RA affects 1% of worldwide population, presents as 3 times in females in relation to males, mostly with age of 35 to 60 years Weddell and Hider, [2] Bullock J et al, [3]. Synovial hyperplasia results in synovial inflammation. While cartilage and bone destruction occur after pannus formation as it mimics tumors in aggressiveness Yun Hyun Huh et al., [1]. Pannus is composed of cells like fibroblast like synoviocytes, mast cells, macrophages, B-lymphocytes, T- lymphocytes. This becomes in parallel with formation of new blood vessels known angiogenesis Firestein et al., [4]. RA not only associated with hyperplasia and angiogenesis but also cytokines in synovial fluid as IL1, IL6, IL17 A, IL10 Yasushi Kondo et al., [5]. The RA initiation depends on innate immune system as macrophages, monocytes and dendritic cells have a role in activation of adaptive immunity that is essential in late disease stages and progression. Synovial macrophages produce potent pro-inflammatory cytokines showed in RA pathogenesis (IL-1β, and IL-6, TNFα), with chemoattractant factors (CCL2 and IL-8) and metalloproteinases Ardura et al., [6]. PRL hormone produced from lactotrophs, these cells were found in anterior pituitary gland as central source, peripheral source found in endometrium, skin, placenta Rovensky et al., [7]. PRL also is produced locally in the synovium of inflammatory arthritis patients and shares in activation of macrophages Tang et al., [8]. PRL activity not including only lactation but also it has the ability to control of calcium metabolism, energy balance in many organs like liver, small intestine, brain, pancreas, adipose tissue Aoki et al., [9]. PRL activity in immune system shows controversy as it has pro-inflammatory and anti-inflammatory effects this results after long time of research on prolactin and its activities Clapp et al., [10]. PRL is responsible for both cytokines production and proliferation of immune cells. Elevated PRL levels is associated with many autoimmune disorders like RA, periodontitis, multiple sclerosis, also it is associated with increased incidence of bone resorption El-Wakeel et al., [11]. Proteolytic cleavage of prolactin by matrix metalloproteinases leads to vasoinhibin production Lenke et al., [12]. Vasoinhibin serum level follows PRL serum level, when prolactin increases vasoinhibin increases Ferraris et al., [13]. prolactin/vasoinhibin axis which consists of hypothalamus, pituitary gland and target organ is responsible for regulation of vasoinhibin release Triebel et al., [14]. Any dysregulation of this axis is reflected in the form of many diseases Zepeda-Romero et al., [15]. Vasoinhibin inhibits vasoactive substances, including VEGF and bradykinin thus results in inhibition of vaso-proliferation and vaso-dilatation, so it reduces angiogenesis hence pannus formation Arredondo Zamarripa et al., [16]. Vasoinhibin also has dual role in immunity A recent study showed that vasoinhibin directly stimulates and indirectly inhibits joint inflammation depending on vasoinhibin concentration and the severity of the disease in which it acts Carmen Clapp et al., [17].

Aim of the work:

- Assessment of levels of prolactin and vasoinhibin in serum of rheumatoid arthritis patients**.**
- Co-relation of serum prolactin and vasoinhibin levels with laboratory and clinical parameters of rheumatoid arthritis patients.

2. Patients and Methods

This case control study was done in the Rheumatology and rehabilitation Department in Al-Zahraa University Hospital. Ninety Participants were invited to participate in this study after written

consent and after approval of ethical committee of Al-Azhar university.

2.1 Inclusion Criteria

Sixty patients of Rheumatoid arthritis with or without complications, with age >18 years old diagnosed according to 2010 American College of Rheumatology\European League against Rheumatism (ACR\EULAR).

2.2 Exclusion Criteria

Patients <18 years, with other diseases affecting joints, smoker patients, also pregnant and lactating patients or patients taking medications affecting serum prolactin level.

2.3 Design & Randomization

Case control study depended on simple random sampling on 60 patients of RA aged (20-62) years, with mean ±SD 39.87± 10.06 considered as group (A), and 30 participants with age (20-56) years, and mean ±SD 37.1±9.55 considered as group (B). Full counseling of participants in this study and informed consent was obtained. Full history was done for all participants in the present study after confirmation of inclusion and exclusion criteria, clinical examination, laboratory monitoring. Musculoskeletal examination: By inspection, palpation, range of motion and other special tests for all of the following joints (MCP, PIP, DIP, MTP, PIP, DIP, wrist, knee, ankle). Disease activity was assessed using a composite disease activity 28 score Saag et al., [18], Clinical disease activity index (CDAI) Smolen et al., [19], Visual Analogue Scale (VAS) Delgado et al., [20].

2.4 Laboratory Investigations

CRP, RF, ESR and anti CCP done to all participants, PRL was measured using Elecsys reagent kits (Turku, Finland) by automated immune assay methodology. Vasoinhibin was assayed by ELIZA kits supplied by Sun Red**.**

3. Results

Our study showed matching in age and gender between all participants, classified to sixty patients as cases, thirty participants as control. These results are presented in **Table (1).** In comparison between patients and controls regarding the laboratory parameters including CRP, ESR, Anti-CCP, RF, it showed statistical significance between 2 groups as P-values were = 0.008 for ESR and high statistical significance with P-values of <0.001 as regard CRP, Anti-CCP, RF **Table (2).** Also, in comparison between patients and controls regarding Prolactin and Vasoinhibin there was high statistical significance between the two groups with P-values of <0.001 **Table (3).** As regard serum prolactin and correlation with clinical parameters it revealed statistical significance with number of tender joints with P-value = 0.011, number of swollen joints with P-value= 0.008, physician global assessment with P-value = 0.021, negative non-significant correlation with disease duration r= -0.005 P-value = 0.967, no statistical significance found between prolactin and morning stiffness, Patient global assessment, VAS P-value >0.05 **Table (4).** As regard correlation between PRL and laboratory parameters it revealed positive significant statistical correlation with CRP with P-value = 0.02, ESR with P-value = 0.04, vasoinhibin with P-value = 0.031 but no statistical significance found between prolactin and RF, Anti-CCP P-value >0.05 **Table (5).** Regarding Correlation between serum level of prolactin and disease activity parameters it showed positive statistically significant positive correlation with DAS28 shows P-value= 0.007 **Figure (1).** sub-classification of DAS-28 in our sample revealed all patients have moderate or severe disease

activity, they showed positive statistical correlation with PRL with P-value = 0.0317. CDAI correlation with prolactin showed significant finding with P-value= 0.01 **Figure (2)**. Sub-classification of CDAI in our sample revealed most patients have moderate or severe disease activity, they showed positive non-statistical correlation with PRL with P-value = 0.224**.** However, as regard serum level of vasoinhibin and correlation with clinical parameters it revealed positive statistical correlation with VAS as P-value = 0.049, while high statistical significance with P-value <0.001 with all of number of tender joints, number of swollen joints, physician global assessment, patient global assessment and no statistical significance with morning stiffness and disease duration with P-value >0.05 **Table (6).** As regard correlation between laboratory parameters and vasoinhibin, it showed high statistical significance with ESR P-value <0.001 and positive non-statistically significant correlation. With RF, CRP, Anti-CCP P-value >0.05 **Table (7).** Serum level of vasoinhibin in correlation with disease activity parameters among the patients showed high statistical significance with DAS-28 with P-value <0.001 **Figure (3),** sub-classification of DAS-28 showed positive high statistical correlation with vasoinhibin with P-value < 0.001**.** Also, vasoinhibin showed positive high statistical significance with CDAI P-value <0.001 **Figure (4)**, sub-classification of CDAI showed also positive high statistical correlation with vasoinhibin with P-value <0.001. As shown in Table .1 No statistical significance difference between patients and control according to age and gender. As shown in Table .2 Positive high statistical significance correlation between patients and control as regard CRP, RF, Anti CCP (P-value < 0.001), Positive statistical correlation as regard ESR (P-value = 0.008).

Table (1): Demographic data between studied groups.

Demographic data		Studied groups			
		patients(N=60)		Controls(N=30)	
		No	%	No	%
Gender	Male	6	10.0	3	10.0
	Female	54	90.0	27	90.0
Age	Range (years)	20-62		20-56	
	Mean ±SD	39.87± 10.06		37.1±9.55	

Table (2): Comparison between patients and controls regarding the laboratory parameters.

Variable	patients No=60	Controls No=30	Test of significance Mann-Whitney U	P value
Anti ccp				
Range Mean ±SD	30-487 80.40 ±74.838	3-17 8.87 ±3.803	7.706	**<0.001****
RF				
Range Mean ±SD	28-435 70.36 ±66.006	4-19 10.38 ±4.134	7.704	**<0.001****
CRP				
Range Mean ±SD	8- 326 43.15 ±56.74	1-14 5.17 ±2.61	6.494	**<0.001****
ESR				
Range Mean ±SD	15-50 28.38±9.37	5-15 9.73±2.959	2.639	**0.008***

Table (3): Comparison between patients and controls regarding Prolactin and Vasoinhibin.

Variable	patients No=60	Controls No=30	Test of significance Mann-Whitney U	P value
Prolactin				
Range Mean ±SD	2-38 13.86±7.32	0-21 6.65 ±5.800	4.647	**<0.001****
Vasoinhibin				
Range Mean ±SD	154- 4196 989.26±833.158	79- 4314 755.05±1115.331	3.971	**<0.001****

As shown in Table .3 above positive high statistical significance correlation between patients and control as regard prolactin and vasoinhibin (P-value < 0.001). As shown in Table .4 below positive statistical significance correlation among patients between prolactin and number of tender joints, number of swollen joints, physician global assessment (P-value < 0.05).

Table (4): Correlation between serum level of prolactin and clinical parameters among the studied patients of rheumatoid arthritis.

Clinical parameter	R	P value
Morning stiffness	0.153	0.242
Disease duration	-0.005	0.967
Number of tender joints	0.324	0.011*
Number of swollen joints	0.340	0.008*
Physician global assessment	0.298	0.021*
Patient global assessment	0.229	0.079
VAS	0.095	0.469

Table (5): Correlation between serum level of prolactin and clinical parameters among the studied patients of rheumatoid arthritis.

Laboratory parameter	S. Prolactin	
	R	P value
Anti-CCP	0.179	0.172
RF	0.192	0.143
CRP	0.397	0.002*
ESR	0.364	0.004*
Vasoinhibin	0.279	0.031*

As shown in Table .5 above positive statistical significance correlation among patients between prolactin and CRP, ESR, vasoinhibin (P-value < 0.05). As shown in Table .6 below Positive high statistical significance correlation among patients between vasoinhibin and number of tender joints, number of swollen joints, physician global assessment, Patient global assessment (P-value < 0.001) and positive statistical significance correlation with VAS (P-value < 0.05). As shown in Table .7 below positive high statistical significance correlation among patients between vasoinhibin and ESR (P-value < 0.001), Positive high statistical significance correlation with prolactin (P-value < 0.05).

Table (6): Correlation between serum level of vasoinhibin and clinical parameters among the studied patients of rheumatoid arthritis.

Clinical parameter	s. vasoinhibin	
	R	P value
Morning stiffness	0.185	0.157
Disease duration	0.185	0.157
Number of tender joints	0.732	<0.001**
Number of swollen joints	0.718	<0.001**
Physician global assessment	0.564	<0.001**
Patient global assessment	0.553	<0.001**
VAS	0.255	**0.049***

Table (7): Correlation between serum level of vasoinhibin and laboratory parameters among the patients.

Laboratory parameter	s. vasoinhibin	
	R	P value
Anti-CCP	0.207	0.113
RF	0.222	0.089
CRP	0.167	0.203
ESR	0.557	<0.001**
Prolactin	0.279	0.031*

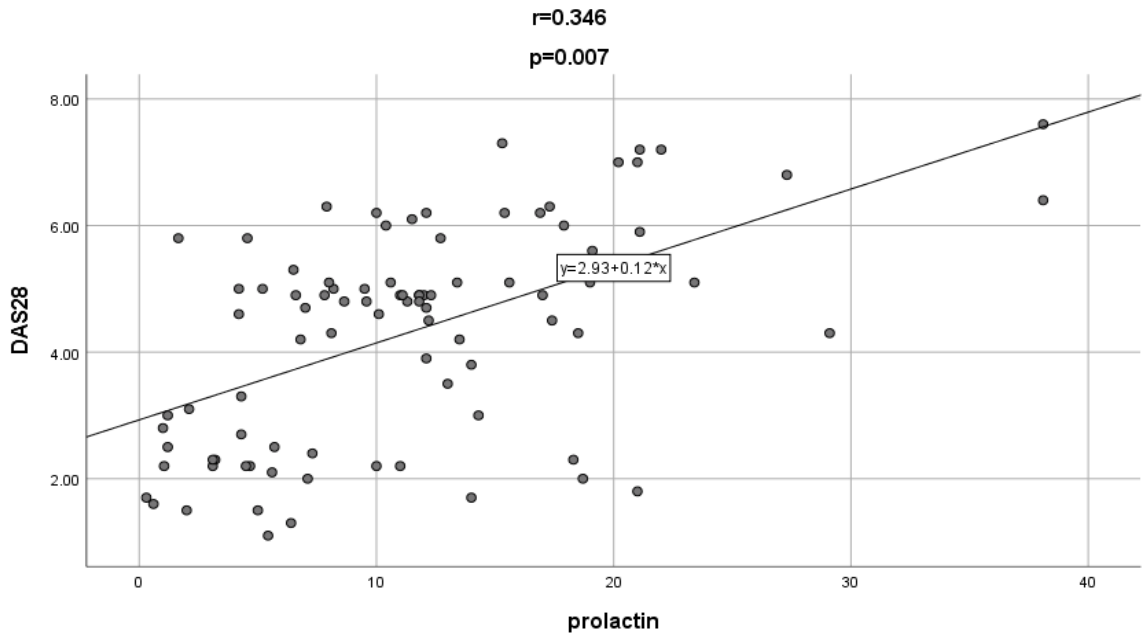

Figure (1): Positive significant correlation between DAS28 and level of prolactin.

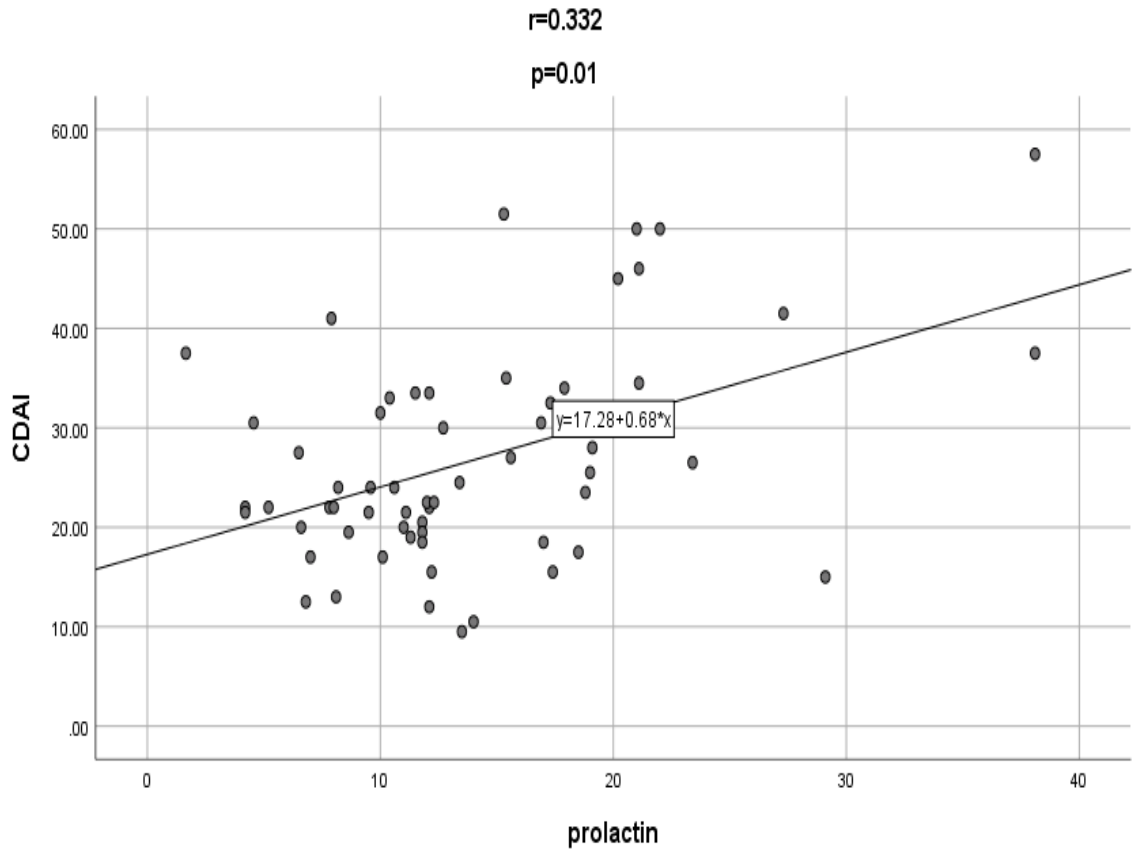

Figure (2): Positive significant correlation between CDAI and level of prolactin.

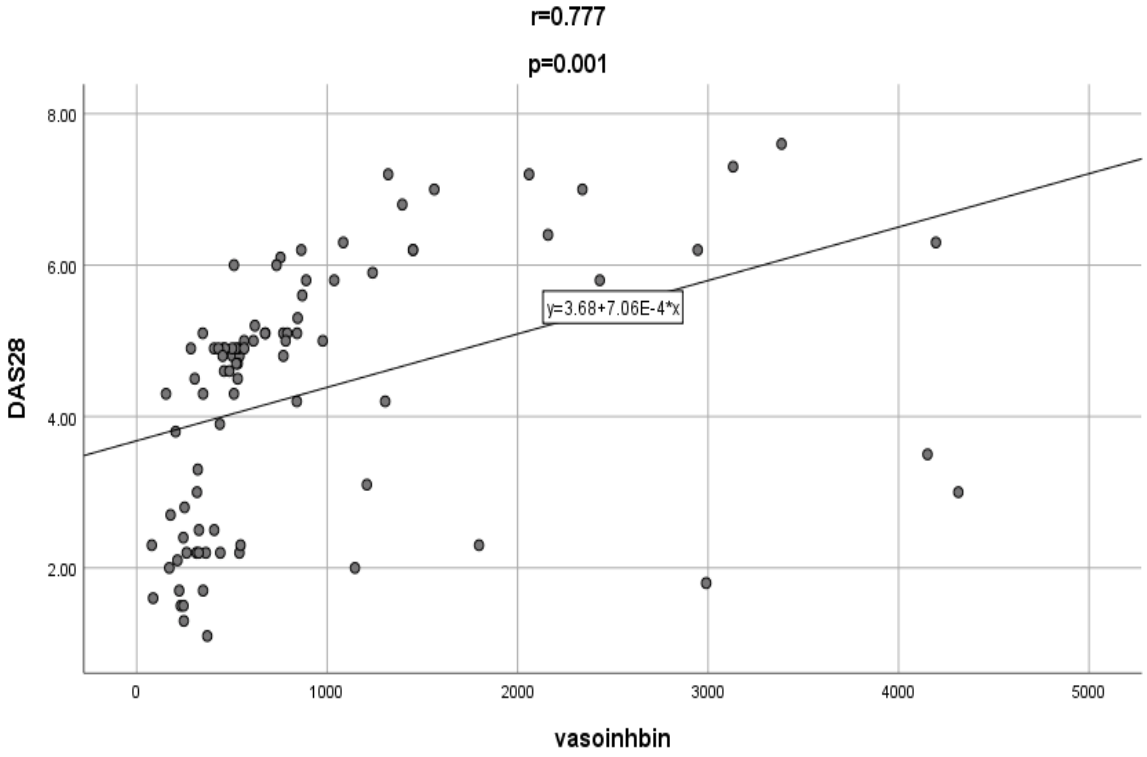

Figure (3): Positive high statistically significant correlation between DAS28 and level vasoinhibin.

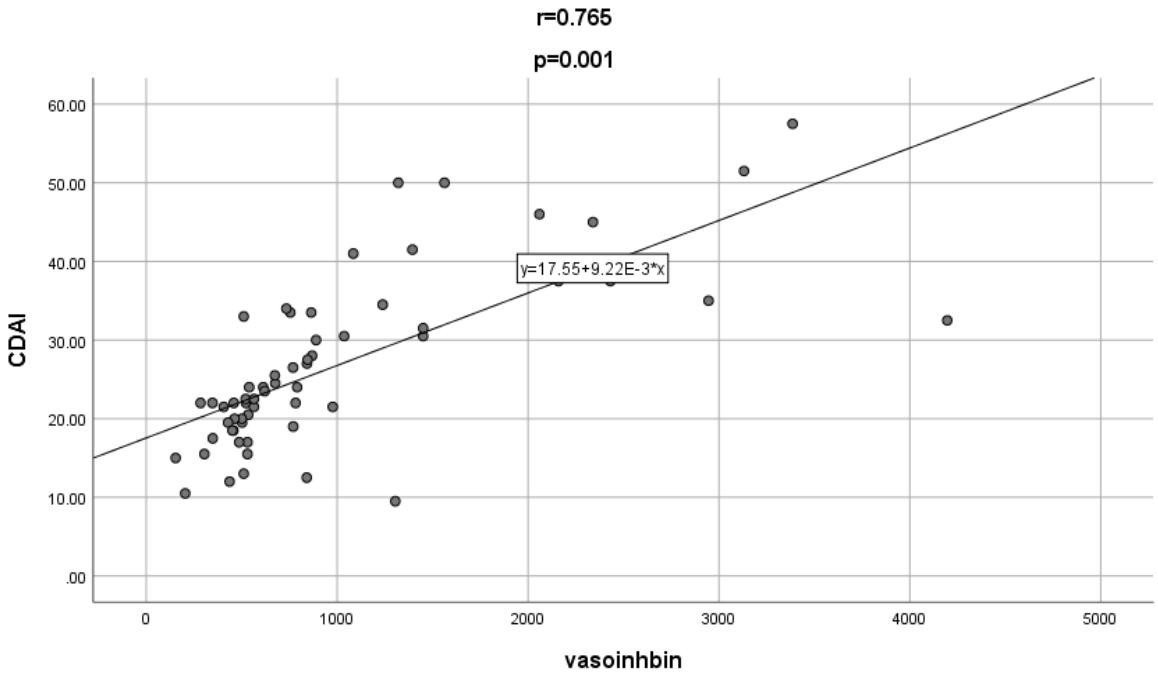

Figure (4): Positive high statistical correlation between CDAI and level vasoinhibin.

4. Discussion

Rheumatoid arthritis is an immune-mediated multisystem disease characterized by joint inflammation, destruction, deformity that may accompanied with disability with probability of extra-articular manifestations Guo et al., [21], Carbone et al., [22]. PRL hormone has an obvious role lactation, reproductive functions, calcium metabolism and immune reactivity. Vasoinhibin results from proteolytic cleavage of PRL by matrix metalloproteinases, cathepsin-D, and bone morphogenic protein 1 Tang et al., [23], Lenke et al., [12]. Our study is a pioneer research project to assess the relationship between vasoinhibin and both clinical and laboratory parameters in rheumatoid arthritis patients. According to laboratory results in our study results Anti CCP, RF, CRP, ESR, prolactin and vasoinhibin showed significant increase in rheumatoid arthritis group when compared to the control group. Our study supported by Wu et al., [24] meta-analysis of 14 published studies, 628 RA patients demonstrates a significantly higher level of circulating PRL in RA patients 95%when compared to healthy controls. Serum level of prolactin showed positive significant correlation with CRP, ESR, Vasoinhibin in patients' group ($p<0.05$). prolactin shows positive non-significant correlation with Anti-CCP, RF ($p >0.05$) . Serum level of vasoinhibin showed positive non-significant correlation with CRP, Anti-CCP, RF ($p >0.05$). Vasoinhibin showed positive significant correlation with prolactin ($p<0.05$), positive high statistically significant correlation with ESR ($p<0.001$). In agreement with our results, Qingmei et al., [25] showed that in RA patients, positive rates of anti-CCP and RF were 70.0% and 77.1%, respectively. These rates were significantly higher than the rates in non-RA patients (2.7% and 4.5%, respectively; $p<0.05$). Moreover, previous study on 30 RA patients showed that Serum prolactin levels positive significant correlation with ESR ($p < 0.048$) Haggag et al., [26]. Similar to our study, clapp et at., [17]. revealed there is positive correlation

between prolactin and vasoinhibin, it observed that hyperprolactinemia promotes conversion of prolactin to vasoinhibin. According to our results, the levels of PRL in the serum as well as in the synovial fluid were not associated with the elevation of levels of serum CRP or with the serum autoantibodies such as IgM-RF or Anti-CPP Fojtíková et al., [13]. According to clinical parameters assessed in our patient group there is a positive significant correlation between serum PRL and number of swollen joints, number of tender joints and Physician global assessment. However, positive non-significant correlation was found between serum level of prolactin and Morning stiffness, patient global assessment and VAS ($p > 0.05$). Serum level of vasoinhibin showed positive high statistically significant correlation with number of tender joints, number of swollen joints, physician global assessment and patient global assessment ($p < 0.001$). Vasoinhibin showed positive statistically significant correlation with VAS ($p < 0.05$), while positive non-significant correlation was found with morning stiffness, disease duration ($p > 0.05$). Similarly, to our results, Halabi et al., [27] revealed positive correlation between prolactin and number of tender and swollen joints. In agreement to our results, Haga et al., [28] found that there was no correlation of serum PRL to e VAS on a study included 307 RA patients . Opposing our results, no correlation was found between PRL and VAS, number of tender joints 28, number of swollen joints 28 according to a study done on 119 RA patients Tang et al.,[23] Negative non-significant correlation was found between serum level of prolactin and Disease duration ($p > 0.05$). Contrarily to our results, disease duration showed positive significant correlation with prolactin provided in a study on 29 RA male patients (Bruno et al., 2006). Our study revealed according to disease activity parameters, Prolactin shows positive high statistically significant correlation with DAS28 ($p=0.007$), Also Prolactin shows positive statistically significant correlation with CDAI ($p < 0.05$). Vasoinhibin shows positive high significant correlation between vasoinhibin and both DAS28, CDAI ($p < 0.001$). According to Fayez et al., [29]. study on 40 RA patients Serum prolactin concentrations in patients were significantly higher. Higher level of serum prolactin was detected in patients with severe disease activity by DAS-28 score (Mean ±SD =13.77±7.288) compared to patients with moderate (Mean ±SD = 5.89±1.03) and low disease activity (Mean ±SD = 4.25±0.35) (p-value = 0.008), this revealed increasing prolactin level in RA patients according to interpretation of DAS-28 in assessing disease activity.
contrary, according to Tang et al., [23]. DAS28 showed no significance with PRL in a study including 119 RA patients.

5. Conclution

- The Serum prolactin and vasoinhibin were high in RA patients with moderate and high disease activity in comparison to control.
- The present study revealed a positive connection between levels of prolactin and vasoinhibin with disease activity assessment through clinical parameters including (DAS28, CDAI, VAS). And laboratory parameters including (ESR, CRP).

6. Recommendation

- Further related studies with large sample size and different groups of RA patients should be conducted to confirm results.

- Using prolactin and vasoinhibin level of prolactin and vasoinhibin in follow up of RA patients.

- Further studies on gene expression of vasoinhibin and prolactin in patients with rheumatoid arthritis.

- Further studies for assessment of anti-prolactin drugs on disease activity of RA patients.

- Further studies for investigation of vasoinhibin in lung tissue in RA patients.

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