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Lipopolysaccharide-binding protein is increased in patients with psoriasis with metabolic syndrome, and correlates with C-reactive protein

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Summary

Lipopolysaccharide-binding protein (LBP) is a reliable indicator of serum lipopolysaccharide (LPS) concentration. Raised levels of circulating LPS can trigger an increase in chronic pro-inflammatory cytokines, which may mediate the development of insulin resistance and obesity. Psoriasis is a chronic inflammatory skin disease that has been associated with metabolic syndrome. We aimed to study the expression of LBP in patients with psoriasis treated with narrowband ultraviolet B phototherapy, and controls matched by age, gender and body mass index (BMI). We did not find any differences in serum LBP concentration between patients and controls, and serum LBP did not correlate with the Psoriasis Area and Severity Index. However, patients with psoriasis and metabolic syndrome had higher serum concentration of LBP than controls. Furthermore, correlation with BMI and apolipoprotein B was present in controls, but not in patients with psoriasis. Serum LBP level did not change significantly after treatment with phototherapy.

Lipopolysaccharide-binding protein (LBP) is an acute-phase protein of 65 kDa in size belonging to the group of antimicrobial inflammatory peptides. It is produced by the liver, and has been implicated in the acute inflammatory response.[1] It has been studied in chronic inflammatory diseases such as rheumatoid arthritis, correlating with levels of C-reactive protein (CRP) and interleukin (IL)-6.[2] Recent hypotheses have linked the triggering of a chronic inflammatory response to endogenous lipopolysaccharide (LPS) generated by intestinal bacterial flora with the onset of obesity and insulin resistance.[3] Increased levels of circulating LPS can provoke a disturbance in the innate immune system, increasing the levels of pro-inflammatory cytokines. Serum LBP reflects the serum LPS concentration.

Psoriasis is a chronic skin disease that has been linked to comorbidities such as metabolic syndrome. The explanation for this association lies in the relationship between chronic inflammation and the initiation of atherogenesis, endothelial dysfunction and insulin resistance through a complex network of common mediators, which include cytokines, adipokines and, very probably, antimicrobial inflammatory peptides.[4] Activation of T lymphocytes in psoriasis might be triggered by antigen-presenting cells reacting against an unknown antigen, and pro-inflammatory cytokines, such as IL-6 or tumour necrosis factor (TNF)-α, produced by these cells, may share a pathogenic pathway with obesity and insulin resistance.

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We studied a group of patients with psoriasis without arthritis and a group of controls matched by age, gender and body mass index (BMI). This cohort has been described in a previous publication, in which we found several differences between patients with psoriasis and controls in terms of inflammation and atherogenesis markers.[5] In this study, we aimed to examine a possible correlation of LBP serum concentration with such markers.

Report

Patients with psoriasis (n = 50; 31 men, 19 women, mean age ± SD 46.06 ± 17.53, range 19–79) and matched controls (n = 50; 31 men, 19 women, age 46.38 ± 17.29, range 19–79) were prospectively recruited in our phototherapy unit between January 2010 and May 2011. Median body mass index was 27.5 kg/m^2 in both groups. The exclusion criteria included the presence of psoriatic arthritis or chronic inflammatory diseases such as inflammatory bowel disease, arthritis, and advanced renal or liver failure.

The patients had a mean Psoriasis Area and Severity Index (PASI) of 15.59. They were treated with a standard course of narrowband ultraviolet (UV)B phototherapy, and PASI decreased to a mean ± SD of 3.5 ± 3.31 after treatment.

Both patients and controls were screened for LBP before therapy, and patients were screened again after completion of phototherapy, using a sandwich ELISA (Hycultbiotech, Uden, the Netherlands). The intra-assay and interassay coefficients of variation for these determinations were between 5% and 10%. Briefly, serum samples were diluted and assayed according to the manufacturer's instructions, then the biotinylated antibody, bound to captured human LBP and the streptavidin–peroxidase conjugate, reacted with the substrate, tetramethylbenzidine. The enzyme reaction was stopped by the addition of citric acid, and the absorbance was measured at 450 nm with a spectrophotometer (iEMA Reader MF; Labsystems FI 01720, Vantaa, Finland).

Datasets were tested for normality, showing a normal distribution, and mean values were compared using the Student paired t-test. For categorical variables, one-way ANOVA was used. Correlations were analysed with a linear regression model. Results are expressed as mean ± SD, and $P < 0.05$ was considered significant.

Baseline LBP serum concentration was found to be 14.81 ± 8.43 μg/mL in patients and 13.56 ± 5.05 μg/mL in controls, and the difference was not significant (P = 0.67). After phototherapy, LBP was 14.27 ± 7.28 μg/mL (P = 0.57).

Patients who fulfilled the International Diabetes Foundation criteria for metabolic syndrome (n = 27) had a mean LBP serum concentration of 17.15 ± 9.04 μg/mL, compared with those not fulfilling such criteria (n = 23), whose LBP concentration was 10.52 ± 6.04 μg/mL ($P < 0.01$). Such differences were not evident in the control group; 21 of the 50 subjects fulfilled the IDF criteria; mean serum LBP concentration was 14.03 ± 4.96 μg/mL in subjects with metabolic syndrome vs. 13.21 ± 5.17 μg/mL in subjects without metabolic syndrome (P = 0.58). After phototherapy, serum LBP did not change significantly in the patient group, regardless of the presence or absence of metabolic syndrome (16.43 ± 7.62 and 11.57 ± 5.97 μg/mL, respectively, P = 0.66).

Using a linear regression model with basal LBP as the dependent variable, and high-sensitivity (hs)-CRP, IL-6, soluble TNF receptor, PASI, BMI, low-density lipoprotein cholesterol and apolipoprotein (apo)-B as independent variables, a significant correlation was seen only for hs-CRP ($P < 0.001$; R^2 = 0.44) (Fig. 1a) in the patient group. In the control group, linear regression disclosed a positive correlation of LBP serum levels with hs-CRP ($P < 0.001$; R^2 = 0.31), BMIx (P = 0.02; R^2 = 0.16) and apo-B (P = 0.02; R^2 = 0.15) (Fig. 1b).

Serum LBP is a reliable indicator of serum endotoxin (LPS) concentration. Recent studies have shown that persistently high concentrations of LPS are associated with a high-fat diet can trigger insulin resistance and obesity.[6] Because psoriasis has been linked to obesity and metabolic syndrome through common pathogenic mechanisms,[7] we examined LBP in our previously studied cohort of patients with psoriasis and matched controls, together with any possible changes after completion of antipsoriatic therapy with UVB phototherapy.

We did not find a higher LBP serum concentration in patients compared with controls, probably because these patients had a low inflammatory profile (exclusion criteria were arthritis and chronic inflammatory diseases) and were not obese. We were unable to find a positive correlation between LBP and PASI, but LBP did correlate with hs-CRP, a sensitive marker of low-grade inflammation in patients with psoriasis. However, in the control group, LBP correlated with hs-CRP, BMI and apo-B, as expected. We hypothesize that the inflammatory disturbance present in patients with psoriasis can modify a finely tuned balance in the LPS buffering system, abolishing

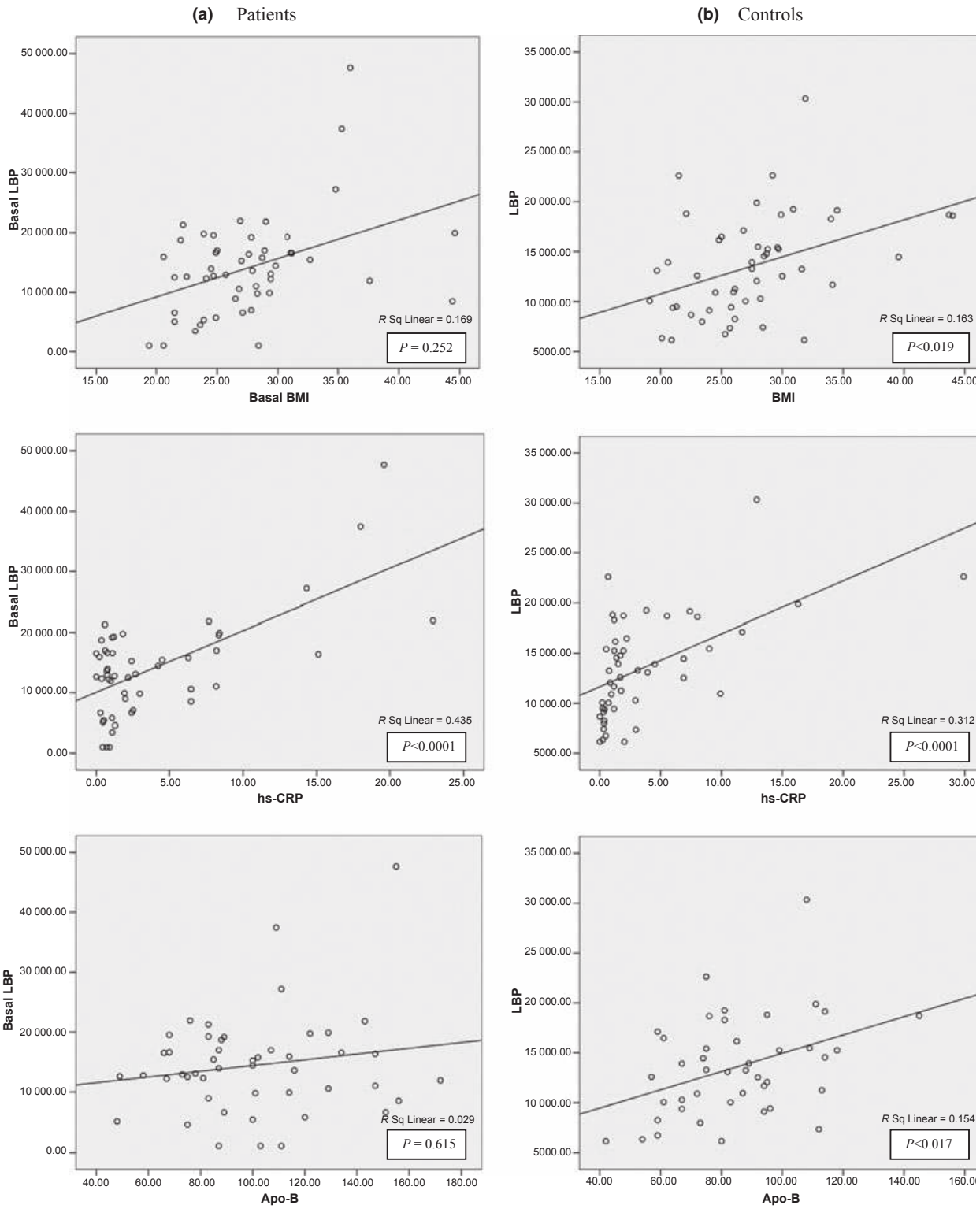

Figure 1 Correlations (linear regression model) between lipopolysaccharide-binding protein (LBP) and body mass index (BMI), high sensitivity C-reactive protein (hs-CRP) and apolipoprotein B (apo-B) in (a) patients (a) and (b) controls.

the normal correlation of LBP with BMI or atherogenesis markers.

Finally, patients with markers of metabolic syndrome had a higher LBP serum concentration than those without such markers, and this finding was not evident in the control group. These results indicate LBP as a possible marker of progression towards metabolic syndrome in patients with psoriasis. However, the lack of correlation between LBP and PASI could indicate that inflammatory and metabolic abnormalities in these patients are present even in mild forms of the disease, and that they are independent of clinical improvement even after an effective treatment such as phototherapy.

Learning points

- Serum concentration of LPS has been associated with metabolic disturbances in chronic inflammatory diseases.
- Lipopolysaccharide-binding protein may be an indicator of systemic inflammation and progression towards metabolic syndrome in patients with psoriasis.

References

1 Hotamisligil GS. Inflammation and metabolic disorders. *Nature* 2006; **444**: 860–7.
2 Heumann D, Bas S, Gallay P *et al.* Lipopolysaccharide binding protein as a marker of inflammation in synovial fluid of patients with arthritis: correlation with interleukin 6 and C-reactive protein. *J Rheumatol* 1995; **22**: 1224–9.
3 Cani PD, Amar J, Iglesias MA *et al.* Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* 2007; **56**: 1761–72.
4 Boehncke WH, Boehncke S, Tobin AM, Kirby B. The 'psoriatic march': a concept of how severe psoriasis may drive cardiovascular morbidity. *Exp Dermatol* 2011; **20**: 303–7.
5 Romaní J, Caixàs A, Carrascosa JM *et al.* Effect of narrowband UVB therapy on inflammatory markers and body fat composition in moderate to severe psoriasis. *Br J Dermatol* 2012; **166**: 1237–44.
6 Moreno-Navarrete JM, Ortega F, Serino M *et al.* Circulating lipopolysaccharide-binding protein (LBP) as a marker of obesity-related insulin resistance. *Int J Obes* 2011. DOI: 10.1038/ijo.2011.256.
7 Kim SK, Park S, Lee ES. Toll-like receptors and antimicrobial peptides expressions of psoriasis: correlation with serum vitamin D level. *J Korean Med Sci* 2010; **25**: 1506–12.