Lipopolysaccharide-binding protein is a sensitive disease activity biomarker for rheumatoid arthritis

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Abstract

Objective

This study was performed to evaluate the performance and clinical significance of lipopolysaccharide-binding protein (LBP) as a disease activity biomarker in rheumatoid arthritis (RA).

Methods

LBP levels were measured by enzyme-linked immunosorbent assay (ELISA). The associations between LBP and the clinical and serological features of RA and its clinical significance as a RA disease activity biomarker were analysed.

Results

The serum level of LBP in RA was significantly elevated compared to those in OA, SLE, pSS and HC. The level of LBP in RA synovial fluid (SF) was higher than that in OA SF. LBP was significantly correlated with RA disease activity parameters such as ESR, CRP, tender joint counts, swelling joint counts and DAS28. Furthermore, LBP positive RA patients were more likely to show higher disease activity (DAS28>5.1), positive APF, interstitial lung disease and metabolic disorders. The predictive value of LBP on high disease activity was comparable with those of CRP and ESR. In 52.5% of the patients with active disease but negative in CRP /ESR, LBP was still positive and correlated with swelling joint counts.

Conclusion

LBP is a sensitive serum biomarker to evaluate RA disease activity, and it could be a promising laboratory marker to assist RA disease activity assessment in active RA patients with negative ESR or CRP.

Key words

rheumatoid arthritis, lipopolysaccharide-binding protein, disease activity

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Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease characterised by the joints erosion and damage (1). Timely and tight control of rheumatoid arthritis (RA) could offer the highest likelihood of preserving articular function and preventing disability, which requires regular measures of disease activity (2-4). To evaluate RA disease activity more accurately and objectively, laboratory tests such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been applied in disease activity assessment (5, 6). However, in large numbers of RA patients with active disease, these markers are still in the normal range and thus are not sensitive and helpful enough for disease activity indication in all RA patients (7, 8). Therefore, identification of novel sensitive and objective biomarkers to assess RA disease activity are still in need.

Lipopolysaccharide-binding protein (LBP) is an acute-phase reaction protein. It plays a key role in promoting innate immunity against Gram-negative bacteria by transferring lipopolysaccharide (LPS) to both membrane-bound CD14 and soluble CD14 (9). LBP could be used as a biomarker in sepsis diagnosis (10, 11). Serial LBP serum measurements may be useful in predicting outcomes in patients with severe sepsis (12). In the early 1990s, Heumann *et al*. demonstrated that LBP levels in serum and in SF were significantly higher in patients with RA than that in the control group with degenerative arthropathies (13). However, the clinical significance of LBP and whether LBP could be a potential biomarker for RA diagnosis or disease activity evaluation are still elusive. In this study, we identified serum LBP as a sensitive biomarker for RA disease activity and revealed that LBP could become a complementary marker of CRP and ESR.

Materials and methods

Patients and samples

Serum samples were obtained from 120 patients with RA, 32 patients with osteoarthritis (OA), 30 patients with primary Sjögren's syndrome (pSS), 30 patients with systemic lupus erythematosus (SLE) and 50 healthy volunteers. The clinical data of RA patients were listed in Table I. Synovial fluid (SF) samples were obtained from 27 patients with RA and 30 patients with OA. Paired sera of 27 RA patients were also collected at the same time. The sera and SF were collected from inpatient or outpatient clinics of the Department of Rheumatology and Immunology, Peking University People's Hospital. The diagnosis of RA was made according to the 2009 revised ACR/EULAR criteria (14), while OA patients were grouped according to the criteria of the 1995 ACR criteria (15-17), pSS patients were diagnosed according to 2012 ACR criteria (18), 2009 SLICC revision of the ACR classification criteria for SLE (19) was used for the diagnosis of SLE. The healthy volunteers were currently free from any symptoms of infections. The study was approved by the Ethics Committee of Peking University People's Hospital according to the declaration of Helsinki with the following reference number: 2015PHB219-01. All patients had been informed and signed the consent for participation in the study.

Measurement of LBP

Serum and SF LBP concentrations were determined with a commercial ELISA kit (HK315, Human LBP, Hycult Biotech), serum samples were diluted 1: 2000 in sample dilution buffer, and the sensitivity of the ELISA test was 4.4 ng/ml according to the manufacturer's instructions. The measurements and data analyses were performed twice independently according to the manufacturer's instructions.

Clinical data and inflammation marker analysis

Clinical data were recorded at the time of sample collection as the following index: age, sex, disease duration, number of swollen joints, and number of tender joints, organ involvements, treatments, history of smoke, infection and metabolic disorders. ESR was evaluated by the Westergren method (positive if more than 20mm/h). Serum levels of immunoglobulins (IgG, IgM and IgA), complements (C3, C4), CRP (positive if more than 8mg/L),

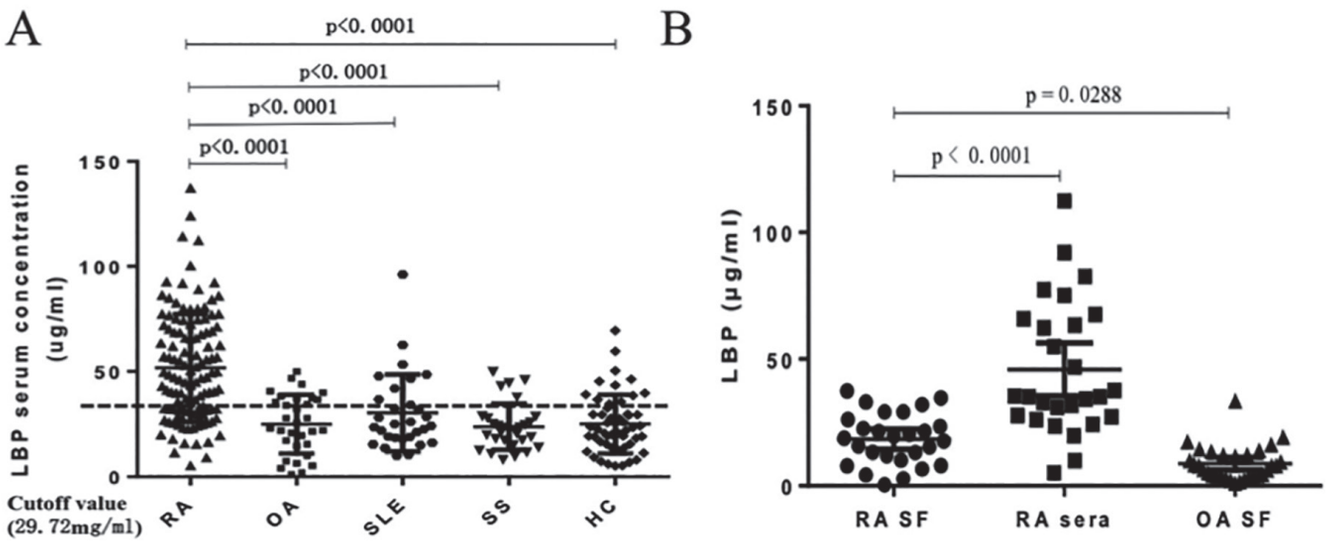

Fig 1. Determination of LBP values in different diseases. **A**: Serum LBP concentrations in patients with rheumatoid arthritis (RA) and the controls. Sera were collected from 120 RA patients, 32 patients with osteoarthritis (OA), 30 patients with pSS, 30 patients with SLE and 50 healthy controls (HC) and measured by ELISA. **B**: LBP concentrations measured by ELISA in matched SF and serum from 27 RA patients as well as 30 OA SF.

and rheumatoid factor (RF)-IgM were examined by immunonephelometry method. Antikeratin antibodies (AKA), antiperinuclear factor (APF) and RF-IgG were tested by indirect immunofluorescence assay. Anti-citrullinated peptide (anti-CCP) antibodies and glucose phosphate isomerase (GPI) were tested by ELISA. The 28-joint count Disease Activity Score (DAS28) was evaluated as described (4).

Definition of the metabolic disorders

Metabolic disorders were defined as presence of one or more of the following three medical conditions: 1) hypertension, *i.e.* systolic blood pressure (SBC) ≥140 mmHg, or diastolic blood pressure (DBP) ≥90 mmHg, or previously diagnosed; 2) dyslipidaemia, *i.e.* fasting triglyceride (TG) ≥1.7 mmol/L, or fasting high density lipoprotein cholesterol (HDL-c) <0.9 mmol/L; 3) hyperglycaemia, *i.e.* fasting blood-glucose (FPG) ≥6.1 mmol/L, or 2h post-meal glucose (PG) ≥7.8 mmol/L, or previously diagnosed.

Table I. The clinical characters of 120 patients with RA.

Index	RA (n=120)
Male/Female	28/92
Age	60.27 ± 10.59
Duration (years)	12.16 ± 8.69
Smoking[a]	25 (20.3%)
Infections[a]	26 (21.1%)
Metabolic disorders[a]	63 (51.2%)
Tender joints	9.33 ± 9.30
Swelling joints	6.83 ± 7.64
ESR (mm/h)	53.28 ± 35.41
CRP (g/L)	34.89 ± 41.33
DAS28 scores	5.13 ± 1.61
Active/Remission	115/5
RF (IU/L)	472.07 ± 838.65
IgG (g/L)	13.57 ± 4.02
IgA (g/L)	3.22 ± 1.32
IgM (g/L)	1.36 ± 0.94

[a]n (%).

Definition of involvements of organs or systems

Interstitial lung disease: pulmonary fibrosis (chronic diffuse interstitial infiltrates on x-ray with a restrictive pattern on pulmonary function studies); Renal involvements: a) persistently elevated urinary pH value (>6.0), b) persistent proteinuria >0.5 g/day, c) altered urinalysis (haematuria, pyuria, red blood cell casts), or d) raised serum creatinine >1.5 mg/dL; Haematological involvements: a) anaemia: haemoglobin level <11 g/d, b) leukopenia: white blood cell count <4,000/mm^3, or c) thrombocytopenia: platelet count <100,000/mm^3.

Statistical analysis

Data analyses were performed using SPSS 17.0 for Windows. Results are presented as the mean ± SD and percentage. Quantitative data were compared by the *t*-test. Qualitative data were compared by the Pearson's chi-square test. Binary logistic regression was used to assess the association between categorical clinical variables and an elevation of LBP. Paired samples were analysed using the Wilcoxon matched pairs test. A difference between groups was considered significant if $p<0.05$. Spearman's rank correlation test was used to assess relationships between two variables. Correlation was considered significant if $p<0.05$. Sensitivities and specificities were calculated to determine the indicative power of LBP by receiver operating characteristics (ROC) analysis. The cut-off value of LBP was chosen when Youden's index took the max value.

Results

Serum LBP level is elevated in RA

LBP levels in serum samples of 120 RA patients and the controls were determined by ELISA. The serum levels of LBP in RA patients (51.67±25.66 μg/ml) were significantly higher than those from healthy controls or patients with OA, SLE and pSS ($p<0.01$, Fig 1A). A cut-off value of 29.72 μg/ml was determined by receiver operating characteristic (ROC) analysis when Youden's index took the max value to distinguish RA patients with over-elevated serum LBP from those with normal serum LBP levels compared to the healthy and disease controls. By this cut-off value, the RA patients could also be distin-

Table II. The clinical and laboratory manifestations in LBP-positive and negative patients with RA.

Index	LBP (+) (n=95) n (%)	LBP (-) (n=25) n (%)	*p*-value in Chi-square test	*p*-value in binary logistic analysis
Female	74 (77.9)	18 (72)	0.535	0.727
Smoke	19 (20)	6 (24)	0.661	0.380
Infection	22 (23.2)	4 (16)	0.440	0.508
Glucocorticoids	33 (34.7)	7 (28)	0.525	0.203
Immunosuppressive drugs	64 (67.4)	19 (76)	0.406	0.922
Biologics	5 (5.3)	2 (8)	0.987	0.630
Interstitial lung disease	51 (54.3)	13 (52)	0.841	0.037*
Renal involvements	2 (2.1)	0 (0)	1.000	0.999
Haematological involvements	39 (41.9)	6 (24)	0.101	0.716
Rheumatoid nodules	15 (16)	2 (8)	0.491	0.463
Metabolic disorders	56 (58.9)	7 (28)	0.006**	0.008**
High disease activity				
(DAS28>5.1)	54 (56.8)	4 (16)	0.000***	0.003**
AKA (+)	56/91 (61.5)	12/24 (50)	0.306	0.603
APF (+)	66/92 (71.1)	9/23 (39.1)	0.003**	0.011*
Anti-CCP (+)	80/91 (87.9)	20/25 (80)	0.491	0.516
RF-IgG (+)	34/89 (38.2)	8/24 (33.3)	0.661	0.822
RF-IgM (+)	73/95 (76.8)	17/25 (68)	0.364	0.388
GPI (+)	40/85 (47.1)	9/23 (39.1)	0.498	0.215

DAS28: 28-joint count Disease Activity Score; AKA: anti-keratin antibodies; APF: anti-perinuclear factor; Anti-CCP: anti-citrullinated peptide antibody; HRF: hidden rheumatoid factor; GPI: glucose-6-phosphateisomerase. *p<0.05; **p<0.01; ***p<0.001.

Table III. Correlation analysis of LBP levels in RA serum with clinical features.

Parameter	Spearman correlation coefficient	*p*-value
Age	-0.083	0.367
Duration	-0.145	0.117
ESR	0.475	0.000***
CRP	0.501	0.000***
RF	0.162	0.081
D-dimer	0.312	0.001**
IgA	0.151	0.106
IgG	0.150	0.108
IgM	0.256	0.006**
C3	0.143	0.130
C4	0.117	0.214
GPI	0.010	0.942
HRF	0.149	0.352
CCP	0.029	0.761
Tender joint counts	0.197	0.031*
Swollen joint counts	0.231	0.011*
DAS28	0.369	0.000***
HDL-c	-0.216	0.019*

*p<0.05; **p<0.01; ***p<0.001.

guished from the healthy and disease controls with 79.17% sensitivity and 70.63% specificity (AUC=0.82). In addition, there's no difference between the positivity of LBP in anti-CCP antibody positive and negative patients (78.0% *vs*. 81.3%, p=0.491).

The level of LBP in the matched serum and SF samples of 27 RA patients was also measured, and was compared with those in SF of 30 OA patients. The SF LBP level of RA patients was significantly higher than that of OA patients (18.44±10.16 μg/ml *vs*. 8.81±6.82 μg/ml, p=0.0288), however, it was lower than that of the matched serum (45.87±26.38 μg/ml, p<0.0001, Fig 1B). No correlation was found between the LBP levels in matched SF and serum (Spearman's r=0.169, p=0.199).

LBP is associated with RA disease activity

According to the cut-off value (29.72 μg/ml), 120 RA patients were grouped into LBP-elevated and LBP-normal groups and their characteristics are shown in Table II. The patients in the two groups were comparable in age, disease duration, gender ratio and treatment. Significantly higher frequency of high disease activity (DAS28>5.1) was observed in the LBP-elevated group than in the LBP-normal group. Furthermore, increased APF positivity frequency was also observed in the LBP-elevated group. Significantly increased incidence of metabolic disorder was observed in LBP-elevated group than in the LBP-normal group. We further confirmed the above association by binary regression analysis. As a result, these parameters above and interstitial lung disease were still significantly associated with elevated LBP (Table II).

Further correlation analysis showed that LBP concentrations in RA patients were positively correlated with DAS28 (r=0.369, p=0.000) and other disease activity indicators including ESR (r=0.475, p=0.000), CRP (r=0.501, p=0.000), swollen joint counts (r=0.231, p=0.011) and tender joint counts (r=0.197, p=0.031). LBP levels were also positively correlated with total IgM levels (r=0.256, p=0.006), negatively correlated with the level of HDL-c (r = -0.213, p=0.019). No correlation was found between LBP and RA associated autoantibodies like anti-CCP antibodies or RF. (Supplementary Fig 1, Table III).

The 120 patients with RA were classified into 3 groups according to the DAS28-ESR: the high activity group (58 patients) was defined as DAS28-ESR >5.1; the moderate activity group (45 patients) was defined as 5.1 ≥DAS28-ESR >3.2; the low activity group (17 patients) was defined as DAS28- ESR ≤3.2. The serum

LBP levels in the three groups were 62.14±25.50 μg/ml, 42.78±22.88 μg/ml and 39.47±19.03 μg/ml respectively, which were decreasing from the high to low activity group. Serum LBP levels were significantly higher in the high activity group than in the moderate and low activity groups (p=0.0002 and 0.0022, resp.; Fig 2A).

LBP is a sensitive indicator in evaluating RA disease activity and can be applied in ESR/CRP negative patients

The ROC curves of LBP, CRP, ESR and RF for identification of high disease activity (DAS28 >5.1) in RA are presented in Figure 2B. Determined by ROC analysis, the sensitivity and specificity of LBP (Sensitivity 58.6%, Specificity 85.2%, AUC 0.739) in predicting high disease activity were comparable to those of CRP (Sensitivity 53.4%, Specificity 91.8%, AUC 0.754) and ESR (Sensitivity 67.2%, Specificity 79.0%, AUC 0.769) (Tables IV-V), which were RA disease laboratory biomarkers most widely applied in clinical practice. Since RF is not a RA disease activity marker but is positively correlated with RA disease activity, we included RF as a control to compare the efficacy of biomarkers on disease activity indication. The result showed that the sensitivity of LBP in disease activity prediction was markedly higher than that of RF (Sensitivity 37.5%, Specificity 88.5%, AUC 0.620) (Fig. 2B), which suggested that unlike RF which could not be applied as a RA disease activity biomarker, LBP could be a potential disease activity marker as ESR and CRP.

In the 120 RA patients recruited in this study, 40 individuals (33.3%) were negative in ESR and/or CRP, which was consistent with previous studies (7, 8). However, 31 (77.5%) of these ESR/CRP negative patients were in moderate or high disease activity according to DAS28-ESR (Fig. 2C). Among the 40 patients who were either ESR or CRP negative, 21 (52.5%) still showed elevated serum LBP levels (Fig. 2D), and 17 of the 21 patients were in moderate or high disease activity. And in 22 patients who were negative in both CRP and ESR, 3 patients were still positive in LBP. And all of the 3 patients were in moderate or high disease activity. In the 22 patients, CRP and ESR were not correlated with the swollen joint counts, tender joint counts, DAS28 and levels of Immunoglobulin (p>0.05) (Supplementary Table I). However, the levels of LBP were still significantly correlated with swollen joint counts by correlation analysis between LBP and disease activity indicators (tender joint counts, swollen joint counts, DAS28 scores, IgM, IgG, etc.) (Supplementary Table II).

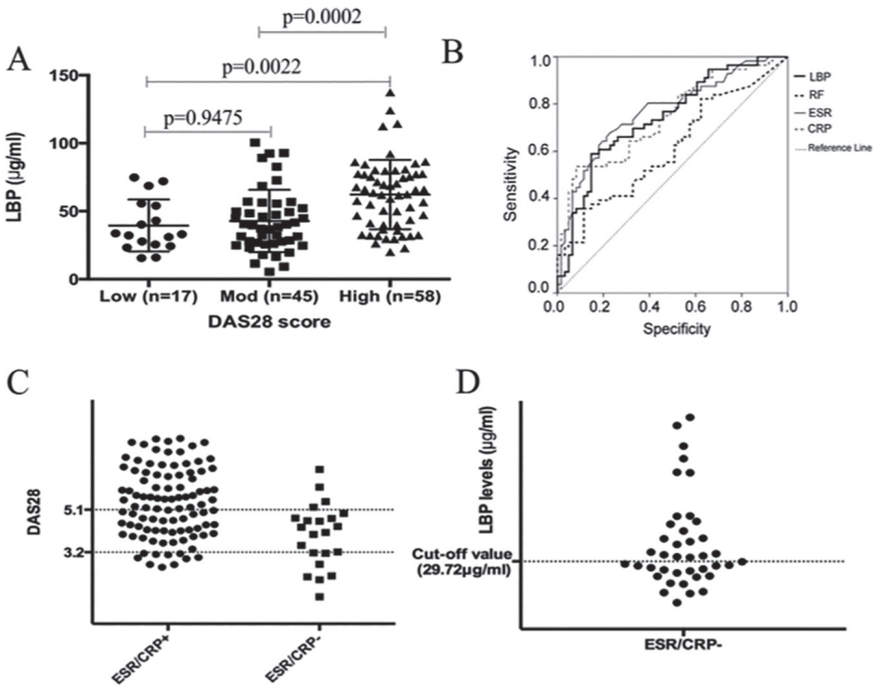

Fig 2. The role of LBP in reflecting disease activity in RA. **A**: LBP levels in sera from RA patients. RA patients were categorised into 3 groups according to the Disease Activity Score based on ESR. Low: low activity group; Mod: moderate activity group; High: high activity group. **B**: ROC curves of LBP, CRP, ESR and RF for identification of high disease activity in RA. **C**: The distribution of DAS28 in ESR/CRP+ and ESR/CRP- patients. 77.5% of these ESR/CRP negative patients were in moderate or high disease activity according to DAS28-ESR. **D**: LBP levels in ESR/CRP negative patients. 52.5% of ESR/CRP negative patients still showed elevated serum LBP levels.

The influence of infection in RA patients on performance of LBP and other disease activity biomarkers

Since LBP is elevated and involved in infectious inflammation, whether its disease activity indicative performance will be affected by infection is to be determined. Despite the role of LBP in infections according to former studies, no significant correlations were found between LBP positivity and overall complicating infections in the RA patients in our study (Table I). We evaluated the serum LBP levels of patients with infections in the studied RA patient cohort. The serum LBP levels increased in almost all patients with infections except the patients with tuberculosis (Supplementary Table III), but statistically significant increase of serum LBP was only observed in patients with bacteremia or pulmonary infections except tuberculosis. To elucidate how infection would affect RA disease activity indicative laboratory biomarkers, we compared the levels of CRP, ESR and LBP in RA patients with and without infections (Supplementary Table IV. In RA patients complicated with infections, all the three disease activity markers, ESR, CRP and LBP, increased compared to patients without infections, however, statistical significance were not reached. This result showed that combined infections in RA would cause the elevation of all laboratory disease activity markers. LBP as well as the current applied RA disease activity markers ESR and CRP all marginally increased when infections complicated RA and the change of LBP

Table IV. Diagnostic values of LBP, CRP and ESR in high disease activity in RA patients.

Index	AUC	std	*p*-value	95%CI for AUC		Cut-off	Sensitivity	Specificity	Youden
				Lower	Upper				
LBP	0.739	0.048	0.000	0.646	0.832	57.325	0.586	0.852	0.439
CRP	0.754	0.046	0.000	0.664	0.845	37.350	0.534	0.918	0.453
ESR	0.769	0.045	0.000	0.680	0.858	49.500	0.672	0.790	0.463

Table V. The comparison of AUC between LBP and other activity indexes (CRP and ESR).

Contrast	e	Stb	95%CI		χ^2	*p*-value
CRP - LBP	0.015	0.053	-0.089	0.120	0.082	0.775
ESR - LBP	0.030	0.051	-0.070	0.131	0.351	0.554

level was comparable to that of ESR or CRP and was not significantly altered by infections.

To directly evaluate LBP's performance on RA disease activity indication in infected RA patients, we examined the disease activity indicative efficiency of LBP in RA patients with infection. The levels of LBP were still markedly disparate in different disease activity groups correlating with DAS28 (Supplementary Fig. 2). The AUC of ROC curve of LBP in predicting high disease activity in patients with infection (0.680) were still comparable to those of CRP (0.693) and ESR (0.650), and significantly superior to the RF control (0.368) (Supplementary Fig 3). These results showed that LBP was still a sensitive disease activity indicator in RA patients with infections.

Discussion

LBP is a key molecular in the pathogen sensing process in innate immunity. Recent studies reported inhibitory effects on inflammation by a high concentration of LBP (20). In addition to LPS from Gram-negative bacteria, several bacterial surface components from Gram-positive pathogens are also recognised by LBP (21). Besides TLR4, LBP could also enhance immune response by activating TLR2 (22, 23). Seibli *et al*. revealed that elevated expression of TLR2 in RA synovial fibroblasts could be a consequence of direct exposure to microbial compounds or of the presence of inflammatory mediators such as TNF-α, IL-1β, LPS in the joint (24), which implicated a connection between LBP and RA autoimmunity. However, the role of LBP in autoimmune diseases including RA was scarcely explored.

For the first time, we compared the level of LBP in RA patients with those with other autoimmune diseases. We observed that serum LBP level was significantly elevated in RA patients compared to patients with SLE, pSS, OA and healthy subjects. By further ROC analysis, we identified LBP as a relatively specific and sensitive biomarker for RA. In clinical practice, it is unlikely that LBP could replace the highly sensitive and specific biomarkers in application such as anti-CCP antibodies. However, LBP levels might be a useful reference when there is a need of distinguishing anti-CCP negative RA patients from patients with arthralgia caused by OA or other autoimmune diseases. Meanwhile, LBP concentration in RA SF was much higher than that in OA SF. The significantly elevated LBP levels in RA SF suggest that it may participate in the autoimmune inflammation in RA joints.

More importantly, our study has shown a close connection between LBP and RA disease activity. Firstly, LBP concentrations in RA patients were positively correlated with DAS28 and levels of a series of disease activity indicators including ESR, CRP, swollen joint counts and tender joint counts. In addition, serum LBP levels were significantly higher in RA patients with high disease activity than in those with moderate or low activity. Furthermore, LBP positivity was comparable with CRP and ESR when used to predict high disease activity. Even in CRP/ESR negative RA patients, more than half of the patients were still LBP positive. A significant correlation between LBP and swollen joint counts was still observed in this CRP/ESR negative group. The ability of LBP to sensitively reflect disease activity would help evaluate the inflammatory status of RA more accurately when CRP and ESR are negative in active RA patients.

Previous studies showed LBP was a predictive marker of infection (25-27). It not only exerts a diagnostic value in sepsis, UTI, periodontitis, etc., but also is related to the prognosis and mortality of some types of infections (10, 28, 29). However, no significant association between infection and LBP elevation was found in RA patients. Infection complication in RA did not specifically affect LBP level compared to traditional RA disease activity biomarkers ESR and CRP. In RA patients with infections, LBP was still comparable to ESR and CRP on the disease activity indicative performance. These results showed that infections would not affect the value of LBP as a disease activity biomarker in RA.

Besides the association with disease activity, we also found that LBP was associated with metabolic disorder in RA patients, which was consistent with previous studies showing LBP correlated with MetS in normal people and patients with psoriasis (26, 27). In our study, we observed a significant positive correlation of LBP with metabolic disorders and decreased HDL-c level, which suggested that elevated LBP levels in RA patients might indicate higher risks of developing metabolic complications or cardiovascular events. Certain factors related to MetS, such as serum lipoprotein, have been proved to be able to trigger inflammation and enhance autoimmune reactions (30), which may further intensify RA inflammation and accelerate disease complication development (31, 32). Increased cardiovascular (CV) risk in RA patients has been associated with increased disease activity and reduction of disease activity was associated with reduced CV risk independently of immunomodulatory treatments (33). As a RA disease activity indicator, determining LBP el-

evation would provide an early warning so that such RA driving metabolic disorder or cardiovascular risk could be tightly monitored and timely interfered. The exact pathological role of LBP on induction of MetS and cardiovascular damages in RA should be investigated in future studies.

Though not significant in Pearson's chi-square test, binary logistic regression showed a markedly increase of interstitial lung disease in RA patients with elevated LBP than those without. Former studies showed that LBP participates in lung injury process under several circumstances, such as infection, smoking, allogeneic stem cell transplantation and cystic fibrosis (12, 34-37). However, there's a lack of related research in pulmonary interstitial fibrosis. Thus the role of LBP in lung inflammation among autoimmune diseases like RA needs further exploration.

There are several limitations in this study. First, the group size of the RA patients recruited are somewhat limited, which lead to RA patients with positive/negative for LBP as two groups largely differ in terms of sample size (95 *vs*. 25 patients), and weakened the conclusion when comparing the clinical and laboratory parameters of RA in these two groups. The other weakness of our study is the lack of direct comparison of LBP levels between RA patients with active and inactive disease. This is because the patients we recruited as they came for treatment in clinics were nearly all in disease active conditions (active/remission ratio was 115/5, Table I) and we were unable to perform an effective and conclusive comparison with so few inactive patients. Although further analyses (Fig. 2 and Tables III, IV and V) strengthened our conclusion that LBP was a sensitive RA disease activity biomarker, an enlarged patient group size based on multi-centre studies in the future is still in need to overcome these limitations of this study.

In conclusion, LBP may be a sensitive serum biomarker to evaluate disease activity in RA, and it could also be used as a potential marker to assist RA diagnosis. With much higher specificity, LBP is comparable with CRP and ESR in assessment of RA disease activity, and could be used to indicate disease activity in CRP/ESR negative patients. The elevation of circulating LBP level in RA and its correlation with disease activity markers implicates its involvement in RA development. Further investigation of specific pathogenic roles of LBP in RA autoimmunity is still in need.

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