

Research Progress on the correlation between MAFLD and psoriasis

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Abstract: In recent years, clinical and animal studies have confirmed that metabolic associated fatty liver disease (MAFLD) is a multisystem disease. The extrahepatic complications of MAFLD, including cardiovascular disease, tumors, metabolic nephropathy, obstructive apnea syndrome, osteoporosis, psoriasis, iron overload, and various metabolic and endocrine diseases, are closely related. The incidence of these diseases is far higher than that of the liver disease itself. This article provides a comprehensive review of the correlation between MAFLD and psoriasis. Studies have shown that MAFLD is a common disease in adult patients with psoriasis. MAFLD is associated with a higher likelihood of developing metabolic syndrome and more severe skin disease in patients with psoriasis. In addition, patients with psoriasis are more likely to develop more severe MAFLD. However, further research is needed to clarify the biological mechanisms of MAFLD and psoriasis. Healthcare providers of patients with psoriasis should watch for the development of this liver disease. The coexistence of MAFLD should also be considered when planning treatment, because of the potential hepatotoxic effects of some conventional drugs for the treatment of psoriasis.

Key words: metabolic associated fatty liver disease, extrahepatic complication, psoriasis.

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Abbreviations: MAFLD, metabolic associated fatty liver disease; IR, insulin resistance; TNF- α , Tumor necrosis factor- α ; IL-6, interleukin-6; HDL, high density lipoprotein; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; MetS, metabolic syndrome; MASH, metabolic-associated steatohepatitis; PASI, psoriasis area and index; OR, odds ratio; CI, confidence interval.

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Introduction

Psoriasis is a chronic inflammatory autoimmune skin disease. The formation and maintenance of psoriasis plaque depends on the patient's innate and adaptive immunity. The correlation between metabolic associated fatty liver disease (MAFLD) and psoriasis has been gradually recognized and valued, and some new progress has been made in recent years.

Research status of correlation between MAFLD and psoriasis

Psoriasis is one of the most common skin diseases in Western countries, with an incidence rate of approximately 2%–3%. The involvement of psoriasis is usually not limited to the skin, but also includes other manifestations, such as arthropathy, uveitis, and inflammatory bowel disease. In patients with psoriasis, the prevalence of metabolic syndrome is higher in individuals aged over 40 years; this correlation is directly proportional to the severity of psoriasis and has nothing to do with obesity. Therefore, metabolic syndrome is associated with both MAFLD and psoriasis-- that is to say, the prevalence of MAFLD is increased in patients with psoriasis. Two recent meta-analyses confirmed these data by estimating the risk of MAFLD in patients with psoriasis to be twice of that in controls; this risk seems to be greater in patients with more severe psoriasis or patients with psoriatic arthritis. In addition, a retrospective cohort study of 29957 children with psoriasis revealed a higher risk of obesity, metabolic syndrome, MAFLD and elevated liver enzyme levels in this population than in children without psoriasis. However, there is no epidemiological study on the prevalence and incidence rate of psoriasis in patients with MAFLD [1-4].

The exact pathophysiological mechanism of psoriasis and MAFLD is unclear; however, insulin resistance (IR), which plays a central role in MAFLD, is a common pathophysiological mechanism in patients with psoriasis. The strong infrared activity of MAFLD and psoriasis affects inflammatory adipocytokines. Tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and leptin are the physiological and pathological basis of inducing persistent low-grade inflammation. They have been found to increase the incidence of nonalcoholic fatty liver in human and animal models, leading to infrared and uncontrolled lipolysis. In patients with psoriasis and MAFLD, intake of etanercept (a TNF- α inhibitor) seems to prevent liver fibrosis, reduce transaminase levels, and improve IR; this supports the hypothesis that the pathophysiological connection between the two diseases is through changes in glucose homeostasis and cytokine imbalance. A subsequent study of patients with psoriasis who were treated with etanercept for 24

weeks showed that the imbalance between pro-inflammatory and anti-inflammatory cytokines was partially resolved and the level of serum adipocytokines decreased; finally, after only one week of treatment with etanercept, insulin sensitivity, high density lipoprotein (HDL), apo A1, and apo B: apo A1 ratio results revealed beneficial regulatory effects. Anti-TNF drugs that have been used to treat psoriasis in patients with MAFLD, such as infliximab and adalimumab, were further evaluated; these preliminary studies showed a good effect on liver inflammation and fibrosis [5].

Leptin, a hormone that regulates appetite and weight, has been found to be increased in obese patients due to leptin resistance. Elevated serum leptin levels were found in NAFLD and psoriasis, and this seems to promote the development of fatty liver, mediate skin proliferation and the anti-apoptotic process of T cells, and increase the secretion of proinflammatory cytokines by keratinocytes. Several studies have shown that anti-hyperglycemic drugs (e.g., glucagon-like peptide-1 [GLP-1] receptor agonists, dipeptidyl peptidase-4 [DPP-4] inhibitors, thiazolidinediones) play an anti-psoriatic role without affecting weight loss and blood glucose control by targeting keratinocyte proliferation and skin inflammation. Furthermore, it has been reported that treatment with pioglitazone and ursodeoxycholic acid may improve the skin lesions in psoriasis and liver injury in MAFLD; however, further research is needed to clarify the effectiveness of this treatment [6,7].

Although both MAFLD and psoriasis are associated with metabolic syndrome (MetS), the prevalence of MAFLD is higher in patients with psoriasis than in those without psoriasis. In a population-based prospective cohort study, 118 (5.1%) of 2292 participants aged 55 years or older had psoriasis. The prevalence of MAFLD was higher in patients with psoriasis than those without (46.2% vs. 33.3%), even after adjusting for tobacco and alcohol use, MetS composition, and alanine aminotransferase levels.

There may also be a higher risk of severe liver fibrosis. In a small study of 109 patients with psoriasis, the overall prevalence of biopsy-confirmed metabolic-associated steatohepatitis (MASH) was 22% [9]; thus, the presence of MAFLD in psoriasis may also be related to the severity of psoriasis. However, it is not clear whether the incidence of psoriasis in patients with MAFLD or MASH is increasing. Future epidemiological studies are needed to assess whether there is a causal relationship between MAFLD and psoriasis. In view of the current observation data, MAFLD is highly prevalent in patients with psoriasis and improves the incidence rate of psoriasis. Clinical understanding of the population potential of NAFLD is necessary [8].

Epidemiological evidence of MAFLD and

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psoriasis

The literature showed that the prevalence of MAFLD in patients with psoriasis was almost twice as high as that in the control group (47% vs. 28%, $P < 0.001$). Even after excluding subjects who drank less than 30 grams of alcohol per day, the difference remained significant (37% vs. 21%; $P < 0.01$). Circulating C-reactive protein, IL-6, and adiponectin levels were also higher in patients with psoriasis and MAFLD than in patients without MAFLD. After adjusting for many cardiovascular metabolic risk factors, MAFLD was associated with a higher clinical severity of psoriasis. In another retrospective study, the prevalence of MAFLD was 59.2% in an outpatient cohort of 142 adult patients with psoriasis. Although there was no difference in psoriasis area and index (PASI) scores between patients with and without MAFLD, the former were more likely to have psoriatic arthritis and more severe MAFLD, according to the noninvasive estimation of their MAFLD fibrosis score. Unfortunately, liver biopsy data were available for only five patients with psoriasis, although three cases were histologically confirmed as MASH [2,3].

It should be noted that multivariate regression analysis showed that patients with psoriasis were 70% more likely to develop MAFLD than patients without psoriasis (odds ratio [OR] 1.70, 95% confidence interval [CI] 1.1–2.6, $P = 0.01$), with adjustment for metabolic syndrome and other common risk factors of MAFLD. In the subsequent analysis of the same cohort, it was reported that the prevalence of advanced liver fibrosis detected by transient elastography in patients with psoriasis was higher than that in patients without psoriasis (8.1% vs. 3.6%, $P < 0.05$). Patients with psoriasis were twice as likely to develop advanced liver fibrosis than healthy individuals (adjusted OR 2.57, 95% CI 1.0–6.6). Similarly, a smaller case-control study by Gisondi et al. revealed a higher MAFLD fibrosis score (i.e., a noninvasive scoring system for identifying advanced liver fibrosis) in patients with psoriasis than in the control group. The researchers concluded that psoriasis is predictive of advanced liver fibrosis, independent of metabolic syndrome characteristics and other potential confounding factors. In addition, similar to previous studies, the study also demonstrated that the PASI scores of patients with NAFLD were significantly higher than those of patients without MAFLD [10–11].

Available data show that the prevalence of MAFLD in patients with psoriasis is very high (affecting 50% of patients), regardless of coexisting MetS components. In addition, the relatively late stage of MASH upon biopsy in patients with psoriasis indicates an increased risk of long-term liver-related complications in this population. Therefore, current evidence suggests that the presence of MAFLD in patients with chronic plaque psoriasis should be monitored and evaluated

carefully [9].

Potential biological mechanism of psoriasis and MAFLD

So far, the connection mechanism between MAFLD and psoriasis remains complex and poorly understood. However, determining the pathophysiological mechanism of these two diseases is clinically significant because it may provide hope for new pharmacological methods.

Psoriasis and MAFLD have a variety of inflammatory and cytokine-mediated mechanisms, and share part of an interesting network of genetic, clinical, and pathophysiological characteristics. In fact, it can be assumed that the relationship between MAFLD and psoriasis is multifactorial, including genetic and environmental factors, and often overlaps with metabolic abnormalities.

Psoriasis and MAFLD are closely associated with visceral obesity and insulin resistance; therefore, it is difficult to distinguish the individual contribution of MAFLD to the inflammatory and metabolic manifestations of psoriasis. Although the direction of the relationship between MAFLD and psoriasis has yet to be clearly defined, it is conceivable that there are several proinflammatory cytokines (e.g., IL-6, IL-17, IL-1, IL-2, IL-3, TNF- α) that are secreted locally by lymphocytes and keratinocytes into the skin of patients with psoriasis and may be at least partially involved in the pathogenesis of systemic insulin resistance. Patients with psoriasis with a high degree of insulin resistance tend to be those with coexisting MAFLD. There is no doubt that expansion and inflammation (dysfunction) of visceral adipose tissue play a key role in the development of insulin resistance, chronic inflammation, and MAFLD. These processes may increase various hormones and proinflammatory adipocytokines (including TNF) by secreting a variety of factors, such as non-esterified fatty acids, IL-6, leptin, visfatin, and resistin. In the case of obesity and insulin resistance, the amount of non-esterified fatty acids flowing into the liver increases. There is sufficient evidence that non-esterified fatty acids play a key role in directly promoting liver injury by increasing intrahepatic oxidative stress and activating inflammatory pathways. The central role of hepatocyte factor production in the progression of MAFLD has been studied; cytokines may replicate all histological features related to MASH, including neutrophil chemotaxis, hepatocyte necrosis, and stellate cell activation. It can be considered that in insulin resistance, the increased release of non-esterified free fatty acids from dilated and dysfunctional adipose tissue may also exacerbate the inflammatory skin injury in psoriasis. However, there is no reliable data to show the direct pathogenic role of non-esterified fatty acids in the pathogenesis of psoriasis. To better clarify

this problem, further research is required [12,13].

Thus far, increasing evidence shows that MAFLD, especially its necrotizing inflammation and progressive form (MASH), may aggravate insulin resistance and easily lead to atherosclerotic dyslipidemia. The release of numerous pro-inflammatory, pro-coagulant, pro-oxidative, and pro-fibrotic mediators (e.g., C-reactive protein, IL-6, fibrinogen, plasminogen activator inhibitor-1, transforming growth factor- β) may play an important role in the pathophysiology of psoriasis. It may adversely affect the severity of psoriasis through increased keratinocyte proliferation, increased inflammation, and upregulation of various vascular adhesion molecules. The experiment also showed that oxazolinone-induced skin inflammation in mice with MAFLD was more evident than that in normal mice; oxazolinone stimulation significantly increased ear weight, nuclear factor- κ B activity, and histological characteristics of skin inflammation in these mice [12,14,15].

The oxazolidone-induced skin inflammation model is not specifically used to study the pathogenesis of psoriasis. However, this simple model can be used to evaluate new strategies for the treatment of NAFLD with coexisting skin inflammation, and to understand the relationship between the two diseases.

Conclusion

Although the published evidence is limited to observational (cross-sectional and case-control) studies, an increasing amount of clinical evidence shows a close relationship between MAFLD and psoriasis. Studies have shown that MAFLD is a very common disease in adult patients with psoriasis (affecting 50% of patients), and patients with both psoriasis and MAFLD are more likely to develop metabolic syndrome and more severe skin disease than patients without MAFLD. In addition, patients with psoriasis are more likely to develop more severe MAFLD, with approximately a quarter of patients with psoriasis developing MASH during the onset; however, determining whether MAFLD is only an epiphytic phenomenon of the coexistence of metabolic syndrome or an independent risk factor for the occurrence and development of psoriasis requires further research. Similarly, further research is needed to clarify the biological mechanisms of MAFLD and psoriasis. This new concept of "liver dermal axis" special mediators need further research to discover innovative drugs and treatments.

Simultaneously, in view of the close relationship between MAFLD and psoriasis, we believe that healthcare providers of patients with psoriasis should pay attention to the development of this potential progressive liver disease. The coexistence of MAFLD should also be considered when planning treatment, because of the potential hepatotoxic effects of some

conventional drugs for the treatment of psoriasis.

These findings suggest that patients with psoriasis should be screened for MAFLD regularly, and physicians should consider referring these patients to liver experts for further evaluation. At present, the best method of screening is liver ultrasonography and transient elastography, combined with the MAFLD fibrosis score or other non-invasive fibrosis scoring systems. This can be used as a first-line option to identify patients with suspected MASH in patients with psoriasis, prior to a biopsy. In addition, all these patients should be followed up regularly to monitor the development of liver-related, metabolic, and cardiovascular complications [16-19].

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