Prevalence of metabolic syndrome and chronic inflammation in psoriasis before and after biologic therapy: a prospective study

Teodora-Larisa Timis[1], Lehel Beni[2], Ioan-Alexandru Florian[2], Meda Orăsan[3], Remus Ioan Orăsan[1]

1) Department of Physiology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

2) Department of Neurosciences, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

3) Department of Pathophysiology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

Abstract

Background. As a chronic inflammatory disease, psoriasis affects not only the skin but also the metabolic profile of the patients. Biologic therapies, including tumor necrosis alpha (TNF-a) inhibitors and interleukin (IL)-12/23 and IL-17 antagonists, have proven effective in the reduction of psoriasis severity; however their impact on the metabolic and chronic inflammatory profiles of the patients remains incompletely elucidated.

Methods. We performed a longitudinal case-control study on 106 psoriasis patients and an equal number of controls without the disease, as well as a prospective study on the patient group with the end point being 6 months of biologic therapy. Patients received either ixekizumab, secukinumab, guselkumab, certolizumab, ustekinumab, risankizumab, or adalimumab. Abdominal circumference, serum fasting glucose, triglycerides (TG), high-density lipoproteins (HDL), erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) were measured for both patients and controls, with an additional measurement for patients after 6 months.

Results. At baseline, the number of psoriasis patients suffering from obesity, metabolic syndrome, and chronic inflammation significantly outnumbered controls (p<0.05), with the calculated odds ratio being 1.88, 6.83, and 81.84 for these conditions in psoriasis, respectively. Biologic therapies increased the abdominal circumference of patients in a slight but significant fashion (p<0.05), as well as significantly improved HDL, CRP, ESR levels at 6 months (p<0.05). Moreover, after 6 months, the number of patients meeting the diagnostic criteria for metabolic syndrome and chronic inflammation was significantly lower than at baseline (p<0.001).

Conclusions. According to our results, biologic therapies improve the overall metabolic and inflammatory profiles of psoriasis patients, the most significant ameliorations being noticed for serum HDL, CRP, and ESR.

Keywords: psoriasis, metabolic syndrome, obesity, diabetes, abdominal circumference, chronic inflammation

Background
Pathogenesis of psoriasis

Psoriasis is a chronic, immune-mediated illness characterized by a hypertrophied and scaly appearing series of skin patches, caused by disturbed immune cells. The typical location for cutaneous lesions is the extensor surfaces of the limbs, the scalp, or the lumbosacral region [1]. In the pathogenesis of psoriasis, oxidative stress, reactive oxygen species [ROS], and a higher concentration of insulin-like growth factor-1 (IGF-1) and epidermal growth factor (EGF) have been demonstrated. Several susceptibility loci for psoriasis have been identified through linkage studies (PSORS1-12). Psoriasis with an early onset is strongly associated with the HLA-Cw6 allele. Regarding biomarkers in psoriasis, additional research is ongoing. Leptin and resistin are considered potential biomarkers for the prediction of insulin resistance and atherosclerosis in obese psoriasis patients [2].

Metabolic syndrome

The metabolic syndrome denotes an accumulation of several interconnected pathologies that lead to an upsurge of the risk of severe complications such as atherosclerotic coronaropathies or cerebral stroke [3-5]. It is a cluster of known cardiovascular risk factors, such as obesity, dyslipidemia, hypertension, and impaired glucose tolerance. It is not a random occurrence that psoriasis and metabolic syndrome are linked. It appears that psoriasis and metabolic syndrome share overlapping pathogenic mechanisms, with systemic inflammation and the elevation of inflammatory markers being present in both [6]. Metabolic syndrome is commonly associated with overweight or obesity. The adipose tissue can be considered as a metabolically active endocrine organ which generates proinflammatory adipokines and cytokines, which in turn attract immune cells with the promotion of macrophage differentiation into M1 cellular subtypes. Such adipokines include TNF-a, IL-6, and leptin, the last of which acts on T cells, macrophages, and other immune cells to promote the production of a broad range of cytokines, resistin, chemerin fibrinogen, and CRP, as well as lower levels of anti-inflammatory factors such as adiponectin. Dysglycemia, atherogenic dyslipidemia, and vascular dysfunction arise as a result of the actions of these factors [7,8]. For a diagnosis of metabolic syndrome to be established, at least three out of five criteria need to be present. According to the National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association (AHA), these are as follows:

- Fasting glucose ≥100 mg/dL (or receiving medical treatment for hyperglycemia);

- Blood pressure (BP) ≥130/85 mmHg (or receiving medical treatment for hypertension – HTN);

- Serum triglyceride (TG) level ≥150 mg/dL (or receiving medical treatment for hypertriglyceridemia);

- High-density lipoprotein (HDL) serum levels <40 mg/dL in males or <50 mg/dL in females (or receiving medical treatment for low level HDL);

- Abdominal circumference ≥102 cm in males or ≥88 cm in females (conditions differing slightly for those of Asian descent: ≥90 cm in males or ≥80 in females).

Chronic inflammation in psoriasis

Inflammation is a precisely controlled, well-regulated immune system response to various stimuli that provides protection and defense against both external and internal threats (such as pathogens, toxins, chemicals, cancer, and damaged cells) and promotes regeneration of damaged tissue [9]. Multiple factors have been implicated in the pathogenesis of psoriasis, including genetic predisposition (polymorphisms in genes regulating various immunological signaling pathways and processes), aberrant individual reactivity, epigenetic factors, oxidative stress, and skin microbiome alteration. These factors influence skin barrier functions; trigger errors in differentiation and proliferation of keratinocytes; promote skin infiltration by immune cells (T cells, macrophages, neutrophils, and dendritic cells); they enhance the production of IL-23, IL-22, IL-17A, TNF, INF, and IL-12; and drive the assembly of inflammasomes, thereby initiating and sustaining inflammation [10,11]. The notion of a systemic inflammatory syndrome refers to a concept standing at the basis of revolutionary therapies both upcoming and present, including for psoriasis [12,13]. It represents the totality of biological alterations that occur during an inflammatory disease. Its causes include, but are not limited to, infectious pathologies, autoimmune diseases (psoriasis, rheumatoid arthritis), and even malignancies. Within chronic inflammation, we encounter changes to the patient's general state (asthenia, anorexia, fever, loss of appetite) as well as certain serum parameters. The diagnosis is however generally clinical, with confirmation through an increase in the erythrocyte sedimentation rate (ESR), a rise of C reactive protein (CRP) levels, and an upsurge of fibrinogen [14-16]. During chronic inflammation, platelets and leucocytes (mainly neutrophils) will rise in numbers, whereas erythrocytes will diminish in size. Out of these parameters, CRP and ESR are considered the most sensible for confirming chronic inflammation, despite them not being specific.

Biologic agents in psoriasis

Although topical and systemic therapies are used and relatively effective, biologic agents that directly intervene in the pathophysiological cascade are sometimes needed in more aggressive or severe forms of the disease. These are represented by the tumor necrosis factor alpha (TNF-a) inhibitors, and interleukin (IL)-12/23 and IL-17 antagonists. TNF-a inhibitors include adalimumab, etanercept, infliximab, and certolizumab. Belonging to the IL-12/23 antagonists, ustekinumab, guselkumab, tildrakizumab, and risankizumab inhibit T-helper (Th) cells types 1 and 17. Lastly, ixekizumab, secukinumab, and brodalumab are all monoclonal antibodies that antagonize IL-17, which is produced by Th-17 and is a major nexus of the inflammatory process [17].

Study aims

The first main objective of this study was to compare the prevalence of metabolic syndrome and chronic inflammation between psoriasis patients and non-affected controls. The second main goal was to determine the influence of biologic therapies upon the metabolic syndrome and chronic inflammation in psoriasis. Specifically, the aim was to establish whether biologic agents have any effect on the amelioration of the clinical and laboratory parameters that act as diagnostic criteria. A secondary objective was to compare the efficacy of biologic agents in this regard.

Methods
Patients and controls

For this study, 106 patients diagnosed with psoriasis were prospectively enrolled. For each patient with psoriasis, we attempted to select a compatible disease-free control of matching gender, background, and age category. All patients and controls were bio-naïve. Psoriasis Area Severity Index (PASI) and Dermatology Life Quality Index (DLQI) were determined for the patients, these being calculated by the main treating dermatologist (O.R.I.), with the reevaluation of psoriatic patients at 6 months of treatment. Controls were only evaluated at baseline, with the purpose of comparing the incidence of metabolic syndrome and inflammation with psoriasis patients.

A clinical examination was performed and biological samples were obtained (peripheral serum from venous blood) from all cases and controls. These included measuring the abdominal circumference and arterial blood pressure, as well as dosing serum TG, HDL, and glucose to establish the presence of metabolic syndrome on one hand, and ESR and CRP for chronic inflammation on the other. The presence of comorbidities such as arterial hypertension (HTN), type II diabetes, and psoriatic arthritis was noted, the association with each of these being coded on an ordinate scale from 0 to 4, as seen in table I for ease of statistical analysis. The treatment was then established by the treating physician alongside with each individual patient, based on clinical features, risk profile, as well as individual preference. After 6 months of therapy, psoriasis patients were reevaluated for all tested parameters and disease severity scores.

Moreover, we checked whether the age at the moment of presentation, duration of the disease, and background had any impact on the development of metabolic syndrome or chronic inflammation in psoriatic patients. Anonymized patient information was then gathered in an electronic spreadsheet in Microsoft® Excel for Mac.

Statistical analysis

For descriptive statistics, we employed the functions of Microsoft® Excel for Mac - including means, minimal and maximal values, standard deviations, and confidence intervals. Histograms, correlation graphs, and box plots were created in the SPSS analytical software. Statistical analysis was performed with the help of the SPSS analytical software. We used the Chi square test to compare the prevalence of associated comorbidities, metabolic syndrome and inflammation between the patient and control group, as well as to calculate the respective odds ratio (OR) for each instance. In testing for the association between psoriasis severity score and parameters for metabolic syndrome and inflammation, we employed Spearman's Correlation test, Linear Correlation graphs, and the Nominal Logistic Regression test. Pearson's R Coefficient and the Spearman Correlation were applied for testing the association between age and the measured parameters as well as psoriasis severity scores. The Mann-Whitney U Test and the Independent-Samples Kruskal-Wallis Test were used to verify the age distribution and mean between psoriasis patients with and without comorbidities. To reduce the chances of false positive results, we then applied the Bonferroni Correction. Differences in values between baseline and 6 months of therapy for the tested parameters were verified with the Related-Samples Wilcoxon Signed Rank Test. The Related-Samples McNemar Change Test was employed to check the differences in prevalence for obesity, metabolic syndrome, and inflammation within the patient group at baseline and study endpoint. The Independent-Samples Kruskal-Wallis Test was also utilized to compare the efficacy of the different biologic agents in terms of reducing CRP and ESR at 6 months of therapy. A p value of <0.05 was considered for statistical significance.

Table I. Grading system for statistical analysis.

Score	Sex	Background	Metabolic syndrome	Chronic inflammation	Comorbidities	Treatment
0	Masculine	Rural	Absent	Absent	None	Ixekizumab
1	Feminine	Urban	Present	Present	HTN	Secukinumab
2					Type II diabetes	Guselkumab
3					HTN + diabetes	Certolizumab
4						Ustekinumab
5						Risankizumab
6						Adalimumab

Abbreviations: HTN, arterial hypertension.

Results

Demographics of patient and control groups

Within the psoriasis patient group, the male sex was predominant, counting 66 cases (62.26%), whereas the female patients were 40 in number (37.74%), the male-to-female ratio being 1.65:1. Regarding the background, 36 patients (33.96%) declared belonging to a rural region, the rest of 70 (66.04%) being from an urban area. The youngest of the study group was 19 years old, while the oldest was 84, with a mean age of 49.5 years (standard deviation – SD 14.13961 years, 95% confidence interval – CI [46.808 – 52.192]). Length of disease was 1 and 52 years at extremes, the average being 15.27 years (SD 10.85 years, 95% CI [13.209 – 17.339]).

In the control group, the male-female ratio was 1.35:1, with 61 males (57.54%) and 45 (42.45%) females being included. Seventy-four individuals (69.81%) came from an urban background, with the remaining 34 living in a rural environment (30.19%). The age extremes were 18 years and 74 years, respectively, the calculated mean being 43.93 years (SD 14.11 years, 95% CI [41.254 – 46.626]).

Comorbidities within patient and control groups

Sixty patients presented metabolic syndrome at baseline (56.6%), while 39 had HTN (36.8%) at the initiation of biologic therapy. Similarly, 44 (41.5%) of cases were diagnosed with obesity initially, compared to 40 (37.7%) at the end of the study interval. At 6 months, the number of with hypertension remained unchanged, although the number of individuals with metabolic syndrome decreased to 40 (37.7%). Abdominal circumference of psoriasis patients ranged between 62 and 150 cm at the start of therapy, averaging at 97.11 cm (SD 15.717, 95% CI [94.118 – 100.102]), and at 6 months it ranged between 63 and 152 cm with an average of 97.66 cm (SD 16.078, 95% CI [94.6 – 100.72]). Within the same group, TG had values between 80 and 310 mg/dL with a mean of 172.58 mg/dL (SD 60.182, 95 CI [161.123 – 184.037] at first measurement and between 85 and 300 mg/dL with an average of 173.44 mg/dL (SD 65.718, 95% CI [46.808 – 52.192]) at 6 months of therapy. The serum HDL levels at the start of treatment varied between 26 and 78 mg/dL, averaging at 46.93 mg/dL (SD 14.418, 95% CI [44.185 – 49.685]), then 26 and 85 mg/dL with a mean of 48.88 mg/dL (SD 16.484, 95%

CI [45.742 – 52.018]) after 6 months, respectively. Lastly, serum fasting glucose ranged between 70 and 144 mg/dL with an average of 96.91 mg/dL at initial measurement (SD 15.902, 95% CI [93.883 – 99.937]), and at 6 months measured between 75 and 150 mg/dL with a mean of 95.98 mg/dL (SD 17.676, 95% CI [92.615 – 99.345]).

Within the study group, 100 patients were diagnosed with chronic inflammation at the beginning of therapy (94.3%), as opposed to only 31 (29.2%) after 6 months. We obtained an ESR average of 21.84 mm/h with extremes being 10 and 35 mm/h (SD 5.265, 95% CI [20.838 – 22.842]) at first evaluation, then 11.15 mm/h with limits of 5 and 27 mm/h at the 6-month mark (SD 5.186, 95% CI [10.079 – 12.221]). Regarding CRP, the initial mean was 3.397 mg/dL and varying between 0.18 and 12 mg/dL (SD 1.957, 95% CI [3.024 – 3.769]), whereas at 6 months it was 0.5127 mg/dL with a minimum of 0.02 and a maximum value of 2.84 mg/dL, respectively (SD 0.469, 95% CI [0.423 – 0.602]). Regarding controls, 29 (27.4%) and 17 (16%) presented obesity and metabolic syndrome, respectively. Chronic inflammation was noticed in only 18 (17%) of controls. Out of the psoriatic patient group, 57 (53.8%) had neither HTN nor diabetes, 33 (31.1%) had only HTN, 10 (9.4%) had only diabetes, and 6 (5.7%) both HTN and diabetes. Additionally, 4 patients also presented psoriatic arthritis (3.8%). As for the comorbidities in the control group, 85 (80.2%) of individuals had none, 14 (13.2%) only HTN, 4 (3.8%) diabetes, and 3 (2.8%) both HTN and diabetes (Table II). Figure 1 shows the mirrored histograms for the measured parameters of metabolic syndrome within the patient group at start and 6 months of therapy. Figure 2 shows histograms for ESR and CRP values at the same intervals.

The lowest initial PASI score among the patients was 13, the highest being 33. Meanwhile, DLQI scores ranged between 10 and 30. After 6 months of treatment, these intervals were reduced from 0 to 8 and from 0 to 9 for PASI and DLQI, respectively.

Regarding the agents employed, 37 patients (34.91%) received ixekizumab, 21 (19.81%) secukinumab, 5 (4.72%) guselkumab, 5 (4.72%) certolizumab, 7 (6.6%) ustekinumab, 16 (15.09%) risankizumab, and 15 (14.15%) adalimumab.

Table II. Frequency of comorbidities in patient and control groups at baseline (percentages in brackets).

Comorbidity	Patients – Baseline		Controls	
	No.	(%)	No.	(%)
Obesity	44	(41.5)	29	(27.4)
Neither HTN nor Diabetes	57	(53.8)	85	(80.2)
HTN	33	(31.1)	14	(13.2)
Type 2 Diabetes	10	(9.4)	4	(3.8)
HTN plus Type 2 Diabetes	6	(5.7)	3	(2.8)
Metabolic Syndrome	60	(56.6)	17	(16)
Systemic Inflammation	100	(94.3)	18	(17)

Abbreviations: HTN, hypertension.
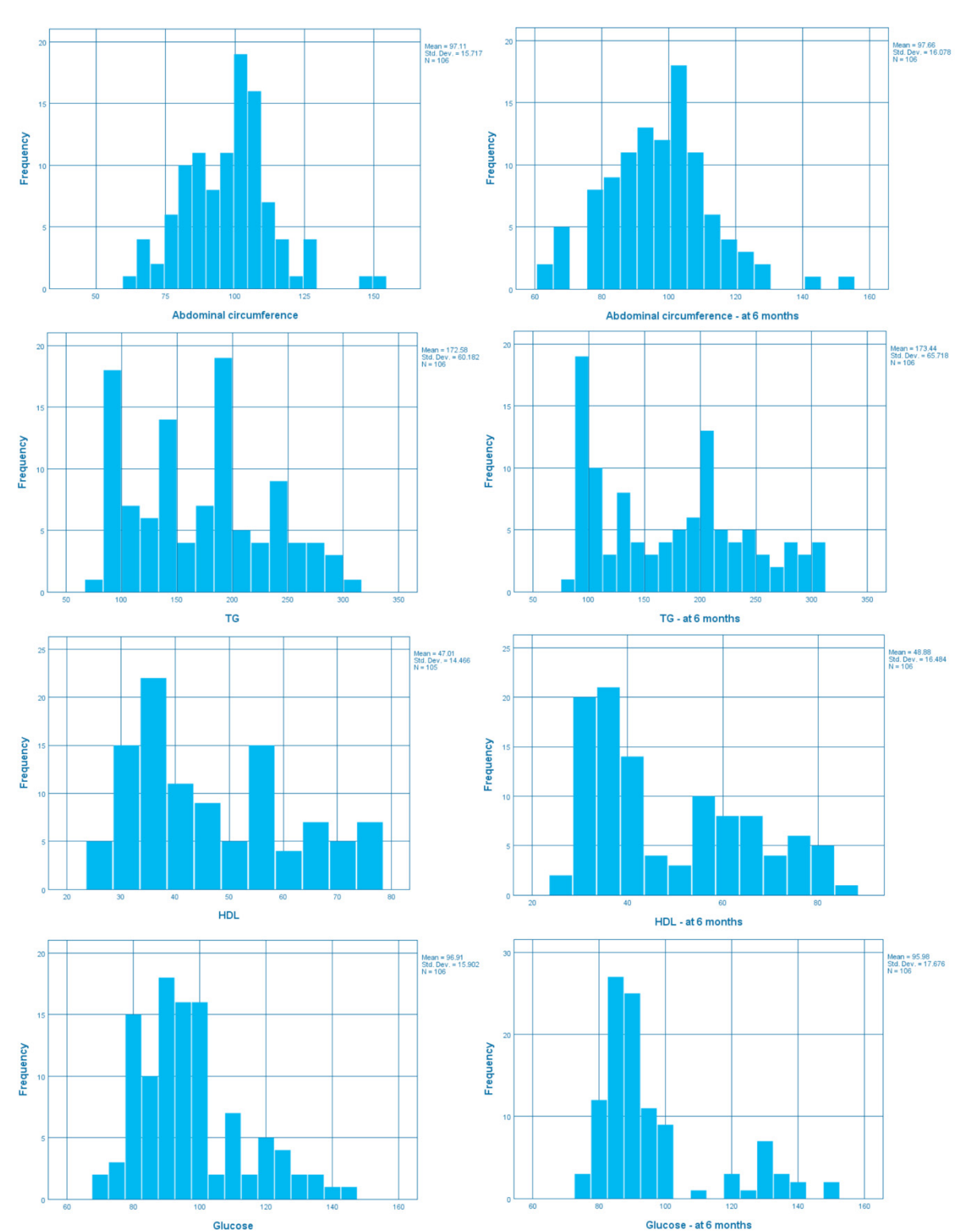
Figure 1. Histograms of the comparative values at therapy initiation (left) and after 6 months (right) for the studied components of the metabolic syndrome: abdominal circumference (in cm) – first row, serum triglyceride (TG, in mg/dL) – second row, high-density lipoproteins (HDL, in mg/dL) – third row, and fasting glucose (in mm/dL) – last row. Abscissa: corresponding values of measured parameters; Ordinate: total frequency of values.
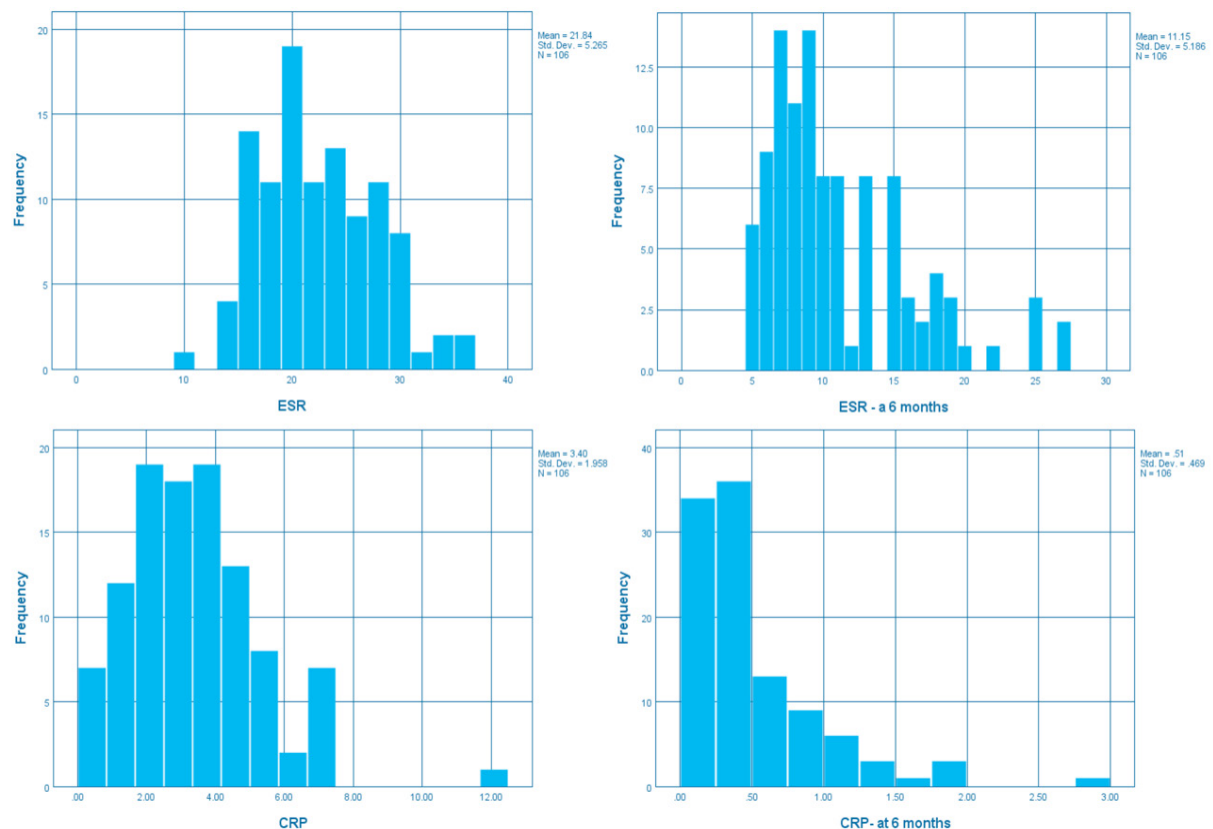
Figure 2. Histograms of the comparative values at therapy initiation (left) and after 6 months (right) for the components of chronic inflammation: erythrocyte sedimentation rate (ESR, in mm/h) – first row, C reactive protein (CRP, in mg/dL) – second row. Abscissa: corresponding values of measured parameters; Ordinate: total frequency of values.

Table III. Detailed characteristics of the patient group (units of measure between brackets).

	Abd. Circ.	TG	HDL	Glucose	ESR	CRP	Abd. Circ. – 6 mo.	TG – 6 mo.	HDL – 6 mo.	Glucose – 6 mo.	ESR – 6 mo.	CRP – 6 mo.
Mean	97.11	172.58	46.93	96.91	21.84	3.3971	97.66	173.44	48.88	95.98	11.15	0.5127
Std. Error of Mean	1.527	5.845	1.4	1.545	0.511	0.19014	1.562	6.383	1.601	1.717	0.504	0.04556
Median	99.5	178	43	93.5	21	3.135	98.5	175	42	90	9	0.38
Std. Deviation	15.717	60.182	14.418	15.902	5.265	1.95763	16.078	65.718	16.484	17.676	5.186	0.46907
Variance	247.035	3621.845	207.891	252.886	27.717	3.832	258.512	4318.821	271.728	312.438	26.891	0.22
Skewness	0.411	0.259	0.568	0.929	0.369	1.057	0.386	0.301	0.59	1.518	1.236	2.07
Std. Error of Skewness	0.235	0.235	0.235	0.235	0.235	0.235	0.235	0.235	0.235	0.235	0.235	0.235
Kurtosis	0.989	-0.921	-0.845	0.438	-0.435	2.505	0.947	-1.074	-0.979	1.258	1.138	5.893
Std. Error of Kurtosis	0.465	0.465	0.465	0.465	0.465	0.465	0.465	0.465	0.465	0.465	0.465	0.465
Range	88	230	52	74	25	11.82	89	215	59	75	22	2.84
Minimum	62	80	26	70	10	0.18	63	85	26	75	5	0.02
Maximum	150	310	78	144	35	12	152	300	85	150	27	2.84

The results of the descriptive analysis within the patient group are available in table III.

Correlation between psoriasis and comorbidites

The first step was to compare the prevalence of obesity between the two groups. Twenty-nine controls (27.36%) and 44 cases (41.51%) presented obesity. Chi square test revealed a statistically significant correlation between psoriasis and obesity (p=0.030 < 0.05), calculated OR being 1.88. Metabolic syndrome was present in 60 psoriatic patients (56.6%) and in 17 controls (16.04%). The correlation between psoriasis and metabolic syndrome had a very powerful statistical significance (p<0.0001) and an OR of 6.83. Concerning chronic inflammation, 100 out of the patient group had this condition (94.34%), compared to 18 controls (16.98%). The correlation between psoriasis and chronic inflammation had a very powerful statistical significance (p<0.0001), the OR being 81.84. Performing the Chi square test, we also found a positive correlation between psoriasis and the presence of HTN (p<0.000), with an OR of 3.0. Upon comparing the frequency of comorbidities (either HTN or diabetes or both) between cases and controls, we obtained a statistical significance for psoriasis patients (p < 0.000).

The next step was to compare the prevalence of obesity between the two groups. Only 29 controls presented obesity (27.36%), whereas this condition was present in 44 cases (41.51%). Chi square test revealed a statistically significant correlation between psoriasis and obesity (p=0.030, < 0.05), calculated OR being 1.88. Similarly for the metabolic syndrome, which was present in 60 psoriatic patients (56.6%) versus only 17 controls (16.04%), the correlation had a very powerful statistical significance in favor of psoriasis (p<0.0001). OR in this case was 6.83. As for chronic inflammation, 100 of the patient group had this condition (94.34%), as opposed to just 18 controls (16.98%). The correlation between psoriasis and chronic inflammation had a very powerful statistical significance (p<0,0001), the OR being as high as 81.84. Performing the Chi square test, we also found a positive correlation between the presence of the tested comorbidities (either HTN or diabetes or both) and the diagnosis of psoriasis (p < 0.000).

Then, we tested for an association between background and the presence of comorbidities in psoriasis. Thirty (42.86%) out of 70 patients from the urban area were obese, in contrast to the 14 (38.89%) out of the 36 from the rural regions. Performing the Chi square test did not yield any statistically significant association (p=0.695, > 0.05). However, in the control group where obesity was present in 26 (35.13%) out of 74 individuals from the urbanized areas and only in 3 (9.38%) of the 32 from the rural background, applying the same test showed a positive correlation between the urban background and obesity (p=0.006, < 0.05) with an OR of 5.24. Concerning metabolic syndrome, this was present in 37 (52.85%) cases from the urban area and in 23 (63.89%) from those in rural communities. Chi square test did not prove any significant association between background and metabolic syndrome in this group (p=0.278 > 0.05). The control group included 14 (18.92%) of persons from the urban area and 3 (9.38%) from rural regions with metabolic syndrome, without there being a statistically significant correlation (p=0.219 > 0.05).

Association between psoriasis severity and diagnostic parameters for the metabolic syndrome and systemic inflammation

We tested the correlation between PASI and DLQI on the one hand and the parameters for metabolic syndrome (abdominal circumference, TG, HDL, and glucose) and inflammation on the other (ESR and CRP) by using Spearman's correlation and corresponding linear inversion graphs. According to these tests, no significant correlations were established between either PASI or DLQI scores and abdominal circumference (p=0.96 and p=0.15, respectively), TG (p=0.43 and p=0.75, respectively), HDL (p=0.43 and p=0.38, respectively), or glucose (p=0.06 and p=0.79, respectively). We obtained statistically significant correlations of moderate intensity between PASI and ESR (R=0.61, p<0.00), DLQI and ESR (R=0.56, p<0.00), and DLQI and CRP (R=0.66, p<0.00), as well as a very strong correlation between PASI and CRP (R=0.77, p<0.00). Linear correlation graphs can be viewed in figure 3.

By performing nominal logistic regression, we tested for any correlations between PASI and DLQI scores on one hand, and the diagnostic parameters for both metabolic syndrome (abdominal circumference, glucose, TG, HDL) and systemic inflammation (ESR, CRP) on the other. Regarding PASI, we observed statistical significance only in the correlation with CRP (p<0.000), with a tendency for significance between PASI and abdominal circumference (p=0.08). Concerning DLQI, there was statistical significance for the correlation with abdominal circumference (p=0.008 < 0.05), ESR (p=0.003 < 0.05), and CRP (p<0.000). The results of both linear regression and nominal logistic regression can be viewed in table IV.
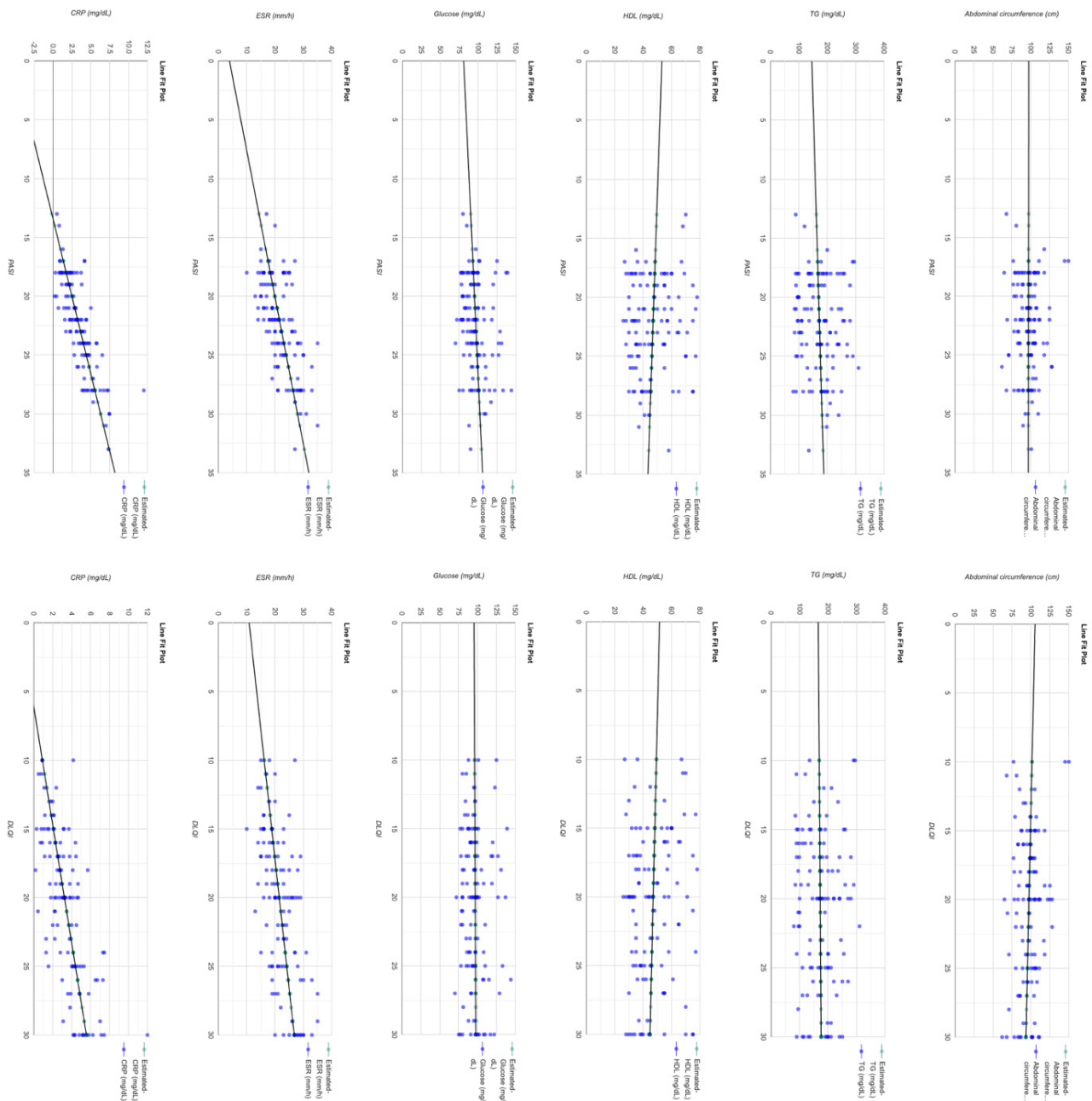
Figure 3. Linear correlation graphs between PASI (left column) and DLQI (right column) on the one hand, and abdominal circumference (top row), serum triglycerides (TG – second row), high-density lipoproteins (HDL – third row), glucose (fourth row), erythrocyte sedimentation rate (ESR – fifth row), and C reactive protein (CRP – final row) on the other. The only statistically significant correlations were between PASI and ESR, PASI and CRP, DLQI and ESR, and DLQI and CRP. Abscissa: PASI (left) or DLQI (right) score. Ordinate: values on respective measurement scales.

Table IV. Results for Linear Regression and Nominal Logistic Regression test results between psoriasis severity scores PASI and DLQI and metabolic syndrome (abdominal circumference, TG, HDL, and glucose) and inflammation (ESR and CRP).

Tested variables	Linear Regression (Pearson's Correlation)				Nominal regression		
	Pearson's R	Significance (p)	Covariance	Statistic	-2 Log likelihood of reduced model	Chi-Square	p
PASI and Abdominal circumference	-0.005	0.96	-0.32	-0.05	351.19	26.95	0.08
PASI and TG	0.079	0.42	19	0.81	336.49	12.25	0.83
PASI and HDL	0.077	0.43	-4.44	-0.79	336.73	12.49	0.82
PASI and glucose	0.179	0.06	11.36	1.86	332.76	8.52	0.97
PASI and ESR	0.61	<0.00	12.71	7.77	344.35	20.1	0.33
PASI and CRP	**0.77**	**<0.00**	**6.03**	**12.43**	**389.39**	**65.15**	**0.00**
DLQI and Abdominal circumference	-0.14	0.15	-12.43	-1.47	**422.58**	**38.35**	**0.008**
DLQI and TG	0.03	0.75	10.69	0.33	407.49	23.26	0.28
DLQI and HDL	-0.087	0.38	-6.97	-0.89	409.29	25.06	0.19
DLQI and glucose	0.027	0.79	2.35	0.27	402.79	18.56	0.55
DLQI and ESR	**0.56**	**<0.00**	**16.41**	**6.9**	**425.47**	**41.24**	**0.003**
DLQI and CRP	**0.66**	**<0.00**	**7.19**	**8.97**	**436.64**	**52.4**	**0.000**

Negative values represent inversely linear correlations. Bolded lines show statistically significant correlations. Abbreviations: PASI, psoriasis area severity index; DLQI, dermatology life quality index; TG, triglycerides; HDL, high-density lipoproteins; ESR, erythrocyte sedimentation rate; CRP, C reactive protein.

Table V. Tested correlations between age and the components of measured metabolic syndrome and chronic inflammation parameters, as well as the psoriasis severity scores PASI and DLQI.

	Test	Value	Standard error	T (approximate)	p
Age and abdominal circ.	Pearson's R	0.316	0.096	3.399	<0.001
	Spearman Correlation	0.358	0.092	3.909	<0.000
Age and TG	Pearson's R	0.325	0.082	3.509	<0.001
	Spearman Correlation	0.306	0.089	3.278	<0.001
Age and HDL	Pearson's R	-0.311	0.094	-3.333	<0.001
	Spearman Correlation	-0.263	0.098	-2.781	<0.006
Age and glucose	Pearson's R	0.329	0.088	3.553	<0.001
	Spearman Correlation	0.286	0.093	3.047	<0.003
Age and ESR	Pearson's R	0.169	0.100	1.753	0.083
	Spearman Correlation	0.166	0.094	1.713	0.090
Age and CRP	Pearson's R	0.444	0.051	5.053	<0.000
	Spearman Correlation	0.532	0.071	6.405	<0.000
Age and PASI	Pearson's R	-0.076	0.098	-0.776	0.439
	Spearman Correlation	-0.090	0.100	-0.917	0.361
Age and DLQI	Pearson's R	-0.261	0.091	-2.762	<0.007
	Spearman Correlation	-0.248	0.094	-2.608	0.010

Abbreviations: Abd. Circ, abdominal circumference; TG, serum triglycerides; HDL, high density lipoproteins; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; PASI, psoriasis area severity index; DLQI, dermatology life quality index.

Correlations between age and diagnostic parameters for the metabolic syndrome and systemic inflammation

We also searched for any correlations between patient age on the one side and abdominal circumference, serum TG, HDL, fasting glucose, ESR, CRP, PASI, and DLQI scores at therapy onset on the other. For this purpose, we used Pearson's R Coefficient and the Spearman Correlation. Regarding age and abdominal circumference, we observed a directly proportional relationship of moderate intensity and strong statistical significance (p<0.001). A similar association was noticed between age and TG (p<0.001). A directly proportional correlation of low intensity according to the Spearman Correlation, although moderate based on Pearson's R Coefficient was found between age and fasting glucose (p<0.001 and p<0.003, respectively). Between age and serum HDL we obtained a statistically significant inversely proportional association of low intensity according to the Spearman Correlation, but of moderate intensity if considering Pearson's R Coefficient (p<0.001 and p<0.006, respectively). No statistically significant correlation could be found between age and ESR (p=0.083 – Pearson and p=0.09 – Spearman, respectively). However, there was a directly proportional moderate intensity association between age and CRP according to Pearson's R coefficient (p<0.000) and of high intensity based on Spearman's Coefficient (p<0.000). Lastly, we identified an inversely proportional correlation of low intensity but strong statistical significance between age and DLQI (p<0.007 – Pearson, and p=0.01 – Spearman), however not with PASI (p=0.439 and p=0.361, respectively). The results of these tests are found in table V.

We established the null hypothesis that the distribution of ages was equivalent in both categories of obesity (absence and presence thereof, respectively). Based on the Mann-Whitney U test, the null hypothesis was rejected with a strong statistical significance (p<0.0001). A similar result was observed when testing the median age between the two categories of obesity (p=0.035 < 0.05), patients without the condition having a lower age median than the absolute median of 49 years (45 years of age), whereas those with obesity had a higher median (53 years of age).

Applying the Independent-Samples Kruskal-Wallis test, we investigated whether the distribution and median age were the same between the psoriasis patients without additional HTN or type II diabetes, and those with HTN, diabetes, and simultaneous HTN and diabetes, respectively. Based on the test results, we rejected the null hypothesis stating that the distribution of ages was equal between these patient categories (p<0.000). Similarly, the median ages between the categories differed significantly (p<0.000), with lower ages found in the group with neither HTN or diabetes. Moreover, when testing between category pairs, we obtained a statistically significant difference for age distribution between those having neither comorbidities

and those with HTN (p=0.000), diabetes (p<0.023), as well as HTN and diabetes concomitantly (p<0.004). Applying the Bonferroni correction for multiple tests, a statistical significance remained only between those without the comorbidities and the group with HTN (p<0.001), and concomitant HTN and diabetes respectively (p=0.021). Figure 4 shows the differences in age distribution between these patient categories.
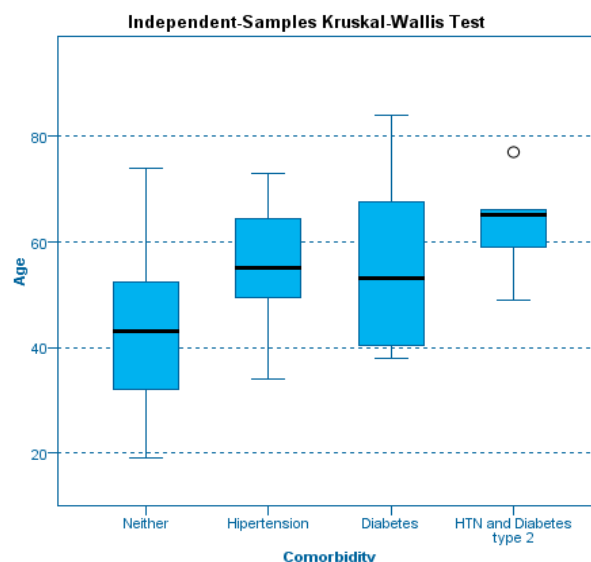

Figure 4. Box plot graph displaying the comparison of age medians between psoriatic patients without hypertension (HTN) or diabetes and those with hypertension, type II diabetes, and HTN and concomitant diabetes, respectively. Overall median is 49 years. Ordinate: age in years.

Then we checked whether the advanced age of psoriasis patients was linked to a higher prevalence of metabolic syndrome or chronic inflammation. Using the Chi square test for each individual patient age, we obtained a statistically significant correlation for both (p=0.026 < 0.05 and p<0.001, respectively).

Effects of biologic therapy in metabolic syndrome and chronic inflammation

Using the Related-Samples Wilcoxon Signed Rank Test we analyzed the differences between the initial values and those at 6 months of therapy for the investigated parameters. As such, we noticed a statistically significant difference between abdominal circumference at the two points (p= 0.002, < 0.05), the values being slightly increased at 6 months. Regarding serum TG, we did not find any statistically significant variation (p=0.727, > 0.05). Nevertheless, there was a significant difference for HDL, most patients (62 cases, or 58.49%) having a higher value at 6 months than at initial evaluation (p<0.001). Differences between serum fasting glucose were nonsignificant (p=0.248 > 0.05), even though most patients presented lower values at 6 months (57 patients, or 53.77%).
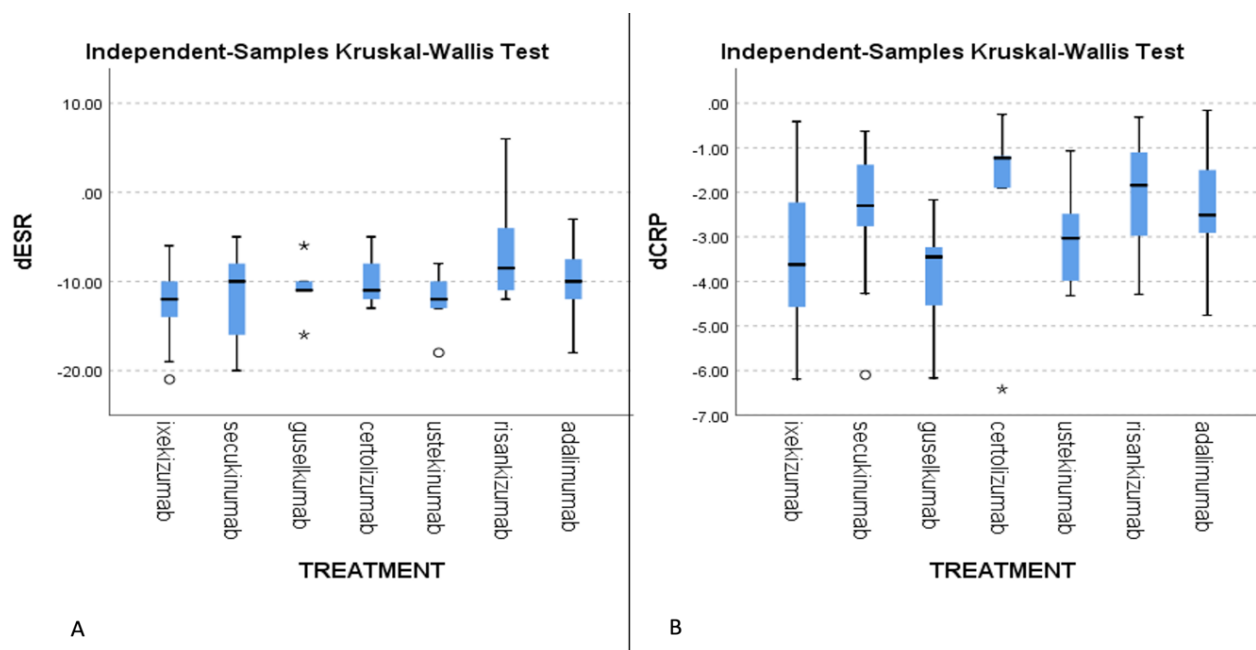
Figure 5. Applying the Independent-Samples Kruskal-Wallis Test for the evaluation of differences in erythrocyte sedimentation rate (dESR) (A) and C reactive protein (dCRP) (B) between treatment onset and 6 months of therapy for each biologic agent used. The most significant decreases in ESR are found for Ixekizumab and Ustekinumab. The most significant decreases in CRP belong to ixekizumab and guselkumab, and the least marked to certolizumab. Abscissa: A) dESR, difference (in mm/h) between the two measurements; B) dCRP, difference (in mm/h) between the two moments.

Applying the Related-Samples McNemar Change Test, we then verified the differences in dichotomic value distribution for the presence of HTN, obesity, metabolic syndrome, and inflammatory syndrome at the two temporal points. Thus, there were no statistically significant differences regarding HTN, the difference consisting of only one patient who measured in the normotensive range at 6 months (p=1). There was a difference in the number of obese patients, yet not significant (p=0.125, >0.05). Regarding the metabolic syndrome, the difference between the two points in time was statistically significant (p<0.001), most patients (66 or 62.26%) not meeting the necessary criteria for diagnosis at 6 months. Also, at the 6-month mark, the number of patients no longer meeting the criteria for chronic inflammation (75 or 70.75%) was markedly higher than those with this condition, the difference between the two moments showing statistical significance (p<0.000).

To compare the efficacy of the seven agents utilized, we checked the difference in values of ESR (dESR) and CRP (dCRP) between treatment onset and 6 months of therapy. By employing the Independent-Samples Kruskal-Wallis Test and the null hypotheses stating that the dESR and dCRP values were equivalent between the groups of patients treated with the respective biologic agents, we could reject both hypotheses with a strong statistical significance (p=0.019, < 0.05 and p=0.007, < 0.01), respectively. Therefore, regarding dESR, the most marked differences

corresponded to the groups treated with ixekizumab and ustekinumab (Figure 5A). Similarly, the group treated with ixekizumab presented the highest values of dCRP (or the greatest difference in CRP between the two measurements), followed by the group receiving guselkumab, whereas those treated with Certolizumab had the lowest CRP difference between measurements (Figure 5B).

Discussion
The association between psoriasis and metabolic syndrome has been intensely and repeatedly debated, especially for more severe forms of psoriasis such as the erythrodermic variant [18-21]. Psoriasis is characterized by elevated IL-6 levels, which can stimulate CRP production and promote adiposity, hypertension, and insulin resistance. [8]. Proinflammatory adipokines such as chemerin, leptin, and resistin were found to be increased in psoriasis and linked to insulin resistance [22]. Even so, a lesser studied aspect is the effect of biologic therapies in psoriasis on this syndrome itself and its components. Similarly, psoriasis has been redefined as the result of a systemic inflammation [23]. This reaction has been incriminated in the appearance of comorbidities linked to psoriasis such as obesity, insulin resistance, and cardiovascular disease [24,25]. This proinflammatory/prothrombotic status has also been identified in psoriasis, especially among patients with increased disease activity. However, elevated levels of

proinflammatory markers have been noticed even during remission, confirming the chronic inflammatory substrate of psoriasis and the susceptibility of patients to metabolic and cardiovascular comorbidities. Thus, the coexistence of metabolic syndrome may negatively impact the clinical course of psoriasis and vice-versa [7,8,26].

Belonging to an urban background was linked to a higher risk of obesity among controls, although the same could not be said about the psoriasis patient group. This could be due to a significantly higher proportion of obese individuals in the psoriasis group overall, the risk of obesity being almost twice as high when compared to controls (OR 1.88). The patient group also presented a much higher prevalence of metabolic syndrome (OR 6.83), as well as chronic inflammation (OR 81.84) in contrast to controls. Regarding the metabolic syndrome, this was significantly more common in the psoriatic patient group described by Girisha et al. when compared to their own controls, even though obesity and an altered glycemic state were similar between the two sets of individuals [27]. On the other hand, another research obtained significant differences between cases and controls concerning TG and altered glycemic state, not merely the prevalence of metabolic syndrome [28]. A populational study conducted in Italy on 1376 patients with psoriasis revealed a much higher rate of obesity and diabetes mellitus in patients from highly urbanized areas when contrasted to those from rural communities [29]. The higher prevalence of obesity and metabolic syndrome in urban areas may be the result of rapidly rising usage of motorized transport, urban development, and decreased opportunities for regular physical activity in housing and occupational contexts. Our modern "obesogenic" environments, with their combination of improper diet and physical inactivity, have severe implications for obesity levels, as well as the impact they have on other chronic diseases like type 2 diabetes and ultimately metabolic syndrome [29]. A plausible reason why our own results did not correspond with the findings of other authors may be attributable to differences in dieting habits and physical activity among the studied territories. As such, psoriasis does correlate with a significantly higher risk of developing metabolic syndrome and practically a guarantee of incurring chronic inflammation before treatment with targeted biologic agents.

The presence of comorbidities such as HTN and diabetes in psoriatic patients was linked with a more advanced age, particularly when HTN and diabetes were simultaneously present. Analogously, Fernandez-Torres et al. showed that the elderly psoriatic patients had a higher prevalence of HTN, diabetes, and altered glycemic states [30], despite that Li and coworkers revealed the contrary regarding diabetes [31]. In a similar way, an advanced age was linked to a higher risk of presenting with metabolic syndrome or chronic inflammation. The association between metabolic syndrome and advanced age in psoriasis has been described in psoriatic patients in previous studies [32,33].

While there is no definitive explanation to this association, it is possible that, with advanced age and a longer disease duration, the accumulation of inflammatory cytokines, a poorer diet, and clinical depression favor the onset of metabolic syndrome [34-36]. A higher BMI was also correlated with more advanced age at disease onset or at the occurrence of psoriatic arthritis [37].

Although nonspecific, CRP is recognized as the most sensitive indicator of inflammation, with the degree of its elevation correlating to the extent of tissue injury and the severity of inflammation. [38] CRP is an easily administered routine laboratory measurement, making it also a useful parameter. It is postulated as predictors of clinical disease course and progression, so accurate detection of CRP levels may be clinically significant. In addition, numerous studies have examined the role of CRP in psoriasis. Two studies by Vanizor et al. indicate that psoriasis patients have substantially elevated CRP levels compared to healthy controls. [39,40]. Mallbris et al. observed a positive correlation between CRP and total plasma cholesterol in psoriasis patients with elevated CRP levels compared to healthy controls [41] Furthermore, Vadakayil et al. demonstrated that CRP was statistically significantly higher in psoriatic patients compared to the control population [42].

After biologic therapy, we noticed a very slight but statistically significant increase in the patients' abdominal circumference. Contrarywise, despite the number of obese patients being lower at the conclusion point in the study, this reduction in number was not statistically significant. According to Pinter and coworkers, psoriatic patients receiving secukinumab presented a decrease in abdominal circumference, BMI, and average body weight concurrently with an increased treatment response [43]. It is very likely that, alongside a proper diet and physical exercise, the effect of biologic therapies indeed improves these clinical aspects. A randomized controlled trial (RCT) showed that a low calory regimen can increase the efficacy of biologic therapy with TNF-a inhibitors in psoriasis [44]. The multicenter prospective Psobioteq trial demonstrated that biologic therapy is more frequently abandoned by obese patients as compared to non-obese individuals, the most cited cause being the inefficacy of the treatment [45]. And according Enos et al., the presence of obesity and diabetes were correlated with an inferior response to biologic agents, particularly TNF-a and IL-17 antagonists [46]. For this very purpose, the METABOLyx, trial, which is still ongoing as of writing this manuscript, aims to compare the difference in efficacy between secukinumab as a singular treatment and secukinumab plus personalized lifestyle improvement therapies [47]. Intriguingly, TNF-a inhibitors were incriminated as heightening bodyweight, unlike IL-12/23 antagonists such as ustekinumab [48]. Since most of our cases were treated with ixekizumab, this could possibly explain why the average waist circumference was also higher after treatment in our patient group. Because of the

multiple conflicting results, the effects and offshoots of biologic agents on obesity and BMI in psoriasis should be assessed further.

Biologic treatment led to a statistically significant increase of HDL, thus improving the patients' lipidic profiles. This effect of biologics on HDL in psoriasis was also observed by Trakaki et al. [49], as well as Olejniczak-Staruch and collaborators. [50]. The latter of these two studies additionally demonstrated a statistically significant reduction of TG and low-density lipoprotein (LDL) levels following TNF-a inhibitor therapy. HTN and cardio-metabolic comorbidities have been identified as factors that diminish the probability of a favorable response to biologic therapy [50], also being associated with a lower treatment compliance [51]. Despite this, a pathologically heightened TG level has not been identified as a risk factor for biologic therapy inefficiency in the study made by Enos et al. [46]. On a more optimistic note, biologics have been described as cardioprotective agents, lessening the chances of cardiovascular events [52], improving endothelial function and arterial rigidity in psoriasis patients [53]. Likewise, biological agent therapy seems to decrease the risk of myocardial infarction in individuals with psoriasis [54]. As such, the benefits of biologic therapy in psoriasis are important, though incompletely established.

As a result of biologic therapy, the number of patients meeting the diagnostic criteria for metabolic syndrome and chronic inflammation was significantly lower at 6 months than at treatment initiation (56.6% vs. 37,7%, p<0.001 and 94.3% vs. 29.2%, p<0.000, respectively). TNF-a antagonists had already been noticed to improve metabolic profiles of patients [55]. Tildrakizumab, an IL-23 antagonist, apparently has a comparable efficacy and safety in patients with and without metabolic syndrome [56]. Although in our study we obtained a significant reduction in ESR and CRP in psoriasis patients with the help of biologics, the study conducted by Akdogan et al. did not yield the same results [57]. And according to the same article, biologics led to a significant increase in the number and percentage of acidophils in peripheral blood of patients. Even so, the prognostic value of acidophils remains unknown. The study of Rahman and collaborators also failed to show a significant reduction in ESR and CRP in their patients [58]. However, in individuals with psoriatic arthritis and treatment naïve, secukinumab seemingly resulted in significantly lower ESR and CRP levels when compared to patients who failed multiple prior treatments [59]. Interestingly, a higher CRP at treatment start is apparently correlated with a better clinical response in psoriatic arthritis [60]. Even so, this association is not consistent throughout the literature, as neither is the one between the response to therapy and factors such as patient age at disease onset and the duration of the disease, sex, ethnicity, or geographical location [61]. A perceived risk of biologics is developing malignancies after the chronic inflammation related to psoriasis, followed by the immunosuppression induced by the treatment itself [62,63]. However, at least in theory, this risk could be counteracted in time by the anti-inflammatory effect. To the extent of our knowledge and after rigorous literature research, there are no other studies performed on the effects of biologic therapy on the amelioration of parameters constituting the diagnostic criteria of the metabolic syndrome in psoriasis. Additionally, the studies focusing strictly on the criteria for chronic inflammation diagnosis in psoriasis and their improvement after biologic therapy are very limited in number. Therefore, a series of unknowns persist when referring to biologics in psoriasis. At least in the group of patients included, the therapy employed was effective in reducing the number of patients fulfilling the diagnostic criteria for metabolic syndrome and chronic inflammation.

It is becoming increasingly apparent that the efficacy, effectiveness, and safety profiles of various biologics vary, highlighting the need to determine which patients and under what circumstances each drug should be administered. There are, nonetheless, a number of studies which directly compare different biologics against one another, especially within the same class [64]. Although anti-IL-17 agents have a faster onset of clinical improvement than anti-IL-23 drugs, a direct comparison between secukinumab and risankizumab showed analogous results at week 16 and superiority of risankizumab at week 52 [65]. Regarding IL-23 inhibitors, there seems to be little difference in effectiveness between individual agents. In an indirect comparison between guselkumab and Risankizumab, Rugierro et al. found that both were comparably effective in reducing PASI and body surface area (BSA) in psoriasis patients [66]. A similar result was obtained between guselkumab, risankizumab, and tildrakizumab, with no significant differences in score reduction or rates of attaining PASI75, 90, or 100 responses (75%, 90%, or 100% reduction in PASI score, respectively) [67]. Despite being considered the first biologic class introduced in the treatment of psoriasis, TNF-a inhibitors have proven inferior to newer classes such as IL-17 antagonists [68]. A Bayesian network meta-analysis by Sawyer and collaborators concluded that brodalumab, ixekizumab, risankizumab and guselkumab outperformed other biologics regarding short-term effects [64]. The authors also found that there were significant differences in efficacy among biologics belonging to the same class. Another recent meta-analysis, which included a total of 167 studies and 58,912 randomized patients across multiple systemic treatment regimens, showed that anti-IL-17 agents had a higher proportion of patients achieving PASI90 compared to all other therapies, except for IL-23 inhibitors [69]. Biologic treatments were superior to all other forms of therapy in reaching PASI90, with infliximab, ixekizumab, risankizumab, and bimekizumab demonstrating the highest rates of PASI90 attainment compared to placebo. These four agents were equally effective when measured against each other. Bimekizumab, ixekizumab and risankizumab also proved superior to other IL-17 antagonists (secukinumab

and brodalumab), as well as guselkumab. Infliximab, IL-17 inhibitors (bimekizumab, ixekizumab, secukinumab and brodalumab) and IL-23 inhibitors risankizumab and guselkumab), except tildrakizumab, demonstrated a higher proportion of patients reaching PASI 90 than ustekinumab and three anti-TNF alpha agents (adalimumab, certolizumab, and etanercept). Adalimumab and ustekinumab were more effective than etanercept, while ustekinumab surpassed certolizumab [69]. Because of the many differences and the heterogeneous nature of the studies included in these meta-analyses, it is difficult, if not impossible, to reach a definitive conclusion regarding the efficacy of biologics in the same classes. However, as a general finding, IL-17 and IL-23 antagonists seem equally effective, being superior to most TNF-a inhibitors.

To the best of our knowledge, this is the first study in the reported literature that demonstrates a significant reduction in the number of psoriatic patients presenting diagnostic criteria for metabolic syndrome after biologic therapy. Moreover, this research reinforced the evidence that biologics aid in the amelioration of chronic inflammation. Despite the promising results of this study, the relatively low number of patients included might prove a potential limitation. Certain correlations could have proven statistically significant with a higher volume of cases. Even so, the results presented suggest that biologics are effective in the amelioration of the metabolic and inflammatory profiles of psoriasis patients, significantly reducing the number of patients eligible for both conditions. Biologics also proved effective in ameliorating HDL, CRP and ESR levels. We are optimistic in that this research may help contribute to the developing body of knowledge regarding the global efficacy of biologics vis-à-vis the metabolic and inflammatory profiles caused and exacerbated by psoriasis.

Conclusions

This study revealed a markedly higher prevalence of obesity, metabolic syndrome and chronic inflammation in the psoriasis patient group as opposed to the unaffected controls. Biologic therapies were correlated with a very slight but statistically significant increase in abdominal circumference, yet no effect on obesity at 6 months of therapy. Additionally, biologics raised serum HDL in patients in a significant fashion, without however significantly reducing serum TG or fasting glucose. Even so, the number of patients meeting the requirements for the diagnosis of metabolic syndrome was significantly lower at the 6-month mark than at the start of treatment. Regarding ESR and CRP, post-treatment improvements were statistically significant, suggesting an amelioration of the inflammatory profiles in these patients, especially in those treated with Ixekizumab. Nontheless, due to conflicting data in the literature, differences in effectiveness of biologics on the long term remain unknown.

References

1. Blackstone B, Patel R, Bewley A. Assessing and Improving Psychological Well-Being in Psoriasis: Considerations for the Clinician. Psoriasis (Auckl). 2022;12:25-33.

2. Badri T, Kumar P, Oakley AM. Plaque Psoriasis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; August 8, 2022.

3. Swarup S, Goyal A, Grigorova Y, Zeltser R. Metabolic Syndrome. In: StatPearls. Treasure Island (FL): StatPearls Publishing; October 24, 2022.

4. Olufadi R, Byrne CD. Clinical and laboratory diagnosis of the metabolic syndrome. J Clin Pathol. 2008;61:697-706.

5. Hernandez-Baixauli J, Quesada-Vázquez S, Mariné-Casadó R, Gil Cardoso K, Caimari A, Del Bas JM, et al. Detection of Early Disease Risk Factors Associated with Metabolic Syndrome: A New Era with the NMR Metabolomics Assessment. Nutrients. 2020;12:806.

6. Welty FK, Alfaddagh A, Elajami TK. Targeting inflammation in metabolic syndrome. Transl Res. 2016;167:257-280.

7. Branisteanu DE, Pirvulescu RA, Spinu AE, Porumb EA, Cojocaru M, Nicolescu AC, et al: Metabolic comorbidities of psoriasis (Review). Exp Ther Med. 2022;23:179.

8. Rodríguez-Cerdeira C, Cordeiro-Rodríguez M, Carnero-Gregorio M, López-Barcenas A, Martínez-Herrera E, Fabbrocini G, et al. Biomarkers of Inflammation in Obesity-Psoriatic Patients. Mediators Inflamm. 2019;2019:7353420.

9. Holmannova D, Borska L, Andrys C, Borsky P, Kremlacek J, Hamakova K, et al, The Impact of Psoriasis and Metabolic Syndrome on the Systemic Inflammation and Oxidative Damage to Nucleic Acid. J Immunol Res. 2020;2020:7352637.

10. Albanesi C, Madonna S, Gisondi P, Girolomoni G. The Interplay Between Keratinocytes and Immune Cells in the Pathogenesis of Psoriasis. Front Immunol. 2018;9:1549.

11. Lorthois I, Simard M, Morin S, Pouliot R. Infiltration of T Cells into a Three-Dimensional Psoriatic Skin Model Mimics Pathological Key Features. Int J Mol Sci. 2019;20:1670.

12. Costache DO, Feroiu O, Ghilencea A, Georgescu M, Căruntu A, Căruntu C, et al. Skin Inflammation Modulation via TNF-α, IL-17, and IL-12 Family Inhibitors Therapy and Cancer Control in Patients with Psoriasis. Int J Mol Sci. 2022;23:5198.

13. Uluçkan Ö, Wagner EF. Chronic systemic inflammation originating from epithelial tissues. FEBS J. 2017;284:505-516.

14. Midtbø H, Kringeland E, Gerdts E, Ueland PM, Meyer K, Linde A, et al. Biomarkers of inflammation and left ventricular remodelling in psoriasis patients treated with infliximab. Int J Immunopathol Pharmacol. 2022;36:3946320221111131.

15. Llorca J, Lopez-Diaz MJ, Gonzalez-Juanatey C, Ollier WE, Martin J, Gonzalez-Gay MA. Persistent chronic inflammation contributes to the development of cancer in patients with rheumatoid arthritis from a defined population of northwestern Spain. Semin Arthritis Rheum. 2007;37:31-38.

16. Pahwa R, Goyal A, Jialal I. Chronic Inflammation. In: StatPearls. Treasure Island (FL): StatPearls Publishing; August 8, 2022.

17. Timis TL, Florian IA, Vesa SC, Mitrea DR, Orasan RI. An updated guide in the management of psoriasis for every practitioner. Int J Clin Pract. 2021;75:e14290.

18. Rathod A, Neema S, Radhakrishnan S, Vendhan S, Tripathy DM, Vasudevan B. Palmoplantar Plaque Psoriasis is Associated with Diabetes, Hypertension, Obesity, and Metabolic Syndrome-A Case-Control Study. Indian Dermatol Online J. 2022;13:606-610.

19. Merola JF, Kavanaugh A, Lebwohl MG, Gniadecki R, Wu JJ. Clinical Efficacy and Safety of Psoriasis Treatments in Patients with Concomitant Metabolic Syndrome: A Narrative Review. Dermatol Ther (Heidelb). 2022;12:2201-2216.

20. Raza MH, Iftikhar N, Mashhood AA, Bin Hamid MA, Rehman F, Tariq S. Frequency Of Metabolic Syndrome In Patients With Psoriasis. J Ayub Med Coll Abbottabad. 2021;33:484-487.

21. Ma AR, Liu F, Wang R, Lin L, Wang Y, Li Q, et al. Prevalence of Metabolic Syndrome in Chinese Patients With Erythrodermic Psoriasis: A Case-Control Study. Front Endocrinol (Lausanne). 2021;12:677912.

22. Hu Y, Zhu Y, Lian N, Chen M, Bartke A, Yuan R. Metabolic Syndrome and Skin Diseases. Front Endocrinol (Lausanne). 2019;10:788.

23. Reich K. The concept of psoriasis as a systemic inflammation: implications for disease management. J Eur Acad Dermatol Venereol. 2012;26 Suppl 2:3-11.

24. Gottlieb AB, Chao C, Dann F. Psoriasis comorbidities. J Dermatolog Treat. 2008;19:5-21.

25. Hamminga EA, van der Lely AJ, Neumann HA, Thio HB. Chronic inflammation in psoriasis and obesity: implications for therapy. Med Hypotheses. 2006;67:768-773.

26. Kaushik SB, Lebwohl MG. Psoriasis: Which therapy for which patient: Psoriasis comorbidities and preferred systemic agents. J Am Acad Dermatol. 2019;80:27-40.

27. Girisha BS, Thomas N. Metabolic Syndrome in Psoriasis among Urban South Indians: A Case Control Study Using SAM-NCEP Criteria. J Clin Diagn Res. 2017;11:WC01-WC04.

28. Sharma YK, Prakash N, Gupta A. Prevalence of metabolic syndrome as per the NCEP and IDF definitions vis-a-vis severity and duration of psoriasis in a semi-urban Maharashtrian population: A case control study. Diabetes Metab Syndr. 2016;10(2 Suppl 1):S72-S76.

29. Altobelli E, Petrocelli R, Maccarone M, Altomare G, Argenziano G, Giannetti A, et al. Risk factors of hypertension, diabetes and obesity in Italian psoriasis patients: a survey on socio-demographic characteristics, smoking habits and alcohol consumption. Eur J Dermatol. 2009;19:252-256.

30. Fernandez-Torres RM, Paradela S, Fonseca E. Psoriasis in patients older than 65 years. A comparative study with younger adult psoriatic patients. J Nutr Health Aging. 2012;16:586-591.

31. Li W, Han J, Hu FB, Curhan GC, Qureshi AA. Psoriasis and risk of type 2 diabetes among women and men in the United States: a population-based cohort study. J Invest Dermatol. 2012;132:291-298.

32. Adışen E, Uzun S, Erduran F, Gürer MA. Prevalence of smoking, alcohol consumption and metabolic syndrome in patients with psoriasis. An Bras Dermatol. 2018;93:205-211.

33. Ferdinando LB, Fukumoto PK, Sanches S, Fabricio LHZ, Skare TL. Metabolic syndrome and psoriasis: a study in 97 patients. Rev Assoc Med Bras (1992). 2018;64:368-373.

34. Nisa N, Qazi MA. Prevalence of metabolic syndrome in patients with psoriasis. Indian J Dermatol Venereol Leprol. 2010;76:662-665.

35. Itani S, Arabi A, Harb D, Hamzeh D, Kibbi AG. High prevalence of metabolic syndrome in patients with psoriasis in Lebanon: a prospective study. Int J Dermatol. 2016;55:390-395.

36. Gui XY, Yu XL, Jin HZ, Zuo YG, Wu C. Prevalence of metabolic syndrome in Chinese psoriasis patients: A hospital-based cross-sectional study. J Diabetes Investig. 2018;9:39-43.

37. Eder L, Abji F, Rosen CF, Chandran V, Gladman DD. The Association Between Obesity and Clinical Features of Psoriatic Arthritis: A Case-control Study. J Rheumatol. 2017;44:437-443.

38. Coimbra S, Oliveira H, Reis F, Belo L, Rocha S, Quintanilha A, et al. C-reactive protein and leucocyte activation in psoriasis vulgaris according to severity and therapy. J Eur Acad Dermatol Venereol. 2010;24:789–796.

39. Vanizor Kural B, Orem A, Cimşit G, Yandi YE, Calapoglu M. Evaluation of the atherogenic tendency of lipids and lipoprotein content and their relationships with oxidant-antioxidant system in patients with psoriasis. Clin Chim Acta. 2003;328:71–82.

40. Vanizor Kural B, Orem A, Cimşit G, Uydu HA, Yandi YE, Alver A. Plasma homocysteine and its relationships with atherothrombotic markers in psoriatic patients. Clin Chim Acta. 2003;332:23–30.

41. Mallbris L, Granath F, Hamsten A, Ståhle M. Psoriasis is associated with lipid abnormalities at the onset of skin disease. J Am Acad Dermatol. 2006;54:614–621.

42. Vadakayil AR, Dandekeri S, Kambil SM, Ali NM. Role of C-reactive protein as a marker of disease severity and cardiovascular risk in patients with psoriasis. Indian Dermatol Online J. 2015;6:322-325.

43. Pinter A, Gerdes S, Papavassilis C, Reinhardt M. Characterization of responder groups to secukinumab treatment in moderate to severe plaque psoriasis. J Dermatolog Treat. 2020;31:769-775.

44. Al-Mutairi N, Nour T. The effect of weight reduction on

treatment outcomes in obese patients with psoriasis on biologic therapy: a randomized controlled prospective trial. Expert Opin Biol Ther. 2014;14:749-756.

45. Assan F, Tubach F, Arlegui H, Viguier M, Beylot-Barry M, et al. First-Line Biologic Therapy and Obesity in Moderate-to-Severe Psoriasis: Results from the Prospective Multicenter Cohort Psobioteq. Dermatology. 2021;237:338-346.

46. Enos CW, Ramos VL, McLean RR, Lin TC, Foster N, Dube B, et al. Comorbid obesity and history of diabetes are independently associated with poorer treatment response to biologics at 6 months: A prospective analysis in Corrona Psoriasis Registry. J Am Acad Dermatol. 2022;86:68-76.

47. Pinter A, Schwarz P, Gerdes S, Simon JC, Saalbach A, Rush J, et al. Biologic Treatment in Combination with Lifestyle Intervention in Moderate to Severe Plaque Psoriasis and Concomitant Metabolic Syndrome: Rationale and Methodology of the METABOLyx Randomized Controlled Clinical Trial. Nutrients. 2021;13:3015.

48. Onsun N, Akaslan TÇ, Sallahoglu K, Gülcan AS, Bulut H, Yabacı A. Effects of TNF inhibitors and an IL12/23 inhibitor on changes in body weight and adipokine levels in psoriasis patients: a 48-week comparative study. J Dermatolog Treat. 2022;33:1727-1732.

49. Trakaki A, Wolf P, Weger W, Eichmann TO, Scharnagl H, Stadler JT, et al. Biological anti-psoriatic therapy profoundly affects high-density lipoprotein function. Biochim Biophys Acta Mol Cell Biol Lipids. 2021;1866:158943.

50. Olejniczak-Staruch I, Narbutt J, Ceryn J, Skibińska M, Bednarski I, Woźniacka A, et al. AntiTNF-alpha therapy normalizes levels of lipids and adipokines in psoriatic patients in the real-life settings. Sci Rep. 2021;11:9289.

51. Enos CW, Ramos VL, McLean RR, Lin TC, Foster N, Dube B, et al. Cardiometabolic multimorbidity is common among patients with psoriasis and is associated with poorer outcomes compared to those without comorbidity. J Dermatolog Treat. 2022;33:2975-2982.

52. Liu B, Schwartz RA. Potential Cardio-protective Effects of Psoriasis Medications. Acta Dermatovenerol Croat. 2018;26:249-254.

53. Pina T, Corrales A, Lopez-Mejias R, Armesto S, Gonzalez-Lopez MA, Gómez-Acebo I, et al. Anti-tumor necrosis factor-alpha therapy improves endothelial function and arterial stiffness in patients with moderate to severe psoriasis: A 6-month prospective study. J Dermatol. 2016;43:1267-1272.

54. Gulliver WP, Randell S, Gulliver S, Connors S, Bachelez H, MacDonald D, et al. Do Biologics Protect Patients With Psoriasis From Myocardial Infarction? A Retrospective Cohort. J Cutan Med Surg. 2016;20:536-541.

55. Botelho KP, Pontes MAA, Rodrigues CEM, Freitas MVC. Prevalence of Metabolic Syndrome Among Patients with Psoriasis Treated with TNF Inhibitors and the Effects of Anti-TNF Therapy on Their Lipid Profile: A Prospective Cohort Study. Metab Syndr Relat Disord. 2020;18:154-160.

56. Lebwohl MG, Leonardi CL, Mehta NN, Gottlieb AB, Mendelsohn AM, Parno J, et al. Tildrakizumab efficacy, drug survival, and safety are comparable in patients with psoriasis with and without metabolic syndrome: Long-term results

from 2 phase 3 randomized controlled studies (reSURFACE 1 and reSURFACE 2). J Am Acad Dermatol. 2021;84:398-407.

57. Akdogan N, Dogan S, Atakan N. Long-term effects of biologic therapies on peripheral blood eosinophils in patients with psoriasis: a 3-year single-center study. J Dermatolog Treat. 2020;31:702-706.

58. Rahman P, Arendse R, Khraishi M, Sholter D, Sheriff M, Rampakakis E, et al. Long-term effectiveness and safety of infliximab, golimumab and ustekinumab in patients with psoriatic arthritis from a Canadian prospective observational registry. BMJ Open. 2020;10:e036245.

59. Ramonda R, Lorenzin M, Carriero A, Chimenti MS, Scarpa R, Marchesoni A, et al. Effectiveness and safety of secukinumab in 608 patients with psoriatic arthritis in real life: a 24-month prospective, multicentre study. RMD Open. 2021;7:e001519.

60. Magee C, Jethwa H, FitzGerald OM, Jadon DR. Biomarkers predictive of treatment response in psoriasis and psoriatic arthritis: a systematic review. Ther Adv Musculoskelet Dis. 2021;13:1759720X211014010.

61. Edson-Heredia E, Sterling KL, Alatorre CI, Cuyun Carter G, Paczkowski R, Zarotsky V, et al. Heterogeneity of response to biologic treatment: perspective for psoriasis. J Invest Dermatol. 2014;134:18-23.

62. Tamer F, Gulekon A. Should Mammography Be a Prerequisite Prior to Initiation of Biological Agents in Patients With Psoriasis? Dermatol Pract Concept. 2022;12:e2022081.

63. Rademaker M, Rubel DM, Agnew K, Andrews M, Armour KS, Baker C, et al. Psoriasis and cancer. An Australian/New Zealand narrative. Australas J Dermatol. 2019;60:12-18.

64. Sawyer LM, Malottki K, Sabry-Grant C, Yasmeen N, Wright E, Sohrt A, et al. Assessing the relative efficacy of interleukin-17 and interleukin-23 targeted treatments for moderate-to-severe plaque psoriasis: A systematic review and network meta-analysis of PASI response. PLoS One. 2019;14:e0220868.

65. Al-Janabi A, Warren RB. Update on risankizumab for the treatment of moderate to severe psoriasis. Expert Opin Biol Ther. 2020;20:1245-1251.

66. Ruggiero A, Fabbrocini G, Cinelli E, Megna M. Real world practice indirect comparison between guselkumab and risankizumab: Results from an Italian retrospective study. Dermatol Ther. 2022;35:e15214.

67. Megna M, Tommasino N, Potestio L, Battista T, Ruggiero A, Noto M, et al. Real-world practice indirect comparison between guselkumab, risankizumab, and tildrakizumab: results from an Italian 28-week retrospective study. J Dermatolog Treat. 2022;33:2813-2820.

68. Green LJ, Yamauchi PS, Kircik LH. Comparison of the Safety and Efficacy of Tumor Necrosis Factor Inhibitors and Interleukin-17 Inhibitors in Patients With Psoriasis. J Drugs Dermatol. 2019;18:776-788.

69. Sbidian E, Chaimani A, Garcia-Doval I, Doney L, Dressler C, Hua C, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev. 2022;5:CD011535