Dermatology Practical & Conceptual

mTORC1 and mTORC2 Levels in Patients with Psoriasis

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ABSTRACT

Introduction: In recent years, there has been a growing emphasis on the role of the mammalian target of rapamycin (mTOR) pathway in the pathogenesis of psoriasis. This intracellular signaling pathway is known as the main control pathway of metabolism and is of particular interest in this context.

Objectives: To investigate the importance of the mTOR pathway in the pathogenesis of plaque psoriasis.

Methods: A total of forty patients with plaque psoriasis and 40 non-psoriatic volunteers were included in this case-control study. The fasting serum levels of mTORC1 and mTORC2 in the study groups were examined by enzyme-linked immunosorbent assay.

Results: Serum levels of both mTORC1 and mTORC2 were found to be significantly lower in patients with plaque psoriasis than in controls (P = 0.001). A positive correlation was identified between serum mTORC1 and serum mTORC2 levels in patients with plaque psoriasis (p=0.001, r=0.826).

Conclusion: The lower serum levels of mTORC1 and mTORC2 complexes, which are active signaling molecules in the cell, were observed in patients with plaque psoriasis. This suggests that these levels may serve as an indicator of increased intracellular activation of these molecules. It is our opinion that agents that can effectively inhibit both mTOR complexes may be more effective in the treatment of psoriasis.

Introduction

Psoriasis is a chronic inflammatory skin disease that is characterized by exacerbations and remissions and that affects 2–3% of the population [1]. The etiology of psoriasis is founded upon the intricate and evolving interplay between genetic and environmental influences, along with the activation of diverse immune pathways. In addition to the innate and adaptive immune systems, several intracellular signaling pathways are involved in the pathogenesis [2]. Among these, the phosphoinositide-3 kinase/protein kinase-B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway has been described as a key signaling pathway for cellular metabolism and is currently being investigated for its It is implicated in a number of diseases, including cancers, metabolic disorders, immune-mediated disorders, and neurodegenerative disorders [3].

mTOR is a serine/threonine protein kinase that forms the catalytic subunit of two multiprotein complexes in eukaryotic cells, mTORC1 and mTORC2. Activation of the mTOR signaling pathway results in the triggering of anabolic processes, which are required for cell growth and proliferation [4]. Furthermore, both the mTORC1 and mTORC2 complexes play a role in regulating the innate and adaptive immune system. This is because immune cells respond to pathogens and antigens by reprogramming their metabolism, and maintaining this homeostasis is crucial to preventing autoimmunity and malignancy [5].

mTOR pathway plays a pivotal role in numerous aspects of epidermal homeostasis, including skin morphogenesis during embryogenesis, the formation of the epidermal barrier, hair growth, and skin repair. Spatiotemporal activation of the pathway in the epidermal layers is essential for the optimal proliferation and differentiation of keratinocytes [6,7]. Consequently, dysregulation of the mTOR pathway is linked to the development of hyperproliferative skin diseases, particularly skin cancers and inflammatory skin diseases [8].

A number of studies have indicated the potential benefits of mTOR inhibitors in the treatment of psoriasis. Consequently, the role of the mTOR signaling pathway in the pathogenesis of psoriasis has become a subject of interest. In a study conducted by Buerger et al., immunohistochemical studies were performed on lesional skin biopsy samples from patients with psoriasis. These studies demonstrated that mTOR activation increased in all layers of the epidermis [9]. Furthermore, staining with phosphorylated S6K and 4EBP1, which are downstream signaling proteins of the pathway, was increased in the suprabasal layers. These results indicate that mTOR signaling plays a significant role in the development of psoriatic epidermal alterations [9]. Proinflammatory cytokines, in particular IL-22, IL-17A, TNF-alpha, and IL-1 beta, have been demonstrated to induce heightened activation of the PI3K/Akt/mTOR pathway by interacting with tyrosine kinase receptors on the cell membranes of keratinocytes. Overactivation of the mTOR signaling cascade has been observed to result in hyperproliferation, coupled with the inhibition of apoptosis and differentiation in keratinocytes [10]. Furthermore, the activation of the PI3K/Akt signaling pathway was observed to be elevated in peripheral blood mononuclear cells of patients with psoriasis in comparison to healthy individuals [11]. mTOR signaling pathway has been identified as a key player in the pathogenesis of psoriasis, with its dysregulation leading to the secretion of proinflammatory molecules. In the initial phase of psoriasis, LL37 and self-DNA complex activate plasmacytoid dendritic cells to produce IFN-alpha via the TLR-9 receptor. This stimulation occurs within the cell through the PI3K/Akt/mTOR pathway [12]. Previous immunohistochemical examinations revealed that CCR7-expressing dendritic cells are present in psoriatic skin, but not in healthy skin. Furthermore, Kuwabara et al. demonstrated that the PI3K/Akt pathway plays a pivotal role in CCR7-related IL-23 production from dendritic cells [13,14]. Additionally, mTORC1 has been shown to enhance the proliferation and activation of Th1 and Th17 cells, thereby perpetuating a vicious cycle of the inflammatory cascade [15]. The excessive release of cytokines, which play a pivotal role in the maintenance phase of psoriasis pathogenesis, is attributable to Th1, Th17, and Th22 cells. Mitra et al. demonstrated that IL-22-induced keratinocyte proliferation is dependent on the PI3K/Akt/mTOR pathway [16]. Another potential mechanism by which hyperactive PI3-K/Akt/mTORC1 signaling may contribute to the pathogenesis of psoriasis is through the inhibition of autophagy. An increase in mTORC1 activity impairs nuclear degradation and contributes to parakeratosis, a defining feature of psoriasis [10]. The aforementioned studies indicate that the activation of the mTOR pathway plays a pivotal role in the development of a psoriatic plaque at all stages of the process [17].

Objectives

Given the dearth of data regarding the serum levels of mTORC1 and mTORC2, our objective was to examine the levels of these complexes in the serum of patients with plaque psoriasis and to contrast these findings with those of non-psoriatic individuals.

Methods

Participants and Protocol

The prospective case-control study was designed to include 40 patients with plaque psoriasis and 40 non-psoriatic control subjects. At the initial visit, each patient's age, sex,

disease duration, treatments received, and severity score calculated by the Psoriasis Activity Severity Index (PASI) were recorded. Routine biochemistry tests (AST, ALT, cholesterol, triglyceride, HDL, LDL, urea, creatinine), complete blood count, sedimentation rate, and CRP values were also examined. In patients with plaque psoriasis, those with a PASI score of ≤10 were grouped as having mild plaque psoriasis, while those with a PASI score of >10 were grouped as having moderate to severe plaque psoriasis. Once the patient cohort had been completed, non-psoriatic volunteers who were comparable in terms of age and sex were included in the study.

The following exclusion criteria were accepted for the patient group: The use of topical treatments (corticosteroid, vitamin D3 analogue, retinoid) within the previous two months, and systemic treatments (corticosteroid, retinoid, phototherapy, immunosuppressive and biological agent) within the previous six months. Additionally, pregnant and breastfeeding women were not included in the study. Patients with a history of eating disorders (anorexia and obesity) as well as those with a history of any systemic disease (including acute or chronic infection, diabetes mellitus, thyroid disorders, chronic renal or liver disease, any malignancy, polycystic ovarian syndrome, or any endocrinologic disorders or autoimmune diseases) were excluded from the study. Individuals with a history of any systemic disease, recent systemic treatment (within the previous six months), or recent topical treatment (within the previous two months) were excluded from the control group. The study population comprised individuals aged 18 years or older with a normal body mass index (BMI) (18.5-25 kg/m²). Prior to their participation in the study, all participants were provided with a comprehensive explanation of the study's purpose, nature, and related procedures. This information was presented in a clear and concise manner, ensuring that all participants had a full understanding of the study and their role in it. The study was approved by the local ethics committee (approval number: 3454).

Serum mTORC1 and mTORC2 analysis

Venous blood samples were collected from participants to evaluate serum mTORC1 and mTORC2 levels. The samples were then centrifuged at 3000 rpm for 20 minutes, and the supernatant of the serum was collected and placed in appropriate tubes. These were stored in a -80 degree cooler until the day of the study. The analysis was conducted using a commercially available BT LAB Human mTOR Complex 1 ELISA Kit (catalog no: E4750Hu) and Human mTOR Complex 2 ELISA Kit (catalog no: E4751Hu). In both evaluations, the results were quantified spectrophotometrically at 450 nm through the utilization of the sandwich ELISA method. The standard curve range for the mTORC1 kit was 10-1500 ng/L, with a sensitivity of 4.95 ng/L, while the standard curve range for the mTORC2 kit was 5-1000 ng/L, with a sensitivity of 2.61 ng/L. The concentrations calculated with the logarithmic curve were expressed in ng/L.

Statistical Analysis

The sample size was calculated using the G*Power Version 3.1.6 program. In light of the fact that a large effect size (effect size = 0.8) between the groups would be deemed acceptable, the minimum sample size for 95% power and an alpha significance level of 0.05 was calculated as 35 patients and 35 controls, resulting in a total of 70 cases. The study was concluded with a total of 80 cases, comprising 40 patients and 40 controls. All analyses were conducted using the IBM Statistical Package for the Social Sciences (SPSS) version 20.0. The normality of the distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. Data exhibiting a non-parametric distribution are expressed as median (interquartile range), while categorical variables are expressed as number (percentage). The independent samples were compared using the Mann-Whitney U test. Categorical variables were analyzed using Pearson's chi-square test. Correlations were calculated using the Spearman correlation coefficient. A p-value of less than 0.05 was considered to be statistically significant.

Results

A total of 80 participants were included in the study, comprising 40 patients with plaque psoriasis and 40 non-psoriatic volunteers. Among the patient cohort, 25 individuals (62.5%) exhibited mild disease, while 15 (37.5%) demonstrated moderate-to -severe disease severity, as determined by PASI scores. There were no substantial differences in age and sex ratio for each variable between patients with plaque psoriasis and controls (P=0.996, P=1.0, respectively). The median (IQR) age of patients with plaque psoriasis was 39 (19) years, with 29 (72.5%) males and 11 (27.5%) females. The median (IQR) age of controls was 39.5 (21) years, with 29 (72.5%) males and 11 (27.5%) females (Table 1).

The median (IQR) serum mTORC1 concentration in patients with plaque psoriasis was significantly lower than that of the controls [158.1 (129.75) ng/L; 266.4 (471.7) ng/L, P=0,001]. Similarly, serum mTORC2 concentration in patients with plaque psoriasis was significantly lower than that of the controls [127.4 (95.1) ng/L; 219.3 (506.5) ng/L, P=0.024] (Table 2). When patients with psoriasis were examined according to disease severity, no statistically significant difference was observed between the mild and moderate-to-severe plaque psoriasis groups in terms of mTORC1 and mTORC2 levels. The median (IQR) serum mTORC1 concentration in patients with mild psoriasis was

Table 1. Demographic Characteristics of Subjects.

	Plaque Psoriasis (n=40)	Controls (n=40)	*P*
Age, years median (IQR)	39 (19)	39.5 (21)	*0,996
Sex, n (%) Male Female	29 (72.5) 11 (27.5)	29 (72.5) 11 (27.5)	**1,0
Psoriasis severity, n (%) Mild Moderate-severe	25 (62.5) 15 (37.5)		
Disease duration, years median (IQR)	10 (13.5)		

*p-value for the Mann-Whitney U test comparing age between patients with psoriasis and healthy controls. **p-value for the Pearson's chi-square test comparing sex ratio between patients with psoriasis and healthy controls.

Table 2. mTORC1 and mTORC2 levels of the patient with plaque psoriasis and control group.

	Psoriasis (n= 40)	Controls (n= 40)	*P*	Psoriasis severity		*P*
				Mild (n=25)	Moderate to severe (n=15)	
mTORC1, ng/L median (IQR)	158.1 (129.75)	266.4 (471.7)	0,001*	159.5 (181.5)	156.7 (103.4)	0,878*
mTORC2, ng/L median (IQR)	127.4 (95.1)	219.3 (506.5)	0,024*	127 (109.9)	127.8 (91)	0,737*

*Mann-Whitney U Test

159.0 (181.5) ng/L, while in those with moderate-to-severe psoriasis, it was 156.7 (103.4) ng/L. The p-value for this comparison was 0,878. The median (IQR) serum mTORC2 concentration in patients with mild psoriasis was 127.0 (109.9) ng/L, while in those with moderate to severe psoriasis, it was 127.8 (91) ng/L. The p-value for this comparison was 0,737 (Table 2).

A strong positive correlation was identified between serum mTORC1 and mTORC2 levels (P=0.001, r=0.826) (Figure 1). No significant correlation was observed between serum mTORC1 and mTORC2 levels and age, sex, PASI scores, CRP, or total cholesterol levels (P> 0.05).

Duration of the Disease

The median (IQR) disease duration for all patients with plaque psoriasis, those with mild plaque psoriasis, and those with moderate-to-severe plaque psoriasis was 10 (13.5) years, 10 (15) years, and 13 (11) years, respectively. A negative correlation was observed between disease duration and both mTORC1 and mTORC2 levels (P= 0.041, r= -0.320; P= 0.046, r= -0.314, respectively) (Figures 2, 3).

Discussion

A significant number of aspects pertaining to the pathophysiology of psoriasis remain to be elucidated, given the intricate interplay between genetic, environmental and immunological factors. Intracellular signaling pathways play a pivotal role in the pathogenesis of psoriasis and other inflammatory dermatoses, as numerous critical pathogenic events in both immune system cells and skin resident cells are linked to dysregulation of these pathways. Among these, the PI3K/AKT/mTOR, JAK/STAT, JNK/MAPK, and WNT signaling pathways are of particular importance in the complex pathogenesis of psoriasis [18]. The mTOR signaling pathway plays a pivotal role, functioning as the primary regulator of cellular metabolism and homeostasis. Previous studies demonstrated elevated activation of the mTOR signaling pathway in tissue samples from patients with psoriasis, as evidenced by immunohistochemical methods [9]. Despite the acknowledged significance of the PI3K/AKT/mTOR signaling pathway in the etiology of psoriasis, there is a paucity of data concerning serum mTORC1 and mTORC2 levels. Therefore, the objective

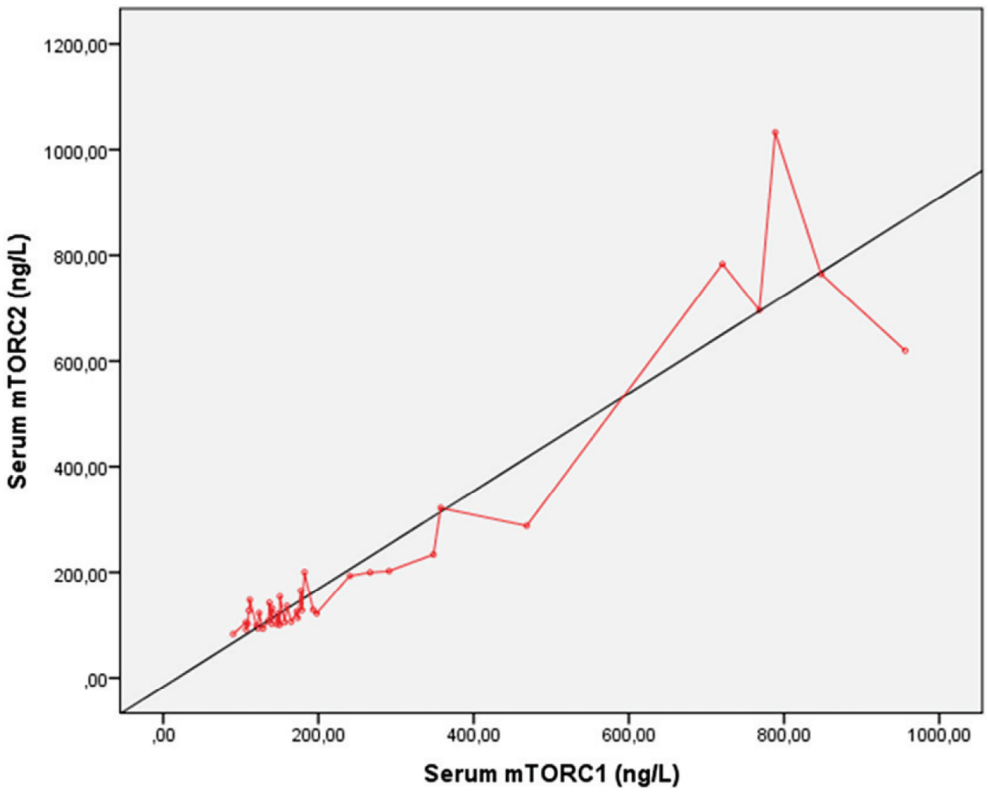

Figure 1. Positive Correlation of Serum mTORC1 and Serum mTORC2 Levels in Patients with Plaque Psoriasis.

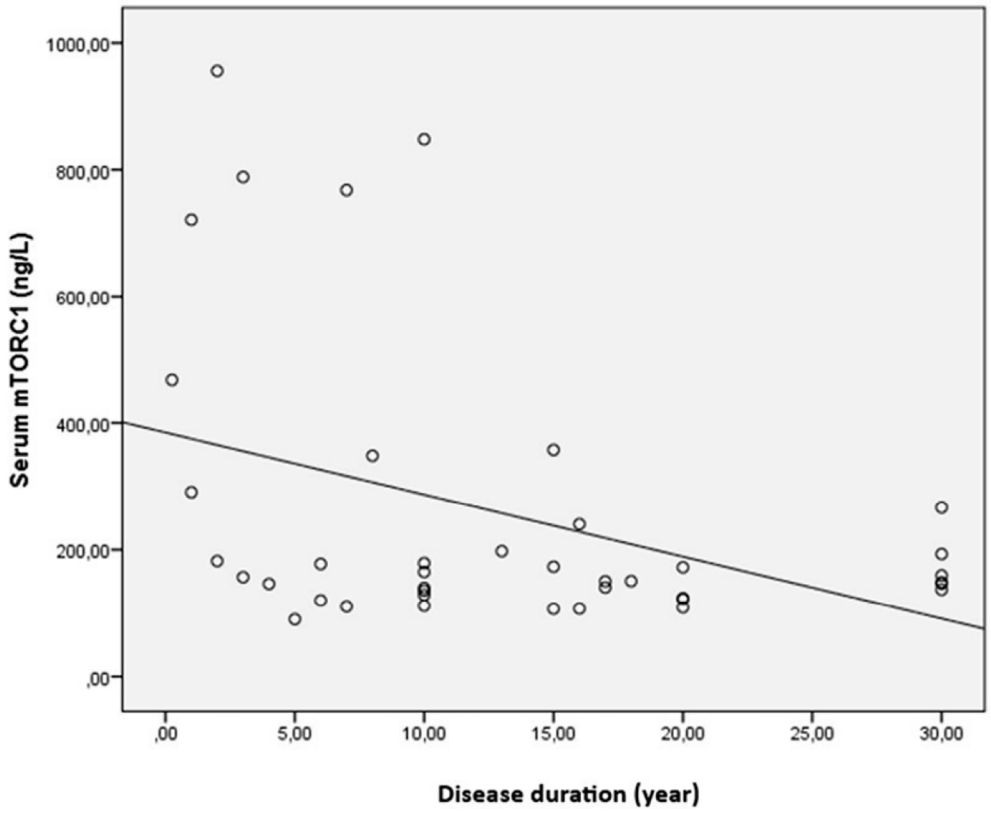

Figure 2. Negative Correlation between Serum mTORC1 Levels and Duration of the Disease in Patients with Plaque Psoriasis (*P*= 0.041, r= -0.320).

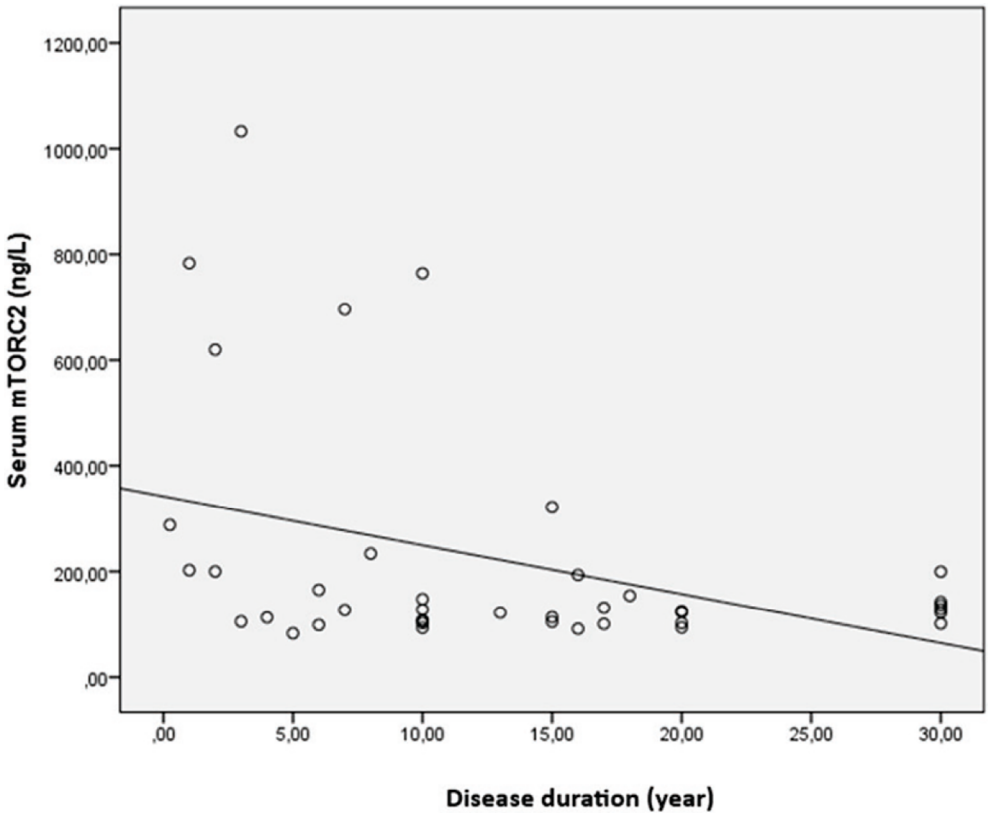

Figure 3. Negative Correlation between Serum mTORC2 Levels and Duration of the Disease in Patients with Plaque Psoriasis (*P*= 0.046, r= -0.314).

of this study was to examine the serum levels of mTORC1 and mTORC2 complexes in a cohort of 40 patients with plaque psoriasis and to compare these levels with those observed in a control group of 40 non-psoriatic individuals.

This study demonstrated that serum mTORC1 and mTORC2 levels were significantly lower in patients with plaque psoriasis compared to control subjects. Another study, conducted by Cheng et al., employed the ELISA method to investigate the serum levels of mTOR and PS6K in order to elucidate the role of the mTOR pathway in sepsis-associated myocardial dysfunction (SIMD) [19]. The researchers observed that the serum mTOR levels in the patient group with SIMD were lower than those in the control group, but this difference was not statistically significant. Conversely, the PS6K level, which is one of the substrates of mTORC1, was found to be higher in the patient group with SIMD, and this difference was statistically significant. Similarly, our study revealed low levels of mTORC1 and mTORC2 in the serum of patients with plaque psoriasis. Nevertheless, it is established in the literature that the activation of mTOR increases in psoriatic tissue. The following explanations may be put forward to account for this discrepancy. Firstly, it should be noted that the ELISA method utilized in this study measures the total mTOR concentration in serum, whereas the main active state of mTOR is in the phosphorylated form within the cell. This suggests that the levels of effector proteins involved in the mTOR pathway in serum may differ from those in tissue. Secondly, it is possible that additional mechanisms may be involved in the activation of the mTOR pathway in psoriatic tissue. However, the precise cause of this discrepancy remains unclear. Consequently, further investigation is required to elucidate the underlying mechanisms.

To ascertain whether there is a correlation between psoriasis disease severity and serum mTORC1 and mTORC2 levels, the patient cohort was stratified into two subgroups, designated as mild and moderate-to-severe, based on their PASI scores. No statistically significant difference was observed between the two groups. This discrepancy is likely due to the limited number of cases with moderate-to-severe psoriasis included in the study. However, a negative correlation was identified between serum levels of both mTORC1 and mTORC2 and disease duration in patients with psoriasis, with a statistically significant result. The observed reduction in serum mTORC1 and mTORC2 levels in individuals with active disease and prolonged disease duration may indicate a role for these factors in the perpetuation of the chronic inflammatory process.

mTORC1 is sensitive to rapamycin, while mTORC2 has been demonstrated to be inhibited in certain cell types by long-term sirolimus treatment [20]. It has been proposed

that agents capable of effectively inhibiting both mTOR complexes, rather than solely mTORC1, may offer greater potential for the treatment of psoriasis [21]. Chamcheu et al. demonstrated that the molecule delphinidin, a naturally occurring antioxidant pigment, could provide improvement in psoriasis lesions in imiquimod-induced psoriasis mouse models by effectively inhibiting the PI3K/Akt/mTOR pathway [22]. In a study conducted by Roy et al. in 2023, the effectiveness of an antioxidant and antiproliferative dietary polyphenol, fisetin, on psoriasis was demonstrated both in vitro and in vivo. Fisetin inhibits S6K and mTOR by covalently binding and reduces PI3K/Akt/mTOR pathway activation. The authors hypothesize that fisetin-induced improvement of these in vitro and in vivo inflammatory responses in psoriasis is associated with mTOR-centered signaling inhibition [23]. We found a positive correlation was observed between serum mTORC1 levels and serum mTORC2 levels in patients, which lends support to the hypothesis that both complexes play an important role in the pathogenesis of psoriasis.

Psoriasis is regarded as a systemic disease, with a high prevalence of cardiovascular comorbidities. Recent studies have indicated that mTOR activation may play a pivotal role in the development of atherosclerotic plaques [24,25]. Loyola and colleagues focused on the identification of novel biomarkers for cardiovascular disease in patients with psoriasis. They analyzed mTOR activation via the detection of phosphorylation of S6R protein, a substrate of the mTORC-1 protein synthesis pathway, in extracted mononuclear cells from 10 patients with psoriasis and compared this with 11 healthy individuals [26]. The study revealed elevated levels of S6Rp in psoriatic patients, particularly in M2 monocytes. The authors proposed that mTOR activity may serve as an early marker of cardiovascular risk in psoriatic patients [26]. Consequently, mTOR activation in patients with psoriasis may be a contributing factor in the increased prevalence of cardiovascular disease. Further research on the levels of mTOR in patients with psoriasis with and without cardiovascular comorbidities may elucidate this potential relationship.

There are several weak points in this study. Firstly, although serum mTORC1 and mTORC2 levels of patients with plaque psoriasis are significantly lower, it is not known how mTORC1 and mTORC2 expression changes at the level of psoriatic plaques because immunohistochemistry was not performed. While the literature indicates an increase in mTOR expression in psoriatic plaques, it is challenging to ascertain a direct correlation between serum levels and the disease. Secondly, the number of patients with moderate-to-severe plaque psoriasis was limited, which precluded the ability to ascertain the relationship between mTORCs and disease severity. Thirdly, in order to gain a more comprehensive understanding of the role of the mTOR pathway and its relationship to variables in patients, such as disease severity and comorbidities, further studies with larger numbers of patients are required.

Conclusion

In conclusion, we found that the serum mTORC1 and mTORC2 levels of patients with plaque psoriasis were lower than those of control subjects. This can be explained by the fact that mTORC1 and mTORC2 complexes, which belong to the mTOR signaling pathway, are active molecules within the cell. To further evaluate these results, it would be beneficial to conduct comparative studies of the activity of the mTOR pathway in tissue and serum. The observed positive correlation between serum mTORC1 and serum mTORC2 levels in the patient group provides evidence that both mTORC1 and mTORC2 complexes play an important role in the pathogenesis of psoriasis. Consequently, molecules that inhibit both complexes may prove to be more effective in the treatment of psoriasis.

Abbreviations: mTOR: mammalian target of rapamycin; mTORC1: mechanistic target of rapamycin complex 1; mTORC2: mechanistic target of rapamycin complex 2; 4EBP1: eukaryotic translation initiation factor 4E-binding protein 1; PI3K: phosphoinositide-3-kinase; ELISA: enzyme-linked immunosorbent assay; S6K1: ribosomal protein S6 kinase 1; JAK/STAT: Janus kinase/signal transducers and activators of transcription; TLR: toll-like receptor; JNK/MAPK: c-Jun N-terminal kinase (JNK)- mitogen-activated protein kinase.

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