Advances in Rheumatology

RESEARCH

Open Access

Gamma-glutamyl transpeptidase and indirect bilirubin may participate in systemic inflammation of patients with psoriatic arthritis

Xu Wang[1†], Yan Mao[1†], Shang Ji[1], Huanrong Hu[1], Qian Li[1], Lichao Liu[1], Shaomin Shi[1*] and Yaling Liu[1*]

Abstract

Background Previous studies have suggested that systemic metabolic abnormalities are closely related to psoriatic arthritis (PsA). Gamma-glutamyl transpeptidase (GGT) and indirect bilirubin (IBIL), two essential active substances in hepatic metabolism that have been demonstrated as an oxidative and anti-oxidative factor respectively, have been proved to be involved in oxidative stress damage and inflammation in several human diseases. However, their role in PsA remains unclear.

Methods In this retrospective comparative cohort study, a case group of 68 PsA patients and a control group of 73 healthy volunteers from the Third Hospital of Hebei Medical University were enrolled. Serum GGT, IBIL, GGT/IBIL ratio and C-reactive protein (CRP), a well applied bio-marker of systemic inflammatory in PsA, were compared between the two groups. Furthermore, the relationship of GGT, IBIL and GGT/IBIL with CRP were explored in PsA patients. Finally, the patients were divided into high inflammation group and low inflammation group according to the median value of CRP. Multivariate logistic regression analyses were used for the association of systemic inflammation level with GGT, IBIL and GGT/IBIL.

Results Compared with healthy controls, PsA patients exhibited significantly higher serum GGT, GGT/IBIL, and CRP levels and lower IBIL levels. Serum GGT and GGT/IBIL were positively correlated with CRP, whereas IBIL were negatively correlated with CRP. Binary logistic regression analysis revealed that serum GGT was a risk factor for high CRP in PsA, whereas IBIL was a protective factor. Furthermore, GGT/IBIL was a better indicator of high CRP condition in PsA patients than either GGT or IBIL alone, as determined by the receiver operating characteristic curves.

Conclusion GGT and IBIL may participate in the pathogenesis of PsA. Additionally, GGT, IBIL and the balance of the two may reflect systemic inflammation mediated by oxidative stress events related to metabolic abnormalities to a certain extent.

Keywords Psoriatic arthritis, Gamma-glutamyl transpeptidase, Indirect bilirubin, C-reactive protein, Inflammation

[†]Xu Wang and Yan Mao have contributed equally to this study.

*Correspondence:
Shaomin Shi
dermatologist_shi@163.com
Yaling Liu
yzling_liu1214@126.com
Full list of author information is available at the end of the article

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory joint disease that occurs in approximately 30% of patients with psoriasis [1, 2]. Currently, the pathogenesis of PsA is unclear. However, oxidative stress is considered an important factor associated with the pathogenesis of both psoriasis and PsA [3].

Gamma-glutamyl transpeptidase (GGT) is a crucial enzyme involved in the catabolism of glutathione (GSH), catalyzing the transfer of glutamyl to amino acids [4]. This process produces large amounts of reactive oxygen species (ROS), leading to the development of oxidative stress in the body [5]. The role of GGT in oxidative stress has received increasing attention in recent years, and previous studies have shown that serum GGT can predict the occurrence of metabolic syndrome, cardiovascular malfunctions and other diseases [6, 7]. However, only a few studies have analyzed the GGT expression in patients with PsA. Indirect bilirubin (IBIL) is the final product of heme catabolism. As early as 1987, Stocker et al. [8] suggested that bilirubin may be a natural antioxidant that can effectively eliminate free radicals and participate in the reduction of oxidative stress. It is known to have anti-inflammatory and immunosuppressive properties and plays a protective role in rheumatoid arthritis and polymyositis [9, 10]. Interestingly, previous reports have proposed contrasting roles for serum GGT and IBIL in metabolic syndrome and systemic lupus erythematosus [11, 12]. However, the roles of GGT and IBIL in PsA are currently unknown.

C-reactive protein (CRP) is a sensitive marker that reflects the inflammatory status of the body [13]. Previous studies have concluded that CRP is the best serum indicator of PsA activity [14]. Therefore, in this study, we used CRP as an indicator of the systemic inflammatory response to PsA and investigated the relationships between serum GGT, IBIL, and CRP levels in patients with PsA.

Materials and methods

Patients and healthy controls

We recruited patients with PsA who visited the Third Hospital of Hebei Medical University from January 2016 to December 2021. All patients met the 2006 Classification Criteria for Psoriatic Arthritis (CASPAR) [15]. Exclusion criteria included the following: pregnancy/breastfeeding, alcohol abuse, acute/chronic inflammatory disease, infection or trauma, hepatobiliary disease, renal insufficiency, coronary artery disease, cancer, hemolytic and autoimmune diseases, and treatment with antioxidants, non-steroidal anti-inflammatory drugs, steroidal drugs, immuno- suppressants, or biologics in the month prior to evaluation. Based on these criteria, 68 patients were enrolled in the study group. An additional 73 healthy volunteers were recruited from the physical examination center of our hospital as controls during the same period. Our trials were conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Third Hospital of Hebei Medical University (2022-023-1).

We retrospectively collected the personal and clinical data of all participants, including age, sex, and serum levels of GGT, IBIL, CRP, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Because GGT and IBIL are known to have oxidant and antioxidant properties, respectively, the GGT/IBIL ratio was included as an additional variable in the analysis.

Statistical analysis

All data were analyzed using SPSS 25.0 (SPSS Inc., Chicago, IL, USA). Normally distributed data were presented as mean ± standard deviation, and differences between groups were assessed using Student's *t*-tests. Nonparametric data were described by median values (interquartile range) and subjected to the Mann–Whitney U test. The chi-square test was used to compare the distribution of categorical variables between groups. Relationships between GGT, IBIL, GGT/IBIL, and CRP were analyzed by Spearman's correlation analysis. The effect of GGT and IBIL on the severity of inflammation was evaluated through binary logistic regression. Finally, the receiver operating characteristic (ROC) curves were constructed based on the results of the logistic regression analysis to evaluate the predictive value of GGT, IBIL, and GGT/IBIL for the degree of inflammation in patients with PsA. All tests were two-tailed with a statistical significance threshold of $P < 0.05$.

Results

Baseline characteristics

The characteristics of 68 patients with PsA and 73 healthy controls are presented in Table 1. No significant differences were observed in the age and sex distributions between patients and controls (all $P > 0.05$). The levels of serum GGT, GGT/IBIL, and CRP were significantly higher ($P = 0.036$; $P < 0.001$; $P < 0.001$) in the patient group than in the control group, whereas IBIL concentrations were significantly lower ($P < 0.001$). ALT and AST levels showed no significant differences between the two groups ($P = 0.068$; $P = 0.111$).

Correlations of serum GGT, IBIL, and GGT/IBIL with CRP

Spearman correlation analysis was used to evaluate the associations of serum GGT, IBIL, and GGT/IBIL with CRP. We found that serum GGT levels were positively correlated with serum CRP levels ($r = 0.4427$, $P < 0.001$),

Table 1 Clinical and laboratory data of PsA patients and controls

	PsA patients (n = 68)	Controls (n = 73)	*P*
Gender (male/female)	44/24	38/35	0.128
Age (years)	44.5 (33.0, 54.8)	44.0 (35.0, 51.0)	0.836
CRP (mg/L)	20.8 (6.9, 60.5)	1.5 (1.2, 2.8)	< 0.001
ALT (U/L)	15.5 (11.0, 25.8)	18.0 (12.0, 27.5)	0.068
AST (U/L)	15.0 (14.0, 19.8)	17.0 (15.0, 20.0)	0.111
GGT (U/L)	24.0 (16.3, 36.8)	19.0 (15.0, 30.5)	0.036
IBIL (μmol/L)	6.9 (4.4, 9.3)	10.1 (8.2, 11.9)	< 0.001
GGT/IBIL ratio	3.8 (2.1, 8.3)	2.0 (1.5, 2.9)	< 0.001

GGT, gamma-glutamyl transferase; IBIL, indirect bilirubin; CRP, C-reactive protein; ALT, alanine transaminase; AST, aspartate transaminase. $P < 0.05$ was considered statistically significant

while serum IBIL levels were negatively correlated with serum CRP levels (r = −0.4187, $P < 0.001$). Furthermore, the ratio of GGT/IBIL was positively correlated with CRP levels (r = 0.6292, $P < 0.001$) (Fig. 1a–c).

Relationship between GGT, IBIL, and the degree of inflammatory response in patients with PsA

To assess the relationship between GGT, IBIL levels and inflammation in patients with PsA, we used CRP levels as a measure of the inflammatory response and divided patients into two groups based on their median serum CRP concentration. No significant differences in age, gender, ALT level, or AST level between the CRP-low (PsA1) and CRP-high (PsA2) groups were detected (all $P > 0.05$). Serum GGT levels and GGT/IBIL were significantly higher in the PsA2 group than in the PsA1 group ($P = 0.002$; $P < 0.001$). Conversely, IBIL levels were significantly lower in the PsA2 group than in the PsA1 group ($P = 0.003$; Table 2). Multivariate logistic regression analysis adjusted for age, sex, and ALT, AST, GGT, and IBIL levels revealed that a high GGT level was a risk factor for high systemic inflammation in patients with PsA (OR = 1.073, 95% confidence interval [CI] 1.006–1.145, $P = 0.032$), whereas a high IBIL level was a protective factor (OR = 0.766, 95% CI 0.633–0.928, $P = 0.006$; Table 3). ROC curves showed that the area under the curve (AUC) value for GGT/IBIL ($AUC_{GGT/IBIL} = 0.814$) was higher than that for GGT and IBIL ($AUC_{GGT} = 0.718$; $AUC_{IBIL} = 0.707$) (Fig. 2).

Table 2 Clinical and laboratory data of PsA1 and PsA2 patients

	PsA1	PsA2	*P*
Gender (male/female)	16/18	22/12	0.143
Age (years)	49.0 (34.0, 55.5)	41.5 (32.8, 54.3)	0.286
ALT (U/L)	14.0 (11.0, 19.0)	16.5 (10.0, 27.5)	0.400
AST (U/L)	15.5 (14.0, 18.3)	15.0 (13.0, 20.3)	0.956
GGT (U/L)	22.5 (15.0, 27.0)	33.5 (20.0, 71.5)	0.002
IBIL (μmol/L)	8.7 (5.5, 12.5)	6.1 (3.9, 7.3)	0.003
GGT/IBIL ratio	2.2 (1.5, 4.3)	7.0 (3.1, 14.7)	< 0.001

GGT, gamma-glutamyl transferase; IBIL, indirect bilirubin; ALT, alanine transaminase; AST, aspartate transaminase. $P < 0.05$ was considered statistically significant

Discussion

PsA is a chronic inflammatory joint disease with complex pathogenesis. An increasing number of studies have recently proved that oxidative stress is associated with the pathogenesis of PsA. Firuzi et al. [16] found that plasma peroxide levels were significantly elevated and sulfhydryl levels were decreased in patients with PsA, suggesting that an imbalance of oxidative and antioxidative processes may contribute to PsA pathogenesis. Oxidative stress-associated ROS production triggers the activation of the nuclear factor-kappaB (NF-κB) signaling pathway in dendritic cells, macrophages, and other immune cells, which results in a release of inflammatory cytokines, such as interleukin 1 (IL-1) and tumor necrosis factor-α (TNF-α). These cytokines stimulate osteoclasts to invade adjacent cartilage and mediate bone resorption, leading to joint deformity and loss of function [17–19].

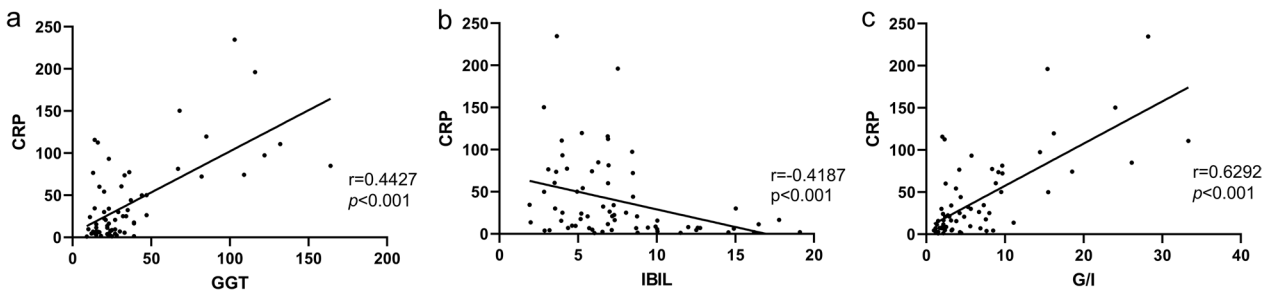

Fig. 1 Correlation between serum GGT, IBIL, and GGT/IBIL with CRP. **a**: Correlation analysis between GGT and CRP; **b**: correlation analysis between IBIL and CRP; **c**: correlation analysis between GGT/IBIL and CRP

Table 3 Logistic regression analysis of the PsA1 and PsA2 patient groups

Parameters	B	SE	Wald	OR	95% CI	*P*
Gender	−0.998	0.664	2.258	0.369	0.100–1.355	0.133
Age	−0.017	0.028	0.377	0.983	0.931–1.038	0.539
ALT	−0.011	0.052	0.047	0.989	0.892–1.095	0.828
AST	−0.065	0.066	0.996	0.937	0.824–1.065	0.318
GGT	0.071	0.033	4.574	1.073	1.006–1.145	0.032
IBIL	−0.266	0.098	7.411	0.766	0.633–0.928	0.006
Constant	2.342	1.751	1.790	10.402	–	0.181

B, estimated coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; GGT, gamma-glutamyl transferase; IBIL, indirect bilirubin; ALT, alanine transaminase; AST, aspartate transaminase. $P < 0.05$ was considered statistically significant

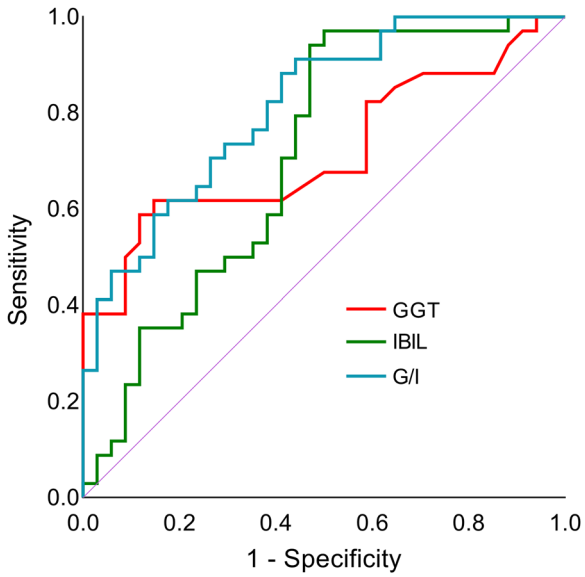

Fig. 2 ROC curve representing effect of GGT, IBIL and GGT/IBIL on inflammatory response in PsA patients

GGT transports glutamyl residues on cell membranes and is responsible for the catabolism of the antioxidant GSH in vivo. Studies have shown that GGT undergoes redox reactions when it hydrolyzes GSH and reduces Fe^{3+}, which can produce large amounts of superoxide anions [4], leading to many events related to oxidative stress in the body. A previous study on coronary artery risk development in young adults suggested that increased serum GGT levels may serve as an early marker of oxidative stress and predict the serum levels of inflammatory factors, such as CRP [20]. Recent studies have demonstrated the involvement of GGT in the pathogenesis of cardiovascular and metabolic syndrome diseases through the oxidative stress reaction, concluding that GGT plays a pro-inflammatory role in these diseases [6, 7]. Furthermore, GGT levels were significantly increased in the inflamed synovial membranes of patients with rheumatoid arthritis. Moreover, injecting anti-GGT monoclonal antibodies into the intraperitoneal cavity of arthritic mice significantly reduced the number of osteoclasts and attenuated bone erosion [21]. Interestingly, GGT is an endogenous activator of Toll-like receptor 4-mediated osteoclastogenesis [22]. Our study builds upon these previous works, as we discovered a positive correlation between the levels of GGT and CRP in patients with PsA, indicating the GGT may serve as a risk factor for PsA-related inflammation.

IBIL is a powerful antioxidant, and the work by Zhao et al. [23] demonstrated that IBIL can directly scavenge superoxide anion radicals at the sites of inflammation. Furthermore, in a mouse model of autoimmune arthritis, exogenous IBIL injections significantly reduced oxidative DNA damage, neutrophil infiltration, and fibrin deposition in the joint cavity, leading to a decrease in inflammation and alleviating the symptoms of joint damage [24]. Additionally, IBIL has been shown to promote the expansion of regulatory T cells [25], which may disrupt the activation and proliferation of autoreactive T cells in PsA, thereby inhibiting the immune response. Moreover, in a study by Balta et al. [26], patients with psoriasis vulgaris exhibited decreased serum IBIL levels and elevated CRP levels, which is consistent with our findings. Thus, we conclude that IBIL plays a protective role in inflammatory and autoimmune diseases, including PsA.

At present, the specific mechanisms underlying the roles of GGT and IBIL in the inflammatory response of patients with PsA are unclear. However, we can glean some insights by connecting the findings of previous reports. The stimulation of bone marrow-derived macrophages with recombinant human GGT1 protein was shown to increase the expression of TNF-α, IL-1β, IL-6, and MIP-1α [22]. Both IL-1β and IL-6 trigger the differentiation of naïve T cells into Th17 cells. These cells secrete IL-17, as a key cytokine driving inflammation in PsA that functions in concert with other

cytokines to increase synovial inflammation [27]. Furthermore, TNF-α and IL-6 activate Th22 cells, which release IL-22. This cytokine activates fibroblast-like synoviocytes through the PI3K-mTOR pathway, thereby inducing osteoclastogenesis [28, 29]. On a related note, Taniguchi et al. [30] demonstrated that in bone marrow stromal cells, GGT stimulates the expression of receptor activator of NF-κB ligand (RANKL), which is a major player in the differentiation of osteoblasts into osteoclasts [31]. In fact, RANKL expression in the synovial membrane was significantly increased in patients with PsA [32]. As an inhibitor of cytoplasmic protein kinase, IBIL could prevent the translocation of NF-κB to the nucleus by blocking the phosphorylation of IκB kinase, which is a master regulator of NF-κB signaling [33, 34]. Besides, NF-κB is also considered to be an important mediator of the pathogenesis of psoriasis [35]. When pro-inflammatory signals downstream of NF-κB are intercepted, the production of inflammatory cytokines such as TNF-α and IL-6 are impaired [36], while IL-6 in turn is the strongest stimulator of CRP formation [37]. The above findings may explain the negative correlation between IBIL and CRP levels identified in our study. Furthermore, our finding that GGT/IBIL was significantly positively correlated with CRP levels suggests that the ratio of GGT to IBIL better reflects the overall inflammatory status of PsA and indicates that the imbalance in oxidation/antioxidation ultimately leads to inflammatory reactions in vivo.

It is important to note that our study is not without limitations. As this was a retrospective study, the prognostic effect of serum GGT and IBIL on PsA could not be evaluated due to the lack of follow-up. In addition, relatively few patients were included in this study, and additional larger-scale studies are required to confirm these findings.

Conclusions

In conclusion, GGT and IBIL may participate in the pathogenesis of PsA. Additionally, GGT, IBIL and the balance of the two may reflect systemic inflammation mediated by oxidative stress events related to metabolic abnormalities to a certain extent.

Acknowledgements
Not applicable.

Author contributions
XW and YM: writing the original manuscript. SS: conception and design. SJ: data collection. HH: performing statistical analysis. QL and LL: revising manuscript content. YL: approving the final version of manuscript. All authors read and approved the final manuscript.

Funding
This research did not receive any specific grants from funding agencies representing the public, commercial, or not-for-profit sectors.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Third Hospital of Hebei Medical University (Ethics number: 2022-023-1) and conducted in accordance to the Declaration of Helsinki principles.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Department of Dermatology, Third Hospital of Hebei Medical University, Shijiazhuang, China.

Received: 31 October 2022 Accepted: 23 October 2023
Published online: 30 October 2023

References

1. van der Heijde D, Gladman DD, Kavanaugh A, Mease PJ. Assessing structural damage progression in psoriatic arthritis and its role as an outcome in research. Arthritis Res Ther. 2020;22:18. https://doi.org/10.1186/s13075-020-2103-8.
2. Chimenti MS, Caso F, Alivernini S, De Martino E, Costa L, Tolusso B, et al. Amplifying the concept of psoriatic arthritis: the role of autoimmunity in systemic psoriatic disease. Autoimmun Rev. 2019;18:565–75. https://doi.org/10.1016/j.autrev.2018.11.007.
3. Lin X, Huang T. Oxidative stress in psoriasis and potential therapeutic use of antioxidants. Free Radic Res. 2016;50:585–95. https://doi.org/10.3109/10715762.2016.1162301.
4. Bulusu S, Sharma M. What does serum gamma-glutamyltransferase tell us as a cardiometabolic risk marker? Ann Clin Biochem. 2016;53:312–32. https://doi.org/10.1177/0004563215597010.
5. Drozdz R, Parmentier C, Hachad H, Leroy P, Siest G, Wellman M. γ-glutamyltransferase dependent generation of reactive oxygen species from a glutathione/transferrin system. Free Radic Biol Med. 1998;25:786–92. https://doi.org/10.1016/s0891-5849(98)00127-0.
6. Emdin M, Pompella A, Paolicchi A. Gamma-glutamyltransferase, atherosclerosis, and cardiovascular disease: triggering oxidative stress within the plaque. Circulation. 2005;112:2078–80. https://doi.org/10.1161/CIRCULATIONAHA.105.571919.
7. Kunutsor SK, Apekey TA, Seddoh D. Gamma glutamyltransferase and metabolic syndrome risk: a systematic review and dose-response meta-analysis. Int J Clin Pract. 2015;69:136–44. https://doi.org/10.1111/ijcp.12507.
8. Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, Ames BN. Bilirubin is an antioxidant of possible physiological importance. Science. 1987;235:1043–6. https://doi.org/10.1126/science.3029864.
9. Juping D, Yuan Y, Shiyong C, Jun L, Xiuxiu Z, Haijian Y, et al. Serum bilirubin and the risk of rheumatoid arthritis. J Clin Lab Anal. 2017;31:8. https://doi.org/10.1002/jcla.22118.
10. Peng Y-F, Zhang L, Pan G-G, Wei Y-S. A potential clinical usefulness of measuring serum bilirubin levels in patients with polymyositis. Eur Rev Med Pharmacol Sci. 2016;20:631–5.
11. Giral P, Ratziu V, Couvert P, Carrie A, Kontush A, Girerd X, et al. Plasma bilirubin and gamma-glutamyltransferase activity are inversely related in dyslipidemic patients with metabolic syndrome: relevance to oxidative stress. Atherosclerosis. 2010;210:607–13. https://doi.org/10.1016/j.atherosclerosis.2009.12.026.
12. Zhang W, Tang Z, Shi Y, Ji L, Chen X, Chen Y, et al. Association between gamma-glutamyl transferase, total bilirubin and systemic lupus

erythematosus in Chinese women. Front Immunol. 2021;12:682400. https://doi.org/10.3389/fimmu.2021.682400.
13. Anderson JL, Carlquist JF, Muhlestein JB, Horne BD, Elmer SP. Evaluation of C-reactive protein, an inflammatory marker, and infectious serology as risk factors for coronary artery disease and myocardial infarction. J Am Coll Cardiol. 1998;32:35–41. https://doi.org/10.1016/s0735-1097(98)00203-4.
14. Nell-Duxneuner VP, Stamm TA, Machold KP, Pflugbeil S, Aletaha D, Smolen JS. Evaluation of the appropriateness of composite disease activity measures for assessment of psoriatic arthritis. Ann Rheum Dis. 2010;69:546–9. https://doi.org/10.1136/ard.2009.117945.
15. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54:2665–73. https://doi.org/10.1002/art.21972.
16. Firuzi O, Fuksa L, Spadaro C, Bousova I, Riccieri V, Spadaro A, et al. Oxidative stress parameters in different systemic rheumatic diseases. J Pharm Pharmacol. 2006;58:951–7. https://doi.org/10.1211/jpp.58.7.0010.
17. Yang Z, Min Z, Yu B. Reactive oxygen species and immune regulation. Int Rev Immunol. 2020;39:292–8. https://doi.org/10.1080/08830185.2020.1768251.
18. Zhou Q, Mrowietz U, Rostami-Yazdi M. Oxidative stress in the pathogenesis of psoriasis. Free Radic Biol Med. 2009;47:891–905. https://doi.org/10.1016/j.freeradbiomed.2009.06.033.
19. Sucur A, Jajic Z, Artukovic M, Matijasevic MI, Anic B, Flegar D, et al. Chemokine signals are crucial for enhanced homing and differentiation of circulating osteoclast progenitor cells. Arthritis Res Ther. 2017;19:142. https://doi.org/10.1186/s13075-017-1337-6.
20. Lee DH, Jacobs DR Jr, Gross M, Kiefe CI, Roseman J, Lewis CE, et al. Gamma-glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Clin Chem. 2003;49:1358–66. https://doi.org/10.1373/49.8.1358.
21. Ishizuka Y, Moriwaki S, Kawahara-Hanaoka M, Uemura Y, Serizawa I, Miyauchi M, et al. Treatment with anti-gamma-glutamyl transpeptidase antibody attenuates osteolysis in collagen-induced arthritis mice. J Bone Miner Res. 2007;22:1933–42. https://doi.org/10.1359/jbmr.070726.
22. Moriwaki S, Into T, Suzuki K, Miyauchi M, Takata T, Shibayama K, et al. gamma-Glutamyltranspeptidase is an endogenous activator of Toll-like receptor 4-mediated osteoclastogenesis. Sci Rep. 2016;6:35930. https://doi.org/10.1038/srep35930.
23. Zhao C, Huang H, Pan Q, Huang W, Peng W, Xu H, et al. Unconjugated bilirubin attenuates DSS-induced colitis potentially via enhancement of bilirubin reabsorption. Front Pharmacol. 2021;12:654808. https://doi.org/10.3389/fphar.2021.654808.
24. Sykora T, Babal P, Mikus-Kuracinova K, Drafi F, Ponist S, Dvorakova M, et al. Hyperbilirubinemia maintained by chronic supplementation of unconjugated bilirubin improves the clinical course of experimental autoimmune arthritis. Int J Mol Sci. 2021. https://doi.org/10.3390/ijms22168662.
25. Rocuts F, Zhang X, Yan J, Yue Y, Thomas M, Bach FH, et al. Bilirubin promotes de novo generation of T regulatory cells. Cell Transplant. 2010;19:443–51. https://doi.org/10.3727/096368909X484680.
26. Balta S, Balta I, Mikhailidis DP, Ozturk C, Demirkol S, Celik T, et al. Bilirubin levels and their association with carotid intima media thickness and high-sensitivity C-reactive protein in patients with psoriasis vulgaris. Am J Clin Dermatol. 2014;15:137–42. https://doi.org/10.1007/s40257-014-0069-5.
27. Benham H, Norris P, Goodall J, Wechalekar MD, FitzGerald O, Szentpetery A, et al. Th17 and Th22 cells in psoriatic arthritis and psoriasis. Arthritis Res Ther. 2013;15:R136. https://doi.org/10.1186/ar4317.
28. Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. The Lancet. 2018;391:2273–84. https://doi.org/10.1016/s0140-6736(18)30830-4.
29. Mitra A, Raychaudhuri SK, Raychaudhuri SP. IL-22 induced cell proliferation is regulated by PI3K/Akt/mTOR signaling cascade. Cytokine. 2012;60:38–42. https://doi.org/10.1016/j.cyto.2012.06.316.
30. Niida S, Kawahara M, Ishizuka Y, Ikeda Y, Kondo T, Hibi T, et al. Gamma-glutamyltranspeptidase stimulates receptor activator of nuclear factor-kappaB ligand expression independent of its enzymatic activity and serves as a pathological bone-resorbing factor. J Biol Chem. 2004;279:5752–6. https://doi.org/10.1074/jbc.M311905200.
31. Ash P, Loutit JF, Townsend KM. Osteoclasts derived from haematopoietic stem cells. Nature. 1980;283:669–70. https://doi.org/10.1038/283669a0.
32. Ritchlin CT, Haas-Smith SA, Li P, Hicks DG, Schwarz EM. Mechanisms of TNF-alpha- and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis. J Clin Investig. 2003;111:821–31. https://doi.org/10.1172/JCI16069.
33. Jangi S, Otterbein L, Robson S. The molecular basis for the immunomodulatory activities of unconjugated bilirubin. Int J Biochem Cell Biol. 2013;45:2843–51. https://doi.org/10.1016/j.biocel.2013.09.014.
34. Hansen TW, Mathiesen SB, Walaas SI. Bilirubin has widespread inhibitory effects on protein phosphorylation. Pediatr Res. 1996;39:1072–7. https://doi.org/10.1203/00006450-199606000-00023.
35. Goldminz AM, Au SC, Kim N, Gottlieb AB, Lizzul PF. NF-kappaB: an essential transcription factor in psoriasis. J Dermatol Sci. 2013;69:89–94. https://doi.org/10.1016/j.jdermsci.2012.11.002.
36. Oeckinghaus A, Ghosh S. The NF-kappaB family of transcription factors and its regulation. Cold Spring Harb Perspect Biol. 2009;1:a000034. https://doi.org/10.1101/cshperspect.a000034.
37. Holzinger D, Foll D. Biomarkers for chronic inflammatory diseases. Z Rheumatol. 2015;74:887–96. https://doi.org/10.1007/s00393-015-0009-7. (**quiz 97**).

Publisher's Note