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Gender-related Therapeutical Response to Apremilast: New Insights in a Tailored Management of Psoriasis

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ABSTRACT

Introduction: Psoriasis is a chronic immune-mediated skin condition. One of the intriguing challenges in studying psoriasis has been identification of correlations between this disease and gender and body weight.

Objectives: A multicenter retrospective study was conducted among patients with moderate-to-severe psoriasis who attended the outpatient clinics of 6 University Hospitals in Italy. The effects of apremilast on weight and body mass index (BMI) according to gender after 24 weeks and 48 weeks of therapy were considered.

Methods: We enrolled retrospectively 120 adult patients with moderate-to-severe psoriasis who underwent apremilast treatment for at least 24 weeks. Baseline characteristics, including age, gender, psoriasis area severity index (PASI), comorbidities, smoking and alcohol habits, relevant medical history and previous psoriasis systemic and biologic treatments were recorded. Weight and BMI were evaluated at baseline (T0) and at 24 (w24) and 48 weeks (w48). A descriptive statistical analysis has been performed.

Results: The analysis showed a significant reduction in body weight in females at w24 and w48 ($P < 0.001$), with a mean difference of –2.6 kg at w24 and of -5.7 kg at w48. We observed a reduction of weight of 3.6% at w24, and 7.9% at w48. Similar assessments were also observed for BMI, which was reduced in women by 3.6% at w24 and 8% at w48. In men, no changes in weight and BMI were observed at w24 and/or w48.

Conclusions: Understanding the interplay between psoriasis, gender, and body weight is essential for effective disease management and improving patient outcomes.

Introduction

Psoriasis is a chronic immune-mediated skin condition, posing both physical and psychological challenges for patients [1]. This complex dermatological condition is characterized by the presence of red, scaly plaques on the skin, often accompanied by itching and pain. However, beyond the physical aspect, psoriasis can heavily affect quality of life, impacting self-esteem, social relationships, and even individuals emotional well-being [2]. One of the most intriguing challenges in studying psoriasis has been the identification of correlations between this disease and various factors, including gender and body weight. In addition to environmental exposures (such as air pollution and sunlight) and lifestyle factors (diet and physical activity), the concept of the exposome also includes psychosocial practices. Meanwhile, its outcomes, including epigenomics, transcriptomics, proteomics, and metabolomics, are gaining attention as key mechanisms in disease development. The term "exposome" refers to all the environmental factors, both infectious and non-infectious, that a person is exposed to throughout their life. It encompasses the cumulative impact of these factors on health, potentially leading to disease or influencing its progression. The exposome plays a role in all skin diseases, including psoriasis. Factors such as lifestyle habits (diet, smoking, obesity, sun exposure), pre-existing conditions, exposure to infectious agents, as well as individual characteristics like skin microbes, oxidative stress, and immune responses, all contribute to the development and progression of psoriatic lesions in different ways [3]. Research has shown that psoriasis may manifest differently depending on the patient gender [4-5]. Regarding sex hormones, estrogens inhibit the production of psoriasis-related cytokines like IL-1β and IL-23. For instance, men are more likely to develop plaque psoriasis on the scalp and trunk, while women are more prone to present lesions on the face and neck [6]. Moreover, while men tend to develop psoriasis at an earlier age and have more severe symptoms, women are more likely to experience fluctuations in disease activity associated with hormonal changes, such as menstruations, pregnancy or menopause [7]. In fact, psoriasis lesions tend to appear or worsen during puberty and improve during menopause [8]. These differences may be attributed to a combination of genetic, hormonal, and environmental factors, requiring further exploration for full understanding. Moreover, an intriguing link has emerged between psoriasis and body weight, considering obesity as a part of the exposome [9]. Epidemiological studies have established a significant association between obesity and a higher risk of developing psoriasis, suggesting a possible role of systemic chronic low-grade inflammation in the disease pathogenetic process [10].

The relationship between psoriasis and obesity is complex and bidirectional. On one hand, obesity may contribute to the onset and severity of psoriasis through mechanisms involving adipose tissue-derived cytokines and insulin resistance, which promote systemic inflammation and exacerbate immune dysregulation [11]. On the other hand, psoriasis itself can influence body weight, as the physical discomfort and self-consciousness associated with skin lesions may lead to lifestyle changes, such as adopting restrictive diets or avoiding physical activities [12]. Adipocytes release a range of cytokines associated with inflammation, contributing to inflammatory responses, including in psoriasis. In psoriatic lesions, unsaturated fatty acids, some of which have anti-inflammatory and anti-proliferative effects, show notable variations. Disruptions in the urea cycle and the phenylalanine-tyrosine pathway can result in higher levels of ornithine and phenylalanine in these lesions. The rapid skin cell turnover in psoriasis also affects nucleotide metabolism, leading to reduced levels of certain metabolites due to increased demand and accelerated breakdown of purines and pyrimidines. Studies have found that elevated levels of proline and hydroxyproline, amino acids involved in the urea cycle and collagen production, may be linked to the severity of psoriasis [3]. This psoriasis-related inflammation and psychosocial stress can adversely affect metabolic health and contribute to weight gain, forming a vicious cycle that further complicates disease management [13]. Gender-specific factors could allow tailored approaches for each single patient, taking in consideration comorbidities, changes in lifestyle but above all therapies. At the same time, managing clinical responses becomes increasingly complex in patients with multi-failure psoriasis, who have undergone multiple biologic treatments, as their immune system undergoes dynamic fluctuations [14]. Addressing their evolving immunologic landscape presents significant challenges, requiring individualized

approaches to achieve therapeutic efficacy among changing treatment paradigms and individual patient responses.

Objectives

In last years, to the already rich therapeutical armamentarium of monoclonal antibodies, the small molecules have found a unique position [15]. Among them, apremilast, a phosphodiesterase-4 inhibitor (PDE4i) approved for the treatment of moderate-to-severe psoriasis and psoriatic arthritis (PsA), has been suggested to have a potential beneficial metabolic effect [16-17]. To further confirm these hypotheses, a multicenter retrospective study was conducted among patients with moderate-to-severe psoriasis attending the outpatient clinic of 6 University Hospital in Italy, considering the effects of apremilast on weight and body mass index (BMI) according to gender after 24 weeks and 48 weeks of therapy.

Methods

We enrolled retrospectively adult patients (aged >18 years) with a confirmed diagnosis of moderate-to-severe psoriasis who underwent apremilast treatment for at least 24 weeks in the period from March 2018 to November 2023. Baseline characteristics, including age, gender, psoriasis area severity index (PASI), comorbidities, smoking and alcohol habits, relevant medical history and previous psoriasis systemic and biologic treatments were recorded. Weight and body mass index (BMI) were evaluated at baseline (T0) and at 24 (w24) and 48 weeks (w48). A descriptive statistical analysis has been performed. One-way or mixed paired ANOVA were used to evaluate the change of weight and BMI among different follow-up visits. A P value less than 0.05 was considered statistically significant.

Results

A total of 120 patients (63 male [M]: 63 [52.5%]) and 57 female [F] [47.5%]) with psoriasis treated with apremilast for at least w24 and with a follow-up visit at w48 were enrolled. Twenty-eight patients (11 M [17.5%]) and 14 F [24.5%]) discontinued apremilast before w48; among them, 5 dropped-out at follow-up visit, 16 patients reported adverse events (gastrointestinal symptoms, diarrhea), and 7 patients had primary failure. The mean age of the patients was 63.5 ± 6.3 years (64.4 ± 13.2 in the male group and 62.6 ± 11.7 in the female group). Mean duration of psoriasis was about 21.9 ± 0.7 years in all patients (23.2 ±14.9 in male and 20.2 ± 13.7 in female). Data about smoking, alcohol habits and comorbidities are reported in Table 1. Considering special sites of psoriasis, 30 patients (25%) had nail involvement (15 M – 23.8% and 15 F – 26.3%), 30 patients (25%) reported involvement of palms and soles (11 M – 17.5% and 19 F – 33.3%), 55 patients (45.8%) on the scalp (23 M – 36.5% and 32 F – 56.1%), and 16 (13.3%) on genitalia (7 M – 11.1% and 9 F – 15.8%). Forty-one patients (34.2%; 19 M – 30.1% and 22 F – 38.6%) had concomitant PsA. Out of 120 patients, 31.7% (n= 38, 17 M – 27% and 31 F – 36.9%) were naïve to systemic therapies and 67.5% (n = 81, 45 M – 71.4% and 36 F – 63.2%) were bio-naïve. Data about previous systemic or biologic therapies are reported in Table 1. The mean duration of therapy with apremilast expressed in months was 25.2 ± 19.4 (28.4 ± 20.9 in males and 21.5 ± 17.1 in females). The mean baseline PASI score for all patients was 10.1 ± 3.39 with higher values in males (10.7 ± 4.8) than females (9.75 ± 1.17). Because the focus of the study was to assess changes in weight and BMI according to the gender of enrolled patients, PASI values were not analyzed at w24 and w48. Patients baseline characteristics are reported in Table 1. In male patients, the average weight was 87.1 ± 19.7 kg at baseline, 86.8 ± 19.5 kg at week 24, and 87 ± 20.1 kg at week 48, with a corresponding BMI of 24.8 ± 5.1 at baseline, 24.7 ± 5.1 at week 24, and 24.6 ± 5.3 at week 48. For women, the average weight decreased from 72.1 ± 15.6 kg at baseline to 69.6 ± 15.3 kg at week 24, and further to 66.4 ± 15.7 kg at week 48. Their mean BMI followed a similar trend, starting at 22.3 ± 4.9 at baseline, dropping to 21.5 ± 4.8 at week 24, and reaching 20.5 ± 5.1 at week 48. The most notable changes were observed in women, with a more significant reduction in both weight and BMI over time. Values about weight and BMI are reported in Table 2. The analysis showed a significant reduction in body weight in females at w24 and w48 ($P < 0.001$), with a mean difference of –2.6 kg (95% confidence interval [CI] –15; –0.2) at w24 and of -5.7 kg; (95% CI –15; –3) at w48. We observed a reduction of weight of 3.6% at w24 ($P < 0.001$), and 7.9% at w48 ($P < 0.001$). Similar assessments were also observed for BMI, which was reduced in women by 3.6% at w24 and 8% at w48 ($P < 0.001$) (Figure 2). In men, no changes in weight and BMI were observed at w24 and/or w48, and the values remained almost unchanged (Figures 1 and 2).

Conclusions

In our research, we detected a notable decrease in both mean weight and BMI in women treated with apremilast. We observed a steady trend of weight reduction as early as w24 and almost doubled at w48. Weight loss was higher in overweight patients who reported mean changes of about 12 kg at both w24 and w48. However, given the documented correlation between weight loss and apremilast use and the potential risks associated with substantial weight reduction,

Table 1. Demographic and Medical History Data at Baseline of Patients Enrolled

	All Patients (100% - N = 120)	Males (52.5% - N = 63)	Females (47.5% - N = 57)
Age (years)	63.5 ± 6.3	64.4 ± 13.2	62.6 ± 11.7
Weight (kg)	79.9 ± 19.3 kg	87.1 ± 19.7 kg	72.1 ± 15.6
BMI	23.6 ± 4.9	24.8 ± 5.1	22.3 ± 4.9
Duration of disease (years)	21.9 ± 0.7	23.2 ±14.9	20.2 ± 13.7
Mean PASI	10.1 ± 3.39	10.7 ± 4.8	9.75 ± 1.17
Smoke • current • former • no	 24.2% (29) 20.8% (25) 55% (66)	 25.4% (16) 30.1% (19) 44.4% (28)	 22.8% (13) 10.5% (6) 66.6% (38)
Alcohol • yes (occasional) • no	 30% (36) 70% (84)	 36.5% (23) 63.5% (40)	 22.8% (13) 77.2% (44)
Special sites • scalp • palms/soles • nails • genitalia	 45.8% (55) 25% (30) 25% (30) 13.3% (16)	 36.5% (23) 17.5% (11) 23.8% (15) 11.1% (7)	 56.1% (32) 33.3% (19) 26.3 (15) 15.8% (9)
Psoriatic arthritis (PsA)	34.2% (41)	30.1% (19)	38.6% (22)
Comorbidities • diabetes • CVDs • HCV • dyslipidemia • hypertension • glaucoma • cancer • depression • thyroidopathy • HS • vitiligo • latent TB	95% (114) 11.7% (14) 5% (6) 0.8% (1) 9.2% (11) 24.2% (29) 0.8% (1) 36.7% (44) 1.7% (2) 2.5% (3) 0.8% (1) 0.8% (1) 0.8% (1)	92.1% (58) 11.1% (7) 6.3% (4) - 7.9% (5) 20.6% (13) - 36.5% (23) - 4.8% (3) 1.6% (1) 1.6% (1) 1.6% (1)	98.3% (56) 12.3% (7) 3.5% (2) 1.8% (1) 10.5% (6) 28.1% (16) 1.8% (1) 36.8% (21) 3.5% (2) - - - -
Previous systemic therapies (phototherapy or cDMARDs)	Naïve 31.7% (38) CyA 36.7% (44) MTX 37.5% (45) ACI 13.3% (16) DMF 22.5% (27) nbUVB 37.5% (45)	Naïve 27% (17) CyA 38.1% (24) MTX 31.7% (20) ACI 15.9% (10) DMF 25.4% (16) nbUVB 39.7% (25)	Naïve 36.8% (21) CyA 35.1% (20) MTX 43.9% (25) ACI 19.3% (11) DMF 10.5% (6) nbUVB 35.1% (20)
Bionaïve	67.5% (81)	71.4% (45)	63.2% (36)
Previous mAbs (number)	1) 14.2% (17) 2) 8.3% (10) 3) 0.8% (1) 4) 2.5% (4) 5) 1.7% (2) 6) 0.8% (1)	11.1% (7) 6.3% (4) 1.6% (1) 1.6% (1) - -	17.5% (10) 10.5% (6) - 3.5% (2) 3.5% (2) 1.8% (1)
Duration of therapy with apremilast (months)	25.2 ± 19.4	28.4 ± 20.9	21.5 ± 17.1

ACI = acitretin; BMI = body mass index; CVDs = cardiovascular diseases; CyA = cyclosporin A; DMF = dimethylfumarate; cDMARDs = conventional disease modifying anti-rheumatic drugs; HS = hidradenitis suppurativa; mAbs = monoclonal antibodies; MTX = methotrexate; nbUVB = narrowband UVB; PASI = Psoriasis Area and Severity Index; TB = tuberculosis.

Table 2. Weight and body mass index According to Gender at Baseline and After 24 and 48 Weeks of Therapy With Apremilast

	Weight			BMI		
	Baseline	Week 24	Week 48 (p < 0.001)	Baseline	Week 24	Week 48 (p < 0.001)
Males	87.1 ± 19.7	86.8 ± 19.5	87 ± 20.1	24.8 ± 5.1	24.7 ± 5.1	24.6 ± 5.3
Females	72.1 ± 15.6	69.6 ± 15.3	66.4 ± 15.7	22.3 ± 4.9	21.5 ±4.8	20.5 ± 5.1

BMI = body mass index.

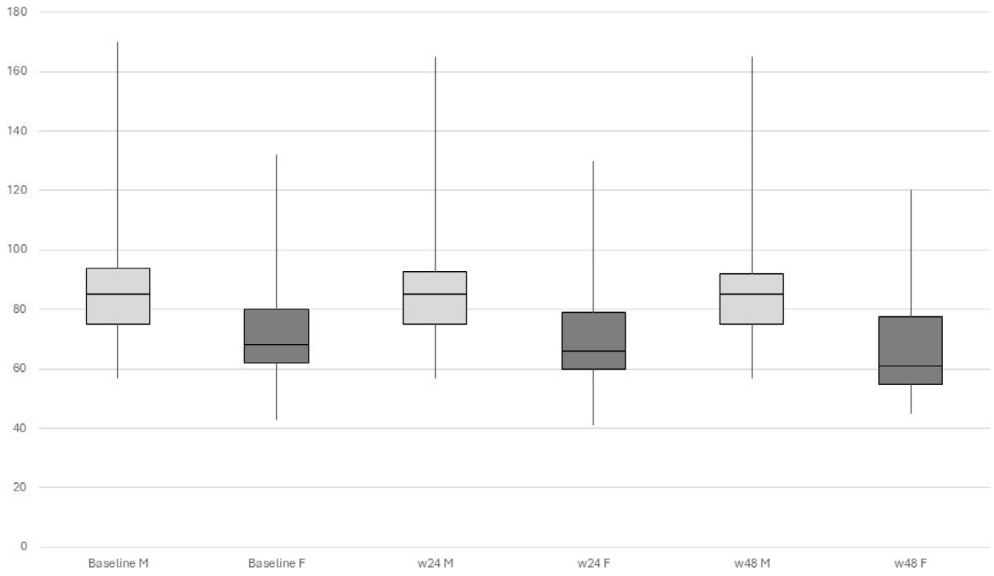

Figure 1. Boxplot of weight. Males (light gray) at baseline, w24 and w48 and females (dark gray) at baseline, w24 and w48.

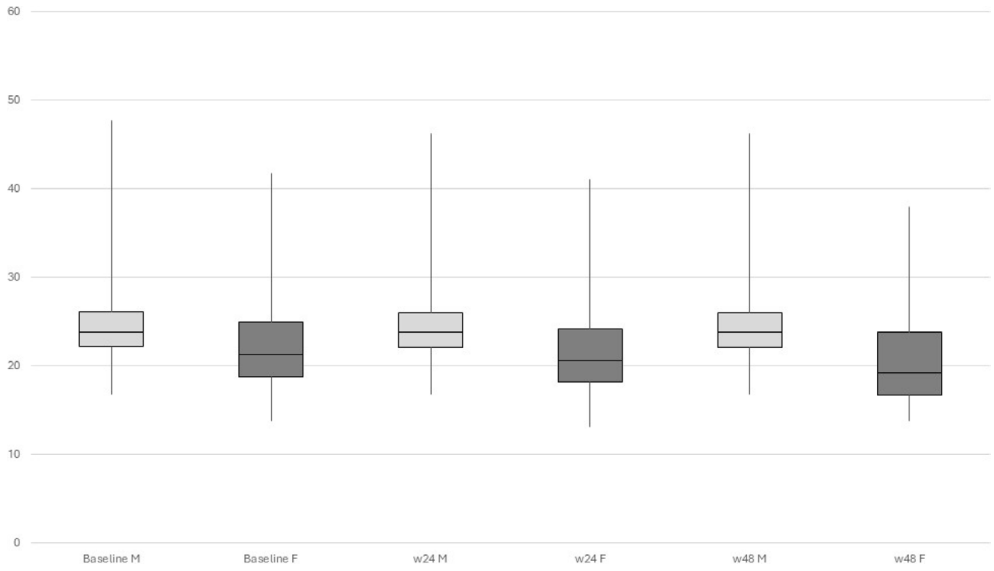

Figure 2. Boxplot of body mass index. Males (light gray) at baseline, w24 and w48 and females (dark gray) at baseline, w24 and w48.

careful monitoring is imperative, particularly for individuals with below-average body weight [18-19].

In accordance with our study findings, pivotal trials have underscored weight loss as a significant adverse event in patients in treatment with apremilast. An amalgamated analysis of phase 3 trials ESTEEM 1 and ESTEEM 2 revealed a mean percentage change in weight of 1.53% over the 156-week treatment period with apremilast [20]. Notably, a higher baseline BMI was associated with a greater proportion of patients experiencing weight loss, primarily observed within the initial year of treatment. Moreover, no discernible correlation was established between gastrointestinal adverse events, such

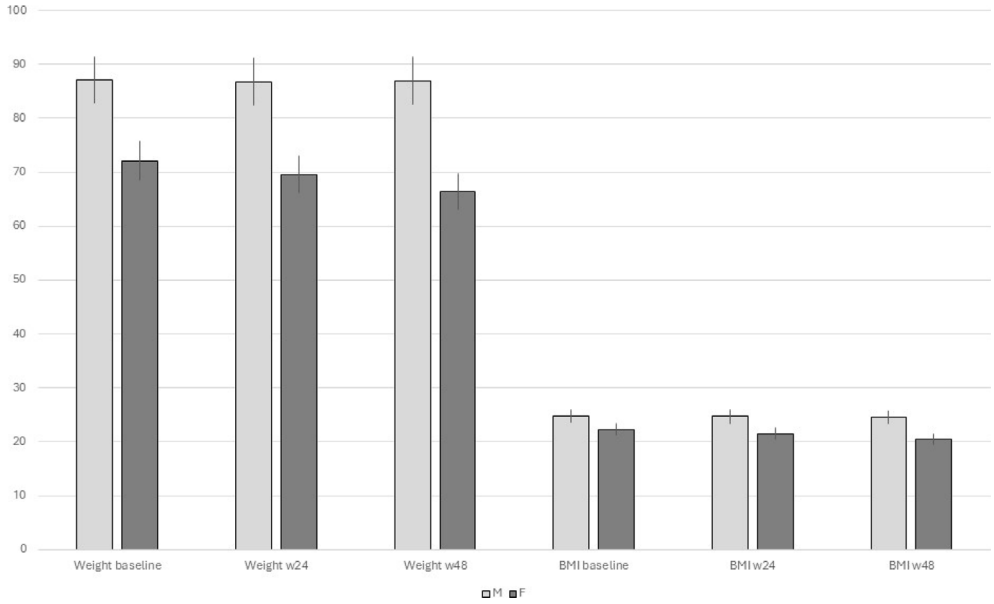

Figure 3. Comparison between males (light gray) and females (dark gray) for weight and bdy mass index at baseline, w24 and w48.

as diarrhea, nausea, or vomiting, and weight loss in patients treated with apremilast [17]. Other studies have evaluated the reduction in weight and/or BMI during apremilast therapy. In a 6-month prospective open-label study involving patients with PsA and psoriasis treated with apremilast, consistent reductions in weight and BMI were reported. The study demonstrated an average weight loss of 2.2 kg, a significant decrease in waist circumference at week 4, and a reduction in hip circumference at week 12 [21]. Further consideration would be needed regarding the possible role of the molecule on visceral fat. The differentiation between visceral and subcutaneous fat assumes significance in the assessment of cardiovascular disease (CVD) risk, given the metabolic activity of the former and its impact on cardiovascular homeostasis [22]. Dysregulated inflammation in visceral adipose tissue exacerbates endothelial dysfunction, altering immune cell and adipokine profiles [23]. A study highlighted a 6% reduction in both subcutaneous and visceral fat in patients treated with apremilast, with a steady downward trend from week 16 to 52 [24]. Consequently, the observed decline in both subcutaneous and visceral fat in patients receiving apremilast treatment suggests a potential protective effect against CVDs. Additionally, interventions targeting weight loss have demonstrated efficacy in reducing psoriasis severity among overweight or obese individuals [25]. Obesity and elevated BMI, recognized as CVDs risk factors, have also been associated with diminished short-term clinical responses to various systemic treatments, particularly biologics [26]. Therefore, the documented influence of apremilast on weight loss and adiposity reduction holds promise for improving metabolic profiles and treatment responses within this specific patient population. This finding is part of the now widespread and shared belief that a comprehensive approach to the psoriatic patient is essential, allowing for targeted action on both skin disease and comorbidities and aiming to restore well-being [27]. From the result of our study, however, weight loss and BMI reduction appear to be the exclusive preserve of women while men are less affected by these changes (Figure 3).

To date, gender dermatology has focused almost exclusively on possible differences in the therapeutic efficacy of systemic drugs or mAbs [28]. The mechanism underlying the results of our study is not fully elucidated. There is a morphological difference between fat accumulation in women and that in men, which gender hormones related, along with the density of their respective receptors [29]. In fact, adipocytes have specific receptors for androgens with a higher density in visceral fat cells than in adipocytes isolated from subcutaneous fat [30]. In particular, alpha1-adrenergic receptors play a significant inhibitory role in lipogenesis, while alpha2-adrenergic receptors inhibit lipolysis [31]. Alpha2s are 17 times more numerous in women than in men [32]. Thus, a role of apremilast on alpha2 inhibition and alpha1 over-activation could be hypothesized, which would explain the greater weight loss in women than in men. However, further studies are needed to substantiate this hypothesis.

Considering these intricate connections, a multidisciplinary approach involving dermatologists and endocrinologists is essential for comprehensive psoriasis care. Collaborative efforts aimed at addressing both the dermatological and systemic aspects of the disease, while considering the unique characteristics of each patient, are crucial for achieving optimal outcomes and enhancing quality of life. In conclusion, understanding the interplay between psoriasis, gender, and body weight is essential for effective disease management and improving patient outcomes. By being able to understand the complexities of these relationships

through further research and clinical practice, we can pave the way for more personalized and holistic approaches to psoriasis care, ultimately empowering individuals to better cope with the challenges posed by this chronic condition.

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