Dermatol Ther (Heidelb) (2023) 13:1617–1627
https://doi.org/10.1007/s13555-023-00958-4

REVIEW

Kynurenine Pathway in Psoriasis—a Promising Link?

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Received: May 5, 2023 / Accepted: May 31, 2023 / Published online: June 16, 2023
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ABSTRACT

Psoriasis is a common dermatosis which affects the patient's skin and general well-being because of its link to diseases such as depression, kidney disease and metabolic syndrome. Pathogenesis remains unknown; however, genetic, environmental and immunological factors seem to play a role in the development of the disease. Due to a lack of complete understanding of the psoriasis pathology, effective treatment is yet to be developed. The kynurenine pathway is one of the ways amino acid tryptophan is metabolised. In comorbidities typical for psoriasis such as chronic kidney disease, depression and atherosclerotic alterations in the activation of the kynurenine pathway were observed, which were mainly characterised by higher activity compared to that in healthy individuals. However, the kynurenine pathway has not been thoroughly studied among patients with psoriasis even though increased levels of L-kynurenine, one of the enzymes in the kynurenine pathway, were found in psoriatic skin lesions. Given the unknown pathogenesis of the disease, this finding seems to be a potential new field of study and shows a possible link between psoriasis and its comorbidities that could also lead to novel effective treatment for this chronic condition.

Keywords: Kynurenine; Kynurenine pathway; Psoriasis; Quinolinic acid

Key Summary Points

Psoriasis' pathogenesis remains unknown, and therefore effective treatment is yet to be developed.

Kynurenine pathway is one of the ways the amino acid tryptophan is metabolised.

In comorbidities typical for psoriasis such as chronic kidney disease, depression and atherosclerosis alterations in the activation of the kynurenine pathway were observed, which were mainly characterised by higher activity compared to that in healthy individuals.

Given the unknown pathogenesis of the disease, this finding seems the be a potential new field of study and a possible link between psoriasis and its comorbidities that could also lead to novel effective treatment for this chronic condition.

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INTRODUCTION

Psoriasis is a chronic skin disease which is diagnosed in approximately 1–3% of the general population and is not only characterised by skin lesions but also affects the whole body [1, 2]. Aetiopathogenesis remains unknown; however, genetic, environmental and immunological factors are believed to play a role in the development of the disease [2]. The unknown cause and pathogenesis are the reasons for the lack of an effective treatment and final cure [2].

Among patients with psoriatic diseases such as Crohn's disease, psychiatric disorders, renal diseases and cardiometabolic syndrome (CMDs) are diagnosed more often than in the general population [3, 4]. It was noted that patients with psoriasis were hospitalized with acute kidney injury at a younger aged compared to a group without this disease [5]. Other studies highlight the fact that drugs used for treatment of psoriasis are nephrotoxic [4]. Therefore, they should be administered with caution as the disease itself is believed to be a factor in the development of renal impairment [4]. Psoriasis is a risk factor for developing metabolic syndrome, which is diagnosed among 20% to 50% of patients with psoriasis, and its prevalence increases with the dermatosis severity [6–8]. Psychiatric disorders are diagnosed more often in patients with psoriasis than in healthy controls [3]. Depression is diagnosed in 7% and 18% of persons with psoriasis; anxiety disorders occur in 25% and 55% of this group [9]. Immunological factors are believed to be responsible for such incidents as cytokines mediate pathways between the brain and immune system [10]. Moreover, the levels of proinflammatory cytokines and C-reactive protein are increased among persons with depression, even in a group where those patients do not suffer from any inflammatory conditions [10]. Another possible explanation for the higher prevalence of mental disorders among patients with psoriasis is the stigmatisation of the disease and sleep disturbances, which lead to increased stress and decreased quality of life [11]. Furthermore, some studies report that patients who suffer from psoriasis and do not receive systemic treatment had an increased risk of developing Alzheimer's disease compared to a group not taking such medications [12].

Tryptophan is an amino acid metabolised to serotonin, which regulates biological processes such as appetite, sleep and mood [13, 14]. However, approximately 99% of tryptophan is catabolised in the kynurenine pathway (Fig. 1) [13]. Tryptophan is metabolised by the enzyme indoleamine 2,3-dioxygenase (IDO) or tryptophan 2,3-dioxygenase (TDO) to N-formyl-L-kynurenine, which is then metabolised to L-kynurenine (KYN) [15]. Further conversions lead to kynurenic, quinolinic and picolinic acid, among others [15]. The main product of the kynurenine pathway is nicotinamide adenine dinucleotide. However, substances such as kynurenine and quinolinic acid, which are by-products of this metabolic route, are biologically active and believed to exhibit neurotoxic properties [16]. Different studies noted that those metabolites have adverse effects on different organs, and they were linked to the development of neurological, autoimmune and cardiovascular diseases, among others [15, 17]. Abnormalities in the kynurenine pathway were also observed in acute kidney injury and chronic kidney disease [18] [Fig. 2].

The goal of this study is to explore the correlation among psoriasis, its comorbidities and their link to the kynurenine pathway as this subject has not been widely studied yet. Few studies report on disturbances in this pathway in psoriasis. Therefore, this analysis can highlight a new possible area of research that can lead to better understanding of psoriasis, its development and the diseases that commonly coexist with it.

METHODS

Studies included in the PubMed database in English, Polish and German were considered for this research. Medical subject headings used to investigate this topic included: 'psoriasis' AND 'kynurenine pathway' AND 'kynurenine' AND 'quinolinic acid' AND 'indolamine 2,3-dioxygenase' AND 'kynurenine in cardiovascular

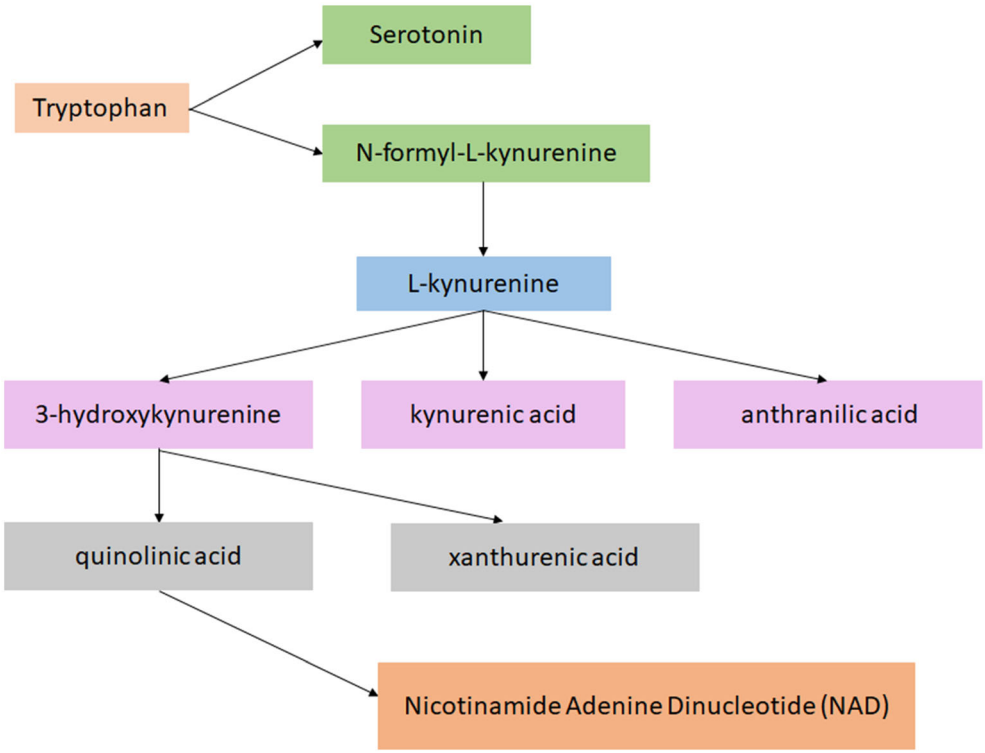

Fig. 1 Tryptophan metabolism in the kynurenine pathway

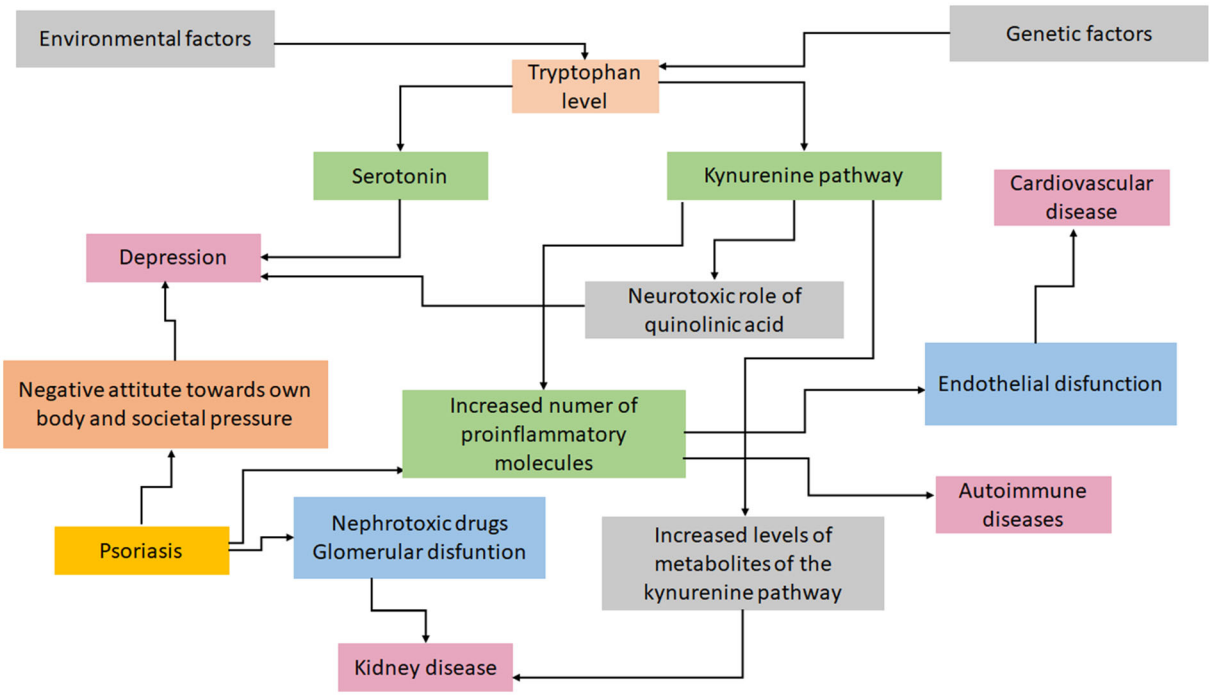

Fig. 2 Links among kynurenine metabolism, psoriasis and its comorbidities

diseases' AND 'kynurenine in depression' AND 'kynurenine in kidney disease' AND 'kynurenine in autoimmune diseases' AND 'kynurenine in psoriasis' AND 'kynurenine pathway in psoriasis' AND 'kynurenine pathway in depression' AND 'kynurenine pathway in kidney diseases' AND 'kynurenine pathway in autoimmune diseases' AND 'kynurenine pathway in cardiovascular diseases'. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

KYNURENINE PATHWAY IN DEPRESSION

Patients suffering from psoriasis are at a greater risk of developing depression and anxiety disorders compared to the general population [16]. One study noted that > 50% of those patients can experience depressive symptoms [16]. In a survey performed by Schuster et al. among 722 patients with psoriasis, 40% fulfilled the criteria for depression and even during the period of decreased disease activity the responders reported poor well-being [19]. Schuster et al. also differentiated between subjective and objective activity of the disease and highlighted that patients' subjective opinion influences the overall well-being more than the objective psoriatic activity [19]. However, the authors considered the participants' recruitment: it is known that people more dissatisfied with their quality of life are more likely to contact self-help organisations, and one of these contacted participants in this study [19]. Contrarily, other studies performed in a medical setting also noted that patients had a higher chance of developing depression or suicidal thoughts when they had moderate and severe psoriasis [20, 21]. In one study performed among 217 patients with psoriasis, 9.7% expressed that they wanted to die [21]. One of the reasons for a high prevalence of mental disorders among patients with psoriasis is the stigmatisation of persons with visible skin lesions that can lead to rejection or discrimination [16, 21]. Other authors have noted that pruritus, which often accompanies psoriatic lesions, decreases patients' quality of life and causes anxiety, which can increase unpleasant sensations and lead to a self-perpetuating cycle [22]. Sanders et al. mentioned that with increased intensity of pruritus, patients' quality of life decreased and their anxiety level rose [22]. It was also observed that patients with vitiligo—a skin disease that is not accompanied by itching but very visible—reported reduced anxiety compared with patients with diseases such as psoriasis and atopic dermatitis that are linked to unpleasant sensory symptoms [22]. However, the role of other mechanisms such as immunological factors or cytokine-mediated pathways is also considered one of the causes for the coexistence of these diseases [16]. Patients who suffer from depression had increased levels of C-reactive protein, tumour necrosis factor and pro-inflammatory interleukins, even if they had not been diagnosed with any inflammatory diseases [10, 20].

Kynurenine pathway is believed to be one of the causes in the pathophysiology of depression and other mental disorders due to its strong connection to serotine, which is one of the neurotransmitters considered in the treatment of depressive disorder as it is known for its role in regulating cognition and mood [16, 23]. The serotonin hypothesis, which is one of the theories explaining the pathophysiology of this disease, is strongly linked to the kynurenine pathway and supported by the fact that variations in genes coding IDO1 and 2 were observed among persons with depression [24]. Some studies support this connection and have shown higher levels of metabolites of kynurenine pathway among patients with depression [24, 25]. However, other studies do not reinforce this thesis as other authors, such as Dahl et al., have noticed a significant negative correlation [26]. It is believed that quinolinic acid, which is formed as a result of the immune processes that activate macrophages and microglia in the brain, can be responsible for development of not only depression but also diseases such as Parkinson's disease, Alzheimer's disease, neurodegenerative diseases or amyotrophic lateral sclerosis [16]. Quinolinic acid itself is known to exhibit neurotoxic properties

due to the activation of the NMDA receptors [16]. Zador et al. reported that decreased concentrations of tryptophan and L-kynurenine but increased levels of quinolinic acid were noted in patients with depression [24]. Given the data showing increased markers of an inflammatory process in depression and the fact that those molecules are responsible for activating indolamine 2,3-dioxygenase, an enzyme regulating the kynurenine pathway, it can be concluded that there is a potential link between the pathophysiology of depression and this metabolic route, perhaps also in psoriasis [24]. Notably, other authors have also noticed increased levels of quinolinic acid, which is one of the metabolites of the kynurenine pathway, among persons with depression [23]. Paul et al. confirmed that metabolic changes in depression and the kynurenine pathway are related [23]. This finding is especially important given the number of people suffering from depression [24]. It is estimated that worldwide > 264 million are affected by this disease [24]. Paul et al. also noted that kynurenic acid, nicotinamide and picolinic acid, which present neuroprotective activity, had a reduced concentration in plasma of patients with depression [23]. Moreover, some studies have shown that patients treated with antidepressants had increased levels of KYNA in astroglial cells [23]. In antidepressant-free persons, lower concentrations of KYNA were noted in a study performed by Paul et al. [23]. Even though depression is often diagnosed in patients with psoriasis, the link between those diseases and the kynurenine pathway has not yet been researched.

KYNURENINE PATHWAY IN KIDNEY DISEASE

Psoriasis is one of the risk factors for chronic kidney disease, and the severity of the disease was positively correlated with the risk of death from kidney-related causes [4]. Even mild psoriasis was noted to increase the chance of death from kidney disease by more than two fold [4]. Abuabara et al. reported that patients with severe psoriasis had a significantly lower age at death compared to a group without this disease [27]. The authors suggested a link between kidney disease and psoriasis that could contribute to this outcome but also highlighted that other diseases such as COPD, malignancy, liver disease or cardiovascular disease that often coexist with psoriasis can lead to shorter live expectancy among those patients [27]. Abuabara et al. noted that the psychological impact of psoriasis could be an important factor contributing to the lower life expectancy as the disease is known to carry great psychological weight and is linked to depression and suicide; therefore, it may negatively impact patients' social and economic status, which could translate to worse access of quality healthcare and decreased peer support [27].

Furthermore, data show that psoriatic patients were hospitalized with acute kidney injury at a median 6 years earlier compared to a group without dermatosis [5]. The possible explanation is the increased risk of cardiovascular diseases among patients with psoriasis and higher chances of developing those diseases earlier compared to the general population [5]. Gonzalez-Parra et al. highlighted that patients with psoriasis suffer from atherosclerosis, hypertension, dyslipidaemia and diabetes—which are known to increase cardiovascular risk—more often than the general population [28]. Furthermore, authors pointed out the nephrotoxic influence of some of the drugs used in psoriasis, such as acitretin and ciclosporin [28]. Glomerular dysfunction, which is typical for autoimmune diseases, was also noted among patients with psoriasis and was more prevalent among patients with psoriatic arthritis and higher disease activity [28]. Contrarily, Singh et al. reported cases of three patients suffering from psoriasis with significant renal insufficiency [29]. In all of them, no drugs, viral infections or other diseases of known nephrotoxic properties were reported, apart from psoriasis [29]. Therefore, the term 'psoriatic nephropathy' was introduced [29]. Singh et al. concluded that renal involvement in psoriasis can vary but patients with psoriasis should be regularly monitored as untreated glomerular disfunction can lead to chronic kidney disease [29].

Increased levels of kynurenine metabolites were noted among patients suffering from acute kidney injury (AKI) [18]. This finding is especially important given the increased risk of AKI among patients with psoriasis [5]. Pires et al. studied rat models with autosomal recessive polycystic kidney disease, which inevitably leads to end-stage renal disease [30]. It was noted that the kynurenine pathway was upregulated in this group [30]. Moreover, in other studies, elevated levels of metabolites where positively correlated with inflammation and septic shock among patients with AKI, and kynurenic acid was the most significant predictor of recovery during the first 2 days of the disease [18]. Among patients with chronic kidney disease, increased levels of indolamine 2,3-dioxygenase, an enzyme responsible for converting tryptophan to kynurenine, and kynurenine were noted compared to a group of healthy individuals [18, 31]. However, this connection has not been researched among patients suffering from psoriasis, although this could potentially lead to a better understanding of the coexistence of this skin condition and kidney diseases and successful therapeutic options.

KYNURENINE PATHWAY IN AUTOIMMUNE DISEASES

Autoimmune conditions such as Crohn's disease, Hashimoto thyroiditis and Graves' disease occur more commonly among patients with psoriasis compared to healthy individuals [32]. This connection is believed to be a result of the systemic inflammation that takes place in psoriasis, which is an autoimmune inflammatory condition itself [32]. Alidrisi et al., in a study performed among 56 patients with psoriasis, observed a link between psoriasis and Hashimoto thyroiditis [33]. Autoimmune thyroid disease was one of the exclusion criteria in this study, yet Alidirisi et al. observed significantly higher levels of anti-thyroid peroxidase and thyroglobulin antibodies among the group that suffered from psoriasis compared to healthy individuals [33]. In ultrasound thyroid examination in patients with psoriasis, higher vascularity, hypoechogenicity and pseudonodules were observed, which are typical for Hashimoto disease [33]. In this study, no difference between males and females was found regarding the thyroid antibodies, which could lead to the conclusion that in this group psoriasis eliminates the commonly observed phenomenon—higher prevalence of Hashimoto thyroiditis among females [33]. Alidrisi et al. also noted significantly higher levels of anti-thyroid peroxidase antibodies among patients with psoriasis who also suffered from obesity compared to the group that was not obese [33]. It is believed that leptin may play a role in the autoimmune processes in the thyroid [33]. This finding may be especially important given the fact that metabolic syndrome, which includes obesity, is diagnosed significantly more often among patients with than without psoriasis [28]. Furthermore, thyroid disfunction was linked to higher Psoriasis Area and Severity Index (PASI) score [32].

In one study it was noted that persons with psoriasis had 1.6 times higher risk of ulcerative colitis and 9.6% suffered from Crohn's disease compared to only 2% in the group without psoriasis [34]. The roles of inflammation, gut macrobiota and genetic and immunological aberrations are considered [35]. De Francesco et al. suggested that gut mucosa may be altered by the systemic inflammation typical for psoriasis and that change could progress to an inflammatory bowel disease [34]. Furthermore, authors noted that this process could also work the opposite way—the inflammatory processes in the intestines could result in the systemic process and later in the development of inflammatory skin diseases such as psoriasis [34].

Kynurenine pathway became an area of research in inflammatory bowel diseases due to the finding that Crohn's disease and ulcerative colitis are connected to depression [36]. Higher prevalence of depression and anxiety among patients with inflammatory bowel diseases was also noted [36]. Due to these data, the metabolic route metabolising tryptophan was researched and significantly lower levels of serum tryptophan were observed among patients with inflammatory bowel disease compared to

healthy individuals [36]. Even after consuming the same amount of dietary tryptophan, the level was lower in the group with Crohn's disease, compared to the patients suffering from ulcerative colitis [36]. Moreover, serum tryptophan levels negatively correlate with inflammatory bowel disease activity [36]. Chen et al. also suggested that further research should focus less on IDO's role in regulating the kynurenine pathway and more on the involvement of subsequent metabolites [36]. In another study, IDO activity was increased in the mucosa of patients suffering from inflammatory bowel diseases [37]. Although a strong correlation among psoriasis, other autoimmune conditions commonly coexisting with psoriasis and the kynurenine pathway was noted, only few studies on that topic can be found. Harden et al. mentioned increased levels of metabolites of the kynurenine pathway and enzymes participating in this route among patients with psoriasis, and they linked this to the general inflammation that can be observed in patients suffering from autoimmune diseases [38].

KYNURENINE PATHWAY IN CARDIOVASCULAR DISEASES

Psoriasis is linked to an increased risk of developing dyslipidaemia, metabolic syndrome and other cardiovascular comorbidities [39]. A similar observation regarding increased cardiovascular risk with other autoimmune inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis was made [39]. Weber et al. noted that a systemic inflammatory process, which is typical for the previously mentioned diseases, alters the immune-mediated mechanisms [39]. This as a result can lead to changes in the circulating platelets and lipids, vascular damage and the development of atherosclerosis, which is diagnosed more often among patients with psoriasis compared to the general population [39]. One reason for this phenomenon is the impaired endothelium, which in patients with psoriasis is believed to secrete an increased number of proinflammatory molecules [39]. These substances are believed to contribute to endothelial dysfunction, which as a result can lead to the formation of atherosclerosis [39]. Furthermore, a correlation between the severity of psoriasis and the number of non-calcified plaques was noted, which further highlights the link between those two diseases [39].

Werber et al. reported that patients with psoriasis had a 50% higher chance of myocardial infarction compared to a group of healthy individuals [39]. Moreover, even for young people suffering from severe psoriasis, the relative risk of myocardial infarction diagnosis was three fold higher than in the control group [39]. Weber et al. also noted that cardiovascular disorders are the most common cause of death in patients with psoriasis, and they decrease their life expectancy by 5–7 years [39]. One of the causes for the higher prevalence of myocardial infarction among persons suffering from psoriasis is the previously mentioned atherosclerosis [39]. Patients with psoriasis are also commonly diagnosed with dyslipidaemia, more often than persons without this dermatosis experience lower HDL and increased LDL levels [39]. One of the causes of this process is the peroxidation of the particles caused by general inflammation in psoriasis [40]. One study reported that amount of oxidised HDL was 15% higher and of oxidised lipoprotein (a) was 30% larger among patients with psoriasis than in the group without this disease [39].

Patients with psoriasis have an increased risk of developing metabolic syndrome and therefore type II diabetes [40]. In one study 10.3% of patients with psoriasis were diagnosed with type 2 diabetes compared to 6.2% in the control group [40]. In a cohort study Wan et al. reported that only 3.44% of people with psoriasis had diabetes [41]. In the general population this was 2.44% [41]. However, Dubreuil et al. noted that among this group the risk of diabetes was 72% higher compared to sex- and age-matched controls [42]. Psoriatics with diabetes also develop micro- and macroangiopathies more often than diabetics without psoriasis [40]. The definite reason for the common coexistence of psoriasis and type II diabetes is not known [40]. However, this disparity is explained by a genetic difference, as psoriasis and type 2 diabetes seem to be determined by the same genes [40]. Insulin

resistance due to the systemic inflammatory process is also considered to be one of the causes [40]. Other possible factors include decrease in physical activity among patients with psoriasis compared to healthy individuals [43]. Masson et al. reported that among people with psoriasis, engagement in vigorous exercise was decreased compared to the group without this disease [40]. Furthermore, more severe psoriasis was linked to a lower intensity of physical activity [40]. Contrarily, in one study the reduced risk of developing incident psoriasis was linked to participating in vigorous exercise [40]. This effect is believed to be a result of the way physical activity influences systemic inflammatory processes [40].

Various studies noted that the kynurenine pathway is up-regulated by inflammation [44]. Indolamine 2,3-dioxygenase, an enzyme regulating the kynurenine pathway, was noted in higher concentration among patients with severe atherosclerosis and cardiac hypertrophy [45]. Higher levels of metabolites of the kynurenine pathway were also found in patients with coronary heart disease and poststroke patients [45]. Furthermore, higher concentration of quinolinic acid, one of the metabolites of the kynurenine pathway, was linked to carotid artery atherosclerosis [46]. Other studies show a higher kynurenine/tryptophan ratio may be an indicator of an increased chance of myocardial infarction and unstable angina [46]. Higher levels of metabolites and enzymes of the kynurenine pathway are also linked to heart failure and stroke [46]. One study also suggested that metabolites of the kynurenine pathway could potentially be a predictor of acute myocardial infarction [47]. In this research patients with stable angina pectoris were analysed [47]. In both this group and a population of healthy, elderly individuals, increased levels of these substances in plasma were linked to an unfavourable prognosis and in urine were associated with increased risk of acute coronary symptoms [47]. However, the connection among psoriasis, cardiovascular comorbidities and the kynurenine pathway has not been studied yet.

KYNURENINE PATHWAY IN PSORIASIS

Kynurenine pathway in psoriasis is not thoroughly studied and the obtained results are often conflicting. After examining skin biopsies Harden et al. noted increased expression of indoleamine 2,3-dioxygenase and L-kynureninase, enzymes regulating the kynurenine pathway, in psoriatic lesions [38]. In the same study a significant positive correlation was found between the levels of these two enzymes and proinflammatory molecules that are believed to participate in psoriasis' pathogenesis [38]. Furthermore, Harden et al. noticed a decrease in the expression of IDO and KYNU after treatment with biological drugs including anti-TNFα and anti-IL-12/23p40 [38]. This finding suggests that the upregulation of the kynurenine pathway is linked to the inflammatory process in general [38]. However, Clement et al. performed a study using a mouse model of psoriasis in which they noted that hydroxy-L-kynurenine has an anti-inflammatory effect and leads to reduction of psoriatic skin lesions [48]. In another study performed using a mouse model with imiquimod-induced psoriatic lesions, Fujii et al. identified that IDO2, an isoform of IDO enzyme, may reduce skin lesions in psoriasis and the inflammatory process by decreasing IL-17 [49]. One study points out the AhR receptor, which seems to regulate gene expression and is present in the skin [50]. This receptor is believed to participate in various cutaneous processes such as regulating immunological response and skin barrier or response to potentially harmful environmental factors such as UV radiation [50]. Some of its ligands are metabolites of the kynurenine pathway [50]. It is suggested that the activation of this receptor may lead to increased production of pro-inflammatory cytokines such as IL-17 and IL-22, resulting in increased skin proliferation and psoriatic lesions [50]. The divergent and scarce data on the kynurenine pathway in psoriasis are not conclusive but seem promising and worth further investigation.

LIMITATIONS

Kynurenine pathway is a novel subject that has not been thoroughly studied yet. Therefore, the literature is limited to studies published in recent years. Based on the data that we have found, the kynurenine pathway seems to be a very promising area of research. Psoriasis still poses a significant challenge due to its wide but unknown pathogenesis, and researchers are continuously searching for newer and more effective therapeutic methods. Therefore, we believe that the kynurenine pathway could potentially offer a new outlook on this disease and its treatment in the future.

CONCLUSIONS

The kynurenine pathway and its link to psoriasis have not been thoroughly researched. Few reports show increased levels of metabolites and enzymes of the kynurenine pathway among patients with psoriasis and in psoriatic lesions. However, studying the alterations in the kynurenine pathway in various psoriatic comorbidities such as other autoimmune diseases, depression, kidney disease and cardiovascular disease in relation to the pathogenesis of psoriasis is a promising new path worth exploring.

ACKNOWLEDGEMENTS

Funding. The Rapid Service Fee is funded by Medical University of Bialystok.

Author Contributions. Conceptualization, investigation, writing—review and editing, and project administration: Anna Stepaniuk and Anna Baran. Methodology, data curation, resources, writing—original draft preparation, and visualization: Anna Stepaniuk. Validation: Iwona Flisiak. Supervision: Anna Baran and Iwona Flisiak. All authors have read and agreed to the published version of the manuscript.

Disclosures. Anna Stepaniuk, Anna Baran and Iwona Flisiak have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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