

# Role of Fetuin-A in the Pathogenesis of Psoriasis and Its Potential Clinical Applications

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**Abstract:** Fetuin-A is a plasma glycoprotein exhibiting multifaceted physiological and pathological functions. It has been determined to be involved in various essential biological functions, such as regulation of calcium metabolism, osteogenesis, and insulin signaling pathway. It also plays a crucial role in the pathogenesis of several disorders, including psoriasis. Psoriasis is a chronic systemic inflammatory disorder caused by a constellation of environmental, immunogenic, and genetic factors. It has been shown that dysregulation of cytokines mediated immune response is responsible for the development of psoriasis. Several recent publications suggest that dysregulation of fetuin-A correlates with psoriasis disease activities, revealing its putative role in the development of psoriasis. Furthermore, clinical application of fetuin-A as a diagnostic marker, prognostic predictor, and therapeutic target for different clinical conditions is in progress, and some are showing promising outcomes. This review primarily focuses on the current understanding of the role of fetuin-A in the pathogenesis of psoriasis and its potential clinical applications, with a brief highlight of psoriasis epidemiology and burden. The information was gathered systematically from various journals via electronic searches using various search engines: PubMed, Google Scholar, HINARI, and Cochrane Library from inception to 2022. The studies involved were restricted to English language. Conversely, articles written in other languages, studies done on fetuin B, or studies conducted on other dermatological diseases were excluded from the review article.

**Keywords:** fetuin-A, role of fetuin-A, psoriasis, pathogenesis, clinical applications

## Introduction

Fetuin-A, also known as alpha2 Heremans-Schmid glycoprotein (AHSG), is a 60 kDa negatively charged plasma protein encoded by a gene located on the 3q27 chromosome and primarily expressed by hepatocytes. It is a dimeric protein possessing a 282 amino acid long A-chain and a 27 amino acid residue B-chain, linked by a single inter-disulfide bond.<sup>1-4</sup> Fetuin-A is a pleiotropic protein that exhibits multifaceted physiological and pathological functions by binding with a plethora of receptors, such as insulin, TGF- $\beta$ , and TLR receptors.<sup>1,5,6</sup> It has been discovered to be involved in myriads of biological activities, including regulation of calcium metabolism, osteogenesis and the insulin signaling pathway. Fetuin-A possesses cystatin-like domains that potentially inhibit the activities of cysteine proteinases, such as papain, calpain, cathepsin, and the caspase family.<sup>7,8</sup> Fetuin-A has also been found to play a key role in the development of various clinical conditions, including psoriasis.<sup>9</sup>

Psoriasis is a common inherited, chronic, and recurrent inflammatory disorder of the skin characterized by rounded, erythematous, dry, scaling patches.<sup>10</sup> It is a complex autoimmune disorder manifested by heightened epidermopoiesis (hyperproliferation) and aberrant differentiation (hyperkeratosis) of keratinocytes, infiltrative inflammatory cells in the dermis and epidermis, and vasodilation of dermal vessels in skin lesions, resulting in sharply demarcated erythematous

squamous papules and plaques.<sup>11</sup> These lesions have a predilection for nails, scalp, genitalia, extensor surfaces, and the lumbosacral region. It ranges in severity from a few scattered red, scaly plaques to virtually the entire body surface being affected. It may get worse with age, or wax and wane in its severity depending on genetic and environmental factors.<sup>12,13</sup> Psoriasis is found to be triggered by chronic inflammation induced by the continual release of immunological mediators and cytokines.<sup>14</sup> Although the dysregulation of the immune system induces the disease's development, the clear immunopathogenesis of psoriasis has yet to be clearly elucidated. Currently, fetuin-A has been discovered to exhibit a novel putative role in the development of psoriasis. In light of its pathological role in the development of psoriasis, the clinical application of fetuin-A as a diagnostic marker and therapeutic target in psoriasis is nowadays in progress. Thus, this review primarily discusses the role of fetuin-A in the pathogenesis of psoriasis and its potential clinical applications.

Studies were systematically searched from various journals via electronic searches using different search engines: PubMed, Google Scholar, HINARI, and Cochrane Library using keywords: fetuin-A, alpha2 Heremans-Schmid Glycoprotein, structure of fetuin-A, functions of fetuin-A, psoriasis, epidemiology of psoriasis, comorbidities of psoriasis, role of fetuin-A in psoriasis, burden of psoriasis, pathogenesis of psoriasis, and clinical application of fetuin-A in psoriasis. All studies regarding fetuin-A in psoriasis were included in the study. Besides, articles providing data on psoriasis prevalence, comorbidities, and burden were included in the review. The studies involved were restricted to the English language. Conversely, articles written in languages other than English, studies done on fetuin B, or studies conducted on other dermatological diseases were excluded from the review article.

## Overview on the Epidemiology and Burden of Psoriasis

Even though the worldwide epidemiological data on psoriatic disease is poorly understood, psoriasis affects nearly 2–3% of the global population.<sup>15</sup> Available data indicate that the occurrence of psoriasis varies according to age and geographic region (countries). Psoriasis is generally a common disease, with its higher estimates in adults than in other age groups, such as children.<sup>13</sup> In adults, the estimates of psoriasis prevalence range between 0.91% and 8.5%, while its incidence rate varies from 30.3/100,000 to 321/100,000 person-years.<sup>13,15</sup> In children (age <18 years), the prevalence of psoriasis ranges from 0.0% to 2.1% and the incidence estimate reported was 40.8/100,000 person-years.<sup>13</sup> On the other hand, the prevalence of psoriasis ranges from 0.14% in East Asia to 1.10–1.50% in high-income southern Latin and North America, 1.83–1.92% in central and western Europe, and 1.99% in Australia. The proportion of psoriasis is higher in high-income countries, reaching 3.2% in the US and 8–11% in some European countries, with the onset most frequently occurring between 15 and 35 years of age.<sup>16,17</sup>

Psoriasis is found to have a significant impact on global healthcare systems and inflicts enormous burdens on economic, social, and private life, resulting in a low overall quality of life.<sup>15,18</sup> The burden of psoriasis is generally greatest in the age group of 60–69 years, with a disproportionately greater burden in high-income countries.<sup>15</sup> Despite the fact that psoriasis is physically and emotionally debilitating and devastating on its own, the occurrence of comorbidities, such as metabolic diseases, cardiovascular diseases (CVD), inflammatory diseases, and psychiatric illness (depression/anxiety) in psoriatic patients increases the burden of the disease.<sup>17,19,20</sup> Psoriatic patients with comorbidities are more likely to seek urgent care, have higher hospitalization rates and more frequent outpatient visits, and incur greater costs than those without comorbidities.<sup>20</sup> The burden of these comorbidities is even worse as the severity of psoriasis increases.<sup>19,21</sup>

## Pathophysiology of Psoriasis and the Role of Fetuin-A

### Pathophysiology of Psoriasis

The pathogenesis and the precise mechanisms underlying psoriatic disease are complex and multifactorial. Even though further elucidating research is needed, the interplay between genetic, environmental, and immunologic factors is thought to be involved in the pathogenesis of the disease.<sup>22,23</sup> Several risk factors have been identified to be involved in the development of psoriasis, including family history and environmental risk factors such as smoking, stress, obesity, and alcohol consumption.<sup>24</sup> More importantly, chronic inflammation mediated by immunological mediators and inflammatory cytokines is found to be a major player in the pathophysiology of psoriasis.<sup>14,25</sup> The cytokines, chemokines, and inflammatory mediators that are involved in psoriasis development are chiefly produced by keratinocytes and immune

cells such as T-cells, neutrophils, monocytes, macrophages, hepatocytes, epithelial, and endothelial cells.<sup>26</sup> Although there are several possible interactions between these cell types that could have a significant impact on psoriasis, it is likely that a cascade of cytokines secreted by various cells in the local environment of the psoriatic plaque plays a central role in the phenotypic responses in psoriasis.<sup>27</sup>

More importantly, psoriasis is a T-cell mediated immunological condition primarily driven by cytokines and chemokines released by activated T-helper 1 (Th1) and Th17 lymphocytes.<sup>14</sup> The key pathomechanism of psoriatic lesion is the immune mediated keratinocyte changes by T-cells and secretions of other inflammatory cells. The T-cell secreted inflammatory cytokines such as TNF- $\alpha$ , interleukin-1 (IL-1), IL-2, IL-6, IL-8, IL-17, and IL-23 increase the release of chemokines, epidermal growth factor (EGF), and TGF- $\beta$ 1.<sup>28</sup> These factors regulate the migration of new inflammatory cells into the skin and increase the activity of these cells and keratinocytes, resulting in psoriasis.<sup>14</sup> Besides, inflammatory cytokines such as IL-1 are linked with proteolysis, signal transduction, adhesion, proliferation, and epidermal differentiation, implying their essential role in the initiation and formation of psoriatic lesions.<sup>29</sup> The pathogenesis of psoriasis also contains an autoimmune facet that presents as autoreactive T-cells, as evident from the association of psoriasis with several autoimmune diseases and the detection of autoreactive T-cells in patients.<sup>30,31</sup>

Psoriasis is not solely a disease involving the skin, but it is a systemic disease that also affects many other parts of the body, such as the joints, cardiovascular system, and central nervous system.<sup>22</sup> Due to the chronic nature of psoriatic disease, it has been observed to be associated with a wide range of comorbidities such as psoriatic arthritis, atherosclerosis, insulin resistance (IR), type 2 diabetes mellitus, obesity, hypertension, dyslipidemia, metabolic syndrome, CVD, stroke, osteoporosis, respiratory diseases, gastrointestinal diseases, autoimmune diseases, inflammatory bowel diseases, malignancies (lymphoma and skin cancers), infectious disease (hepatitis C virus), and bullous pemphigoid.<sup>15,17,32–39</sup> All different manifestations (comorbidities) of psoriatic disease show common pathogenetic, immunological, and metabolic signatures.<sup>40–42</sup> Although the exact mechanism underlying the comorbidities of psoriasis remains blurred, systemic chronic inflammation has been reported to be involved in their pathophysiology. Proinflammatory cytokines spill over from the active lesions of psoriasis into the bloodstream, and causing inflammation in distant tissues or comorbidities, which is known as the “psoriatic march”.<sup>43,44</sup> These inflammatory cytokines that are involved in psoriasis pathology are thought to cause endothelial injury, immunological dysregulation, and metabolic changes, thereby deriving comorbidities.<sup>14</sup>

Multiple epidemiological studies outline a possible correlation between psoriasis and respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and airway infections.<sup>45–47</sup> Respiratory diseases share common inflammatory pathogenic mechanisms with other psoriasis comorbidities.<sup>48</sup> The systemic state of inflammation caused by psoriasis acts de novo on respiratory tissues and heightens the preexisting inflammation from asthma or COPD.<sup>49–51</sup> Several immunogenetic studies have also suggested that the coexistence of psoriasis and CVD is caused by resistance-induced release of inflammatory markers such as TNF- $\alpha$  and IL-6 leading to skin inflammation.<sup>52–55</sup>

Moreover, psoriatic arthritis is a systemic inflammatory arthritis affecting about 30% of the psoriatic patients, with more prevalence in those with more extensive skin disease.<sup>56</sup> Dysregulation of the immune response, such as T-cell over-activation has also been proposed as a cause for the coexistence of psoriasis and psoriatic arthritis.<sup>49</sup> Furthermore, psoriasis also coexists with bullous pemphigoid and their association is found to be bidirectional. A large-scale population-based study by Kridin et al. confirms that patients with bullous pemphigoid are 2.6-times more at risk of psoriasis, while patients with a prior psoriasis history are 1.5-times more likely to have bullous pemphigoid compared to those without psoriasis.<sup>39</sup> The pathogenesis underlying this association is largely uncertain, but the generation of autoantibodies against the basement membrane, the release of neutrophil secreting metalloproteases that break down matrix proteins, cytokines, and T-cell polarization are factors involved in the coexistence of bullous pemphigoid and psoriasis.<sup>39</sup>

## The Role of Fetuin-A in the Pathogenesis of Psoriasis

Currently, a plethora of recent data report a strong correlation between fetuin-A and psoriasis disease activity, suggesting involvement in psoriasis pathogenesis though its role is still not entirely clear (Table 1).<sup>25,57</sup> A substantial body of data found that people with psoriasis had significantly lower levels of fetuin-A than healthy controls.<sup>58–62</sup> This result is in

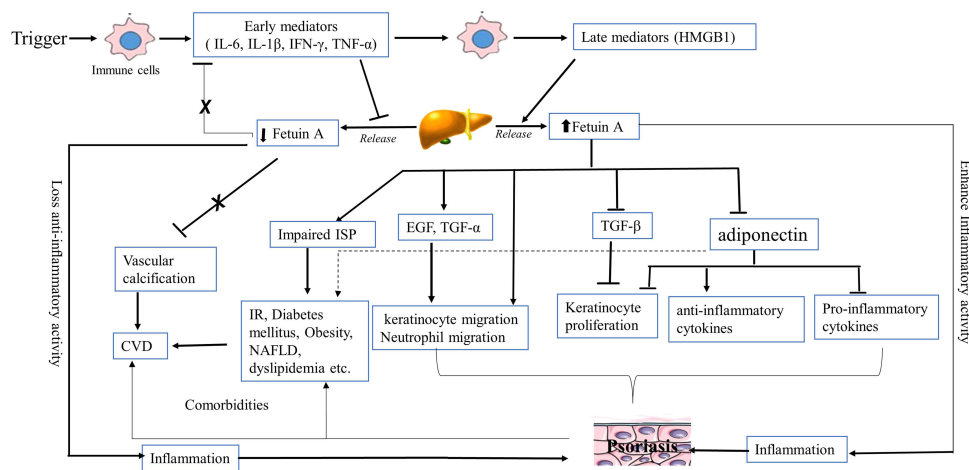
**Table 1** A Summary Table on the Relationship Between Fetuin-A and Psoriasis

Studies	Sample Size	Findings	Reference
Demirbaş et al 2020	158 (80 patients with psoriasis and 78 controls)	Fetuin-A values were found to be statistically and significantly higher in psoriasis patients. But no detected correlation between Fetuin-A and PASI scores.	[57]
Uyar et al 2015	136 (70 patients and 66 controls)	A significantly lowered fetuin-A levels were found in patients with psoriasis compared with healthy controls. But there were no observed significant correlations between fetuin-A and PASI scores	[69]
Borsky et al 2021	50 (28 patients and 22 controls)	In the group of persons with psoriasis, there was a significantly decreased serum level of fetuin-A compare to healthy controls	[58]
Genc et al 2016	80 (40 Patients and 40 healthy volunteers)	Fetuin-A levels in psoriasis patients were found to be low; however, they did not find any association between levels of fetuin-A and disease severity.	[59]
Uysal et al 2014	88 participants (58 patients and 30 controls)	There was a significantly higher level of fetuin-A in patients with psoriasis than the control group. Fetuin A values were positively correlated with PASI score.	[25]
Gulle et al 2021	154 (97 patients and 57 controls)	Fetuin-A levels were significantly down-regulated in patients with psoriatic arthritis. There were significant correlations between fetuin-A levels and PASI score	[60]
Gerdes et al 2014	159 (79 patients and 80 controls)	A significantly lowered fetuin-A levels were observed in patients with psoriasis compared with healthy controls	[63]
Okan et al 2016	90 (45 patients and 45 controls)	Elevated levels of fetuin A in psoriatic patients than control groups. Fetuin-A levels were significantly correlated with PASI score,	[26]
Shehata et al 2020	80 (40 patients and 40 controls)	The mean serum levels of fetuin-A were significantly lower in patients with Psoriasis vulgaris than the healthy control groups. No significant correlation was found between serum level of fetuin A and PASI score.	[61]
Grochowicz et al 2021	88 (60 psoriatic patients and 28 non-psoriatic skin disease as controls)	The concentration of fetuin-A was significantly higher in psoriasis than the control group.	[70]
Agamia et al 2019	45 (30 patients and 15 age- and sex-matched controls)	Patients with psoriasis demonstrated a significantly lower fetuin-A than controls. Psoriasis area and severity index score showed no significant correlation with fetuin-A levels.	[62]

**Abbreviation:** PASI, Psoriasis Area and Severity Index.

accordance with the findings of another study that reported significantly lower mean serum values of fetuin-A in patients with psoriasis compared to the healthy control groups.<sup>63</sup> The systemic levels of fetuin-A are down regulated in patients with psoriasis, most likely due to psoriasis-related inflammation (negative acute phase reactant). This is in agreement with Ataseven et al that reported an inverse relationship between serum levels of fetuin-A and CRP in psoriatic patients.<sup>64</sup>

According to different rat and human studies, the gene expression of fetuin-A is reduced by inflammation-induced inhibition of active HMGBP1 release and subsequent expression of inflammatory cytokines (Figure 1).<sup>63,65</sup> Inflammatory cytokines such as IL-6, IL-1 $\beta$ , interferon- $\gamma$  (IFN- $\gamma$ ) and TNF- $\alpha$  repress the C/EBP regulatory sequences, resulting in downregulated fetuin-A gene expression and a robust inflammatory response.<sup>66</sup> Accumulated evidence indicated that the decreased level of fetuin-A may underlie the pathogenesis of psoriasis, though further clarification is still warranted. Thus, the decreased fetuin-A level is postulated to contribute to the development of psoriasis, which may be owing to the decreased anti-inflammatory function of fetuin-A that antagonizes inflammatory cytokines (such as TGF- $\beta$ , TNF- $\alpha$  and IL-6) and EGF.<sup>9,67,68</sup>



**Figure 1** Hypothetical role of fetuin-A in the pathogenesis of psoriasis. Early inflammatory mediators (IL-6, IL-1 $\beta$ , IFN- $\gamma$ , TNF- $\alpha$ ) are released from immune cells in response to primary triggers. These early mediators repress the C/EBP regulatory sequences and downregulate hepatic fetuin-A gene expression (release). Low fetuin-A decreases its anti-inflammatory function by counteracting inflammatory cytokines (TGF- $\beta$ , TNF- $\alpha$  and IL-6, EGF) and promoting inflammation and vascular calcification, thereby psoriasis and comorbidities like CVD. On the other hand, the excess late pro-inflammatory mediators (HMGB1) stimulate hepatic release of fetuin-A. High level of fetuin-A stimulates keratinocyte proliferation by inhibiting TGF- $\beta$ , activates keratinocyte and neutrophil migration directly or by inducing EGF and TGF- $\alpha$ , reduce the adiponectin expression by adipocytes and thereby increases pro-inflammatory cytokines and decreased anti-inflammatory cytokines, ultimately cause inflammation and psoriasis. High level of fetuin-A, by impairing ISP and counteracting adiponectin action, results in IR, diabetes mellitus, obesity, NAFLD, and dyslipidemia, which may eventually end with CVD.

**Abbreviations:** C/EBP- $\beta$ , CCAAT enhancer-binding proteins- $\beta$ ; CVD, cardiovascular disorder; HMGB1, high mobility group box protein 1; EGF, epidermal growth factor; IFN, interferon; IL, Interleukin; ISP, insulin signaling pathway; TNF, tumor necrosis factor; TGF, transforming growth factor; NAFLD, nonalcoholic fatty liver disease.

In contrast, a study by Uyar et al reported no significant relationship in fetuin-A values between the patients with psoriasis and the control group.<sup>69</sup> However, several other recent publications have shown positive correlations between fetuin-A with psoriasis and its concomitant disorders, which demonstrated elevated values of fetuin-A in patients with psoriasis than in healthy individuals.<sup>25,26,57,70</sup> The elevated levels of fetuin-A demonstrated in patients with psoriasis could probably be due to the excess accumulation of late pro-inflammatory mediators (eg, HMGB1) in response to the strong inflammatory response underlying the disease. Subsequent HMGB1-stimulated hepatic expression of fetuin-A restores serum levels of fetuin-A in the disease process.<sup>71</sup> Furthermore, while a number of studies revealed no correlations between fetuin-A and the Psoriasis Area and Severity Index (PASI) score, results from several other studies claimed that fetuin-A levels are significantly and positively correlated with the disease severity of psoriasis (PASI score).<sup>25,26,57,59,61,62,69</sup> The elevated levels of fetuin-A in psoriasis indicate that the proinflammatory attributes of fetuin-A in mediating the development and progression of psoriasis.

Several mechanisms have been proposed for the role of fetuin-A in the development of psoriasis, albeit more research is needed. One proposed mechanism is that fetuin-A acts as an endogenous inhibitor of TGF- $\beta$ , which inhibits keratinocyte proliferation. Hence, the increased level of fetuin-A is associated with reduced TGF- $\beta$  and causes excessive proliferation of keratinocytes in patients with psoriasis.<sup>9,27</sup> Furthermore, fetuin-A has recently been discovered to play a pivotal role in keratinocyte migration via signaling pathways resembling those pro-migratory pathways induced by EGF and TGF- $\alpha$  activation and to significantly induce actin-rich protrusions in human primary keratinocytes.<sup>72</sup> In addition, fetuin-A may cause psoriasis by reducing the expression of adiponectin by fat cells. Adiponectin found to have anti-inflammatory effect by acting on keratinocytes and T-cells to decrease the inflammation underlying psoriasis. Thus, fetuin-A induced lowering of adiponectin levels result in an increase in contents of pro-inflammatory cytokines and a decrease in levels of anti-inflammatory cytokines.<sup>73</sup> The decrease in adiponectin levels further leads to reduced E2F1 gene activation via the AMPK pathway in keratinocytes, thus leading to excessive keratinocyte proliferation and psoriasis.<sup>73,74</sup> Figure 1 diagrammatically summarizes the hypothetical role of fetuin-A in the pathogenesis of psoriasis.

Serum fetuin-A level derangement is not only implicated in the pathogenesis of psoriasis but also responsible for the development of several comorbidities of psoriasis. Low level of fetuin-A is associated with suppressed anti-inflammatory (protective) effects and a high degree of calcium accumulation in soft tissues (eg, vascular calcification), leading to

comorbidities like CVD.<sup>59</sup> On the other hand, conditions associated with elevated values of fetuin-A, such as IR, diabetes mellitus, dyslipidemia, and metabolic syndrome, may also cause CVD.<sup>9,63,70</sup>

## The Potential Clinical Applications of Fetuin-A in Psoriasis

Fetuin-A is a soluble protein that has nowadays gained researchers' attention due to its potential clinical relevance in patients with a variety of clinical diseases, including psoriasis. In light of its key pathological role in psoriasis, fetuin-A found to have potential implications in the clinical practice as a diagnostic marker, prognostic predictor, and therapeutic target for psoriasis. Henceforth, this review highlights the potential clinical implications of fetuin-A in diagnosis and therapy of psoriasis and related comorbidities.

## The Potential Diagnostic Implications of Fetuin-A

Collective body of evidence demonstrated that fetuin-A could be useful as a potential diagnostic marker for various disease conditions in clinical practice.<sup>75</sup> Many researchers have reported the correlation of fetuin-A with psoriasis and its role in the development of the disease.<sup>25,26,57–62,70</sup> Other studies have also shown a significant positive association between fetuin-A and the severity of psoriasis (PASI score).<sup>25,26</sup> Altogether, these findings suggest the usefulness of fetuin-A as a possible diagnostic marker and severity indicator of psoriasis in clinical settings.

Fetuin-A levels in the blood and tissues could also serve as a useful marker in various clinical conditions that occur alongside or independently of psoriasis, such as atherosclerosis, CVDs, metabolic syndrome, chronic kidney disease (CKD), liver dysfunction, tumors, and other inflammatory diseases.<sup>8</sup> In recent years, there has been considerable interest with respect to fetuin-A and atherosclerosis. Fiore and coworkers reported a significantly positive correlation between serum levels of fetuin-A and intima-media thickness in the early stages, establishing it as a surrogate marker for early atheromatous alterations.<sup>76</sup> In contrast, more recent studies showed that fetuin-A level is inversely associated with the severity of atherosclerosis and plaque formation, indicating low fetuin A level that promotes vascular calcification, and hence it may serve as a novel biomarker of vascular calcification and atherosclerosis.<sup>77,78</sup> Moreover, fetuin-A is a well-established pathological contributor to CVD, and it may serve as a biomarker.<sup>79</sup> A study by Borsky et al assessed the suitability of fetuin A for detection of the early stages of CVD in people with psoriasis and implied that this biomarker could be considered as an appropriate marker in detecting cardiac risk and early stages of CVDs.<sup>58</sup> However, the variable nature of the correlation of fetuin-A in the early and advanced stages of atherosclerosis as well as the biphasic association of fetuin-A with the occurrence of CVD depending on the stage of atherosclerosis may limit its clinical usefulness as a diagnostic biomarker.<sup>79</sup> In order to use fetuin-A in routine clinical practice, additional rigorous and extensive research is needed to provide supporting evidence harmonizing the contradictory results and prove the diagnostic importance of fetuin-A in CVD.

Fetuin-A is also found to be elevated in liver dysfunctions such as NAFLD, and it has been observed to have positive correlations with accumulated liver fat and liver fibrosis score index.<sup>80</sup> However, it is negatively associated with severe liver damage, which could be as a result of reduced hepatic fetuin-A synthesis.<sup>8,81</sup> This shows that fetuin-A can serve as a marker for the progression of simple hepatic steatosis to advanced stages of NAFLD. Thus, fetuin-A could be employed as a liver function marker, severity predictor, and prognostic marker in patients with liver disease in the future.

Fetuin-A deficiency has also been linked with CKD, which is usually accompanied by vascular calcification, suggesting that fetuin-A may be clinically important in patients with severe CKD.<sup>1,82</sup> Recent studies have also shown that fetuin A can be used as a promising biological marker for type 2 diabetes mellitus, obesity, tumors, neurodegenerative diseases, multiple sclerosis, cognitive decline, and COPD.<sup>75,83</sup> Fetuin-A is currently reported to be a novel urinary biomarker of the progression of diabetic nephropathy in type 2 diabetes mellitus.<sup>84</sup> A substantial body of evidence shows anti-fetuin-A auto-antibodies are frequently seen in the blood of tumor patients and have potential as early diagnostic biomarkers.<sup>83</sup> Based on the finding that fetuin-A has a pathological role in the disease process of neurodegenerative disorders, its cerebrospinal fluid (CSF) level is has recently been identified as a potential biomarker in degenerative diseases such as multiple sclerosis.<sup>85</sup> On the other hand, Laughlin et al demonstrated that fetuin-A will be used as a new vascular biomarker of age-related cognitive decline in older adults.<sup>75</sup> In COPD, fetuin-A may serve as a biomarker of disease activity and progression, with lower fetuin-A indicating more severe disease.<sup>86</sup>

Although human fetuin-A is one potential candidate as a diagnostic biomarker for psoriasis and various related diseases, there are several obstacles that limit its clinical utility. Many scholars have uncovered a number of flaws associated with fetuin-A that make it unsuitable for use as a metabolic biomarker at this time. The first is the absence of standardized reference values, leading to confusion and discordancy.<sup>87</sup> This perhaps associated with inconsistent reference ranges from different commercial enzyme-linked immunosorbent assays (ELISA) though the differences among the various ELISA not yet well elucidated. The second reason for the erratic results could be due to individual (genetic) variations in serum levels of fetuin-A.<sup>75</sup> The other reason is the unclear effect of post-translational processing on human fetuin-A measurements.<sup>88</sup> For instance, the species-specific glycosylation of fetuin-A is created by distinct expression systems, resulting in products with variable glycosylation patterns and thus serum values.<sup>89,90</sup> Overall, to minimize misinterpretation and to use fetuin-A as a diagnostic marker consistently, standardization of fetuin-A assays and consistent normal reference ranges are urgently needed.

## The Potential Therapeutic Role of Fetuin-A in Psoriasis

### The Treatment Approaches of Psoriasis

Psoriasis is a lifelong disease with a chronic relapsing course requiring long-term treatment for most patients. The disease's evolution is unpredictable, and the extent of skin involvement can range from mild to very severe forms. Remission of psoriasis is achieved through the long-term efficacious control of skin lesions.<sup>91</sup> The treatment approaches for psoriasis involve topical medication, systemic drugs, and phototherapy, which are considered as conventional treatments.<sup>91</sup> The therapeutic paradigms for psoriasis are changing due to poor tolerability, drug resistance, and adverse effects linked with the long-term use of conventional treatments. Especially, as molecular pathways of psoriasis immunopathogenesis are elucidated, a mechanistic approach to therapy has revolutionized medicine over the most recent decade. The therapeutic landscape for psoriasis has been revolutionized recently by biologic (targeted) therapies.<sup>15,91</sup> Several commercially available biologic agents for treating psoriasis are constantly growing, including, but not limited to, inhibitors of TNF, IL-17 receptor, IL-17, IL-12/23, IL-23, phosphodiesterase, and Janus kinases (JAK).<sup>15</sup> Biologic drugs have been discovered to be game changers in psoriasis treatment due to their high efficacy and promising safety, and they are now the standard treatment for moderate-to-severe psoriasis.<sup>92</sup> These drugs are particularly effective in patients who do not respond or have contraindication to conventional therapy. Moreover, because of better tolerability and safety, biologics are more feasible for long-term use than conventional therapy.<sup>91</sup>

Treatment goal for psoriasis is generally evaluated using the PASI between weeks 12 and 16 at the end of the induction therapy. The PASI is a useful tool to assess treatment efficacy, with a percentage reduction in the PASI score indicating the decrease in psoriasis severity and the increase in the effectiveness of treatments.<sup>91</sup> While PASI 75 is the current benchmark of primary endpoints for most clinical trials of psoriasis, PASI 90 response is the ultimate goal of therapy, which is currently considered as the most relevant treatment outcome, particularly in patients with severe disease.<sup>93,94</sup> When there is no improvement by 50% in the PASI score, the patient is said to be a non-responder.<sup>95</sup>

Despite significant therapeutic advances, psoriasis therapy has become challenging for clinicians in recent years, as more patients have developed resistance to the available biologic therapies such as TNF- $\alpha$ , IL-23 and IL12/23 inhibitors. This is due to loss of response, lack of response, discontinuation due to adverse effects, or the chronic nature of the disease.<sup>15</sup> Roughly 10–30% of the psoriatic patients treated with TNF or IL12/23 inhibitors are partial or non-responders, or experience adverse effects, leading to treatment discontinuation.<sup>96,97</sup> This therapeutic challenge of psoriasis doubles when it coupled with psoriasis-related comorbidities that make systemic treatment difficult. If the treatment goal is not achieved, several therapeutic strategies can be adopted, such as raising the dose of the drug, reducing the time gap between administrations, combination therapy, drug switching, and targeting novel target site.<sup>37,91</sup> These strategies play a pivotal role in limiting the detrimental progression of psoriasis and worsening of the patient's quality of life as measured by the significant improvements in PASI and the Dermatology Life Quality Index (DLQI), respectively. Switching patients to other treatments is a relatively common practice that is indicated when the other mentioned strategies are ineffective or inappropriate.<sup>98</sup> The switch from IL-12/23 and TNF inhibitors to IL-17 inhibitors has been recently found to be a safe and effective therapeutic strategy in psoriatic patients.<sup>98,99</sup> IL-17 inhibitors such as

Ixekizumab display higher efficacy than both TNF and IL-12/23 inhibitors, which increased the treatment goal from PASI 75 to PASI 90 or even PASI 100.<sup>100</sup> In addition, therapeutically targeting fetuin-A currently proposed to be a potential option for dermatologists in the treatment of psoriasis.

## The Potential Role of Fetuin-A in the Treatment of Psoriasis

Currently, fetuin-A has been discovered to serve as a therapeutic target for the treatment of various disease conditions, in addition to its possible use as a biomarker. The growing role of fetuin-A in the development of diseases such as psoriasis necessitates the development of appropriate therapies designed to manipulate fetuin-A levels. Thus, fetuin-A is expected to become a novel target for psoriasis treatment. Fetuin-A is thought to play a role in psoriasis development by modulating the chronic inflammation that underpin the disease. Thus, treating by targeting fetuin-A-mediated inflammatory pathways in psoriatic patients may provide a new therapeutic approach that improves clinical outcomes while more research is needed. Elevated level of fetuin-A in psoriasis is suggested to have anti-inflammatory role and calcification inhibitory activities. Thus, therapeutically increasing the level of fetuin-A in psoriatic illness may have a protective effect, opening up a new avenue for psoriasis therapy. It is supported by Ketter et al who reported that boosting fetuin-A levels may be a solution to undesirable extraosseous calcification, although its diverse activities need to be addressed during treatment.<sup>1</sup> Furthermore, since fetuin-A has been identified as an endogenous ligand for TLR4 promoting lipid-induced insulin resistance, it may serve as a new therapeutic target for treating IR and type 2 diabetes coexisting with psoriasis.<sup>101</sup>

Extensive efforts are being made to develop effective therapeutic options for modulating fetuin-A levels. To date, adiponectin, salsalate, curcumin, and vitamin D have been identified as promising agents to modulate the serum levels of fetuin-A.<sup>102–104</sup> A study by Jung et al shows adiponectin and salsalate has been proven to reduce palmitate-induced fetuin-A gene expression and ameliorate hepatic steatosis in hepG2 cells.<sup>102</sup> Moreover, curcumin administration reduces serum fetuin-A in rats on a high-fat diet, presumably by curcumin-mediated AMPK activation.<sup>103</sup> Treating rats with a megadose of vitamin D also lowers blood fetuin-A levels and enhances vascular calcification.<sup>104</sup>

## Discussion

The pathomechanisms underlying psoriatic disease are complex and multifactorial, and the interplay between genetic, environmental, and immunologic factors is thought to be involved in the pathogenesis of the disease. Notably, a systemic chronic inflammation mediated by immunological mediators and inflammatory cytokines was found to be a major player in the pathophysiology of psoriasis and its comorbidities. However, the exact pathophysiology of psoriasis is not entirely clear, which warrants further elucidating researches. Nowadays, a considerable body of data has reported the close association of fetuin-A derangement with psoriasis and its comorbidities, suggesting its novel putative pathological role in psoriasis. However, the study findings are still discordant and the role of fetuin-A in the pathogenesis of psoriasis remains vague. In other words, consensus has not been reached on whether fetuin-A has an exacerbating or protective effect on psoriasis. This inconsistent property can be due to the dual roles of fetuin-A in psoriasis, where it can act as an inflammatory and anti-inflammatory agent as well as due to the presence of confounding morbidities coexisting with psoriasis. Therefore, it still remains an area of active research that needs further extensive studies to resolve the opposing findings and to uncover the enigmatic issues and arrive at a conclusion.

In light of its role in the pathogenesis of psoriasis, fetuin-A nowadays attracts researchers' interest towards its potential implications in clinical practice as a diagnostic marker, prognostic predictor, and therapeutic target for psoriasis. Thus, many attempts are currently being made to better understand the emerging clinical implications of fetuin-A for diagnostics as well as therapeutics. Several findings suggest the usefulness of fetuin-A as a possible diagnostic marker and severity indicator of psoriasis in clinical settings in the future. However, several obstacles such as absence of standardized reference values, individual variation, endogenous effect of post-translational processing on fetuin-A value may limit its clinical utility. Therefore, more research is needed to properly determine the concentration range for fetuin-A in psoriatic diseases and in specific group of patients.

Although several anti-psoriatic therapies are nowadays available in the pharmaceutical market, psoriatic patients may experience therapeutic failure even with the most effective biologics due to the chronic nature of the disease, leading to



loss of response, lack of response or treatment discontinuation. Thus, several therapeutic strategies have been adopted, including increasing the drug dose, reducing the time gap between drug intake, combination therapy, drug switching, and targeting novel sites to limit the progression of psoriasis and worsening of patients' quality of life. In this scenario, targeting fetuin-A is a great new street to approach patients with psoriasis. To date, adiponectin, salsalate, curcumin, and vitamin D have been identified as promising agents to modulate the serum levels of fetuin-A. Generally, fetuin-A could be a promising therapeutic target in future clinical practice, though therapeutic adaptation against different comorbid disorders such as vascular diseases needs to be considered in treatment planning. Hence, more in-depth studies that clearly show the role of fetuin-A in psoriasis and comorbidities are needed.

Despite our extensive effort to provide a comprehensive and up-to-date review on fetuin-A and psoriasis, this review primarily focuses on the role of fetuin-A in psoriasis, though it has an important pathological role in various other clinical conditions. Besides, this review did not incorporate the paralogue of fetuin-A, known as fetuin-B, that has critical role in different diseases.

## Concluding Remarks

In summary, psoriasis is a multifactorial chronic inflammatory disease mediated by different inflammatory mediators that act as an important hallmark in its pathogenesis. Interestingly, fetuin-A has currently been observed to play an essential pathological role in psoriasis. It is recently found to be involved in the chronic inflammatory process underlying psoriasis, though its role is very complex and still not entirely clear. Various studies have shown the correlation between fetuin-A and psoriasis, but the results are contrasting and equivocal. More extensive studies are warranted to reconcile the opposing findings and to throw more light on the possible role of fetuin-A in psoriasis pathogenesis. Fetuin-A is currently attracting researchers' attention due to its diagnostic and therapeutical clinical relevance. It is proposed to serve as a diagnostic tool for psoriasis and related comorbidities in future clinical practice. Despite the diagnostic potential of fetuin-A for psoriasis and the availability of multiple assays, fetuin-A readings are variable, limiting its clinical utility and necessitating standardization. Fetuin-A has also been found to be a promising therapeutic target for the treatment of psoriasis. Although therapeutic options are limited in modulating fetuin-A levels, salsalates, curcumin, and vitamin D are intriguing future agents. Nevertheless, the available information is still insufficient and the relevance of fetuin-A in psoriasis is still of concern.

## Abbreviations

AHSG,  $\alpha$ 2-Heremans-Schmid glycoprotein; APP, acute phase protein; CKD, chronic kidney disease; CRP, C reactive protein; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; EGF, epidermal growth factor; ELISA, enzyme-linked immunosorbent assays; ESRD, end-stage renal disease; HMGBP1, high mobility group box protein 1; IBD, inflammatory bowel disease; IFN- $\gamma$ , interferon- $\gamma$ ; IL-1, interleukin-1; IR, insulin resistance; NAFLD, non-alcoholic fatty liver disease; NF-1, nuclear factor-1; PASI, Psoriasis Area and Severity Index; RTK, TGF- $\beta$ , transforming growth factor- $\beta$ ; TGF, transforming growth factor; TLR-4, Toll-like receptor 4; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

## Disclosure

The authors report no competing interests in this work.

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