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Obesity and fibromyalgia predict the development of “difficult-to-manage” psoriatic arthritis phenotype associated with adverse outcome

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Abstract

Background.

The concept of difficult-to-manage (D2M) psoriatic arthritis (PsA) has been recently proposed. Herein, we report on the prevalence, predictors and outcomes of D2M PsA.

Methods.

This is a prospective single-center cohort study of PsA patients initiating b/tsDMARDs from 01/01/2009 until 01/01/2025. The EULAR proposed definition for D2M PsA was applied. Baseline parameters were assessed as predictors of D2M development using multiple logistic regression models. Long-term outcomes were compared between D2M and non-D2M patients by evaluating functional progression and adverse event rates.

Results.

During a median follow-up time of 3.4 years, 46/350 patients (13.1%) developed D2M disease. Compared with non-D2M, those with D2M had significantly higher baseline functional impairment ($p < 0.05$), a greater burden of obesity, osteoarthritis and fibromyalgia ($p < 0.05$) and no improvement in disease activity at 6 months ($p < 0.0001$). Independent predictors of D2M PsA were fibromyalgia and obesity (OR 4.634 and 2.265, respectively; $p < 0.05$ for both), whereas the absence of multimorbidity was associated with a lower probability of developing D2M phenotype (adjusted odds ratio 0.416, $p = 0.02$). During 1630 patient-years of follow-up, D2M patients showed higher functional impairment, rates of serious adverse events and hospitalizations compared with non-D2M patients.

Conclusion.

Thirteen percent of PsA patients starting b/tsDMARDs developed D2M and had a worse prognosis compared with non-D2M subgroup. Fibromyalgia and obesity independently predicted progression to D2M. If confirmed in other cohorts, these findings could contribute to better characterization and improved therapeutic approaches for this subgroup of PsA patients.

Background

Treatment strategies and therapeutic choices for patients with psoriatic arthritis (PsA) have significantly expanded in recent years. Nevertheless, a substantial proportion of patients do not achieve satisfactory treatment responses, and attainment of treatment targets remains suboptimal. Depending on the outcome measure used, low disease activity (LDA) or remission is achieved in 36%-60% and 13%-42% of patients, respectively.[1] Combined with the inflammatory burden, the multimorbid aspect of the disease

with the presence of psoriasis and the high prevalence of metabolic and pain-related diseases (fibromyalgia, osteoarthritis) poses significant therapeutic challenges. Although great variability has been shown in real-world data, long term biologic disease modifying antirheumatic drugs (bDMARDs) survival is rather low; three years overall bDMARDs survival has been reported up to 36.2% in a French study, while it ranges between 54% (for anti-IL12/23) and 68.9% (for anti-IL17) in a German report and was 45% (for anti-IL17) in our analysis.[1–3] Thus, comparable to what has been reported for rheumatoid arthritis (RA) and axial spondyloarthritis (axSpA), a "difficult-to-manage" (D2M) phenotype has been proposed. EULAR has recently published a consensus definition for "D2M" and "treatment refractory" (TR) PsA, with the ultimate intention of improving disease management in these patients.[4]

Although there are several studies reporting for "difficult-to-treat" PsA patients with failures to multiple biologics and targeted synthetic DMARDs (tsDMARDs)[5–10] studies applying the recently proposed EULAR definition are very sparse.[11] Clinical data of cohorts characterized according to the recently proposed criteria are needed, both to validate the criteria proposed in clinical practice as well as to better characterize this group of patients. In the present study we analyzed prospective data from a single center and report on the prevalence, predictors and outcome of PsA D2M patients.

Methods

Study design. This is an observational, prospective, single-center, cohort study, based on the University of Crete Rheumatology Clinic Registry (UCRCR), established in 2004.[12–15] Adults ≥ 18 years old with inflammatory arthritis are included in UCRCR at the time of initiation of the 1st bDMARD or tsDMARD and they are prospectively followed regardless of treatment switches for as long as they receive therapy. All treatment decisions are made by the attending rheumatologists based on clinical assessments, national and EULAR guidelines, taking into consideration patients' preferences. Ethical approval was obtained from the Institutional Review-Board of the University Hospital of Heraklion, Crete (decision-number:1476/20-03-2012). All participants provided written informed consents.

Setting and patient inclusion. For the present study we analyzed patients registered in the UCRCR with a diagnosis of psoriatic arthritis, starting the 1st b/tsDMARD therapy from 01/01/2009 until 01/01/2025. Patients were followed until discontinuation of all b/tsDMARD therapies, death, loss of follow-up, or 01/01/2026 (data extraction date), whichever came first. We excluded patients with < 12 months of follow-up time and those who had received their 1st b/tsDMARD therapy before 01/01/2009. The clinical diagnosis of the attending rheumatologist was used to select patients, but the fulfillment of the CASPAR classification criteria for PsA were also recorded.[16] No predefined level of disease activity was required to initiate or switch a targeted therapy and the choice of treatment was left at the discretion of the treating physician.

Data source. According to the UCRCR protocol, data on demographics, disease characteristics, comorbidities, disease activity, function and quality of life are collected at the 1st b/tsDMARD initiation and every 3–6 months for the first 2 years and yearly thereafter.[12] Treatment discontinuations and

reasons of treatment discontinuation, classified as “inefficacy”, “adverse event”, or “other”, as well as any adverse events are registered prospectively by the attending physician. In cases of loss of follow-up of a patient for more than one and a half years, the patient is reported as “lost to follow-up” at the date of the last recorded follow-up visit.

Definitions

For a patient to be characterized as D2M PsA, all three of the criteria proposed by the recently published “EULAR consensus definition of D2M psoriatic arthritis” should have been fulfilled.[17] More specifically, we documented that our patients had: 1. Failure to achieve or maintain response to ≥ 2 b/tsDMARDs with different mechanisms of action, defined as treatment failure due to insufficient response, drug reaction/allergy or adverse event. 2. The management perceived as problematic by the patient and/or rheumatologists defined as a global “VAS patient” and/or “VAS physician” ≥50/100. 3. Evidence of persistent disease as defined by ≥ 1 of the below points: a) Failure to achieve or maintain low disease activity (regardless of whether this is driven by inflammation, comorbidities, psychosocial, or other factors), b) The presence of active extra-musculoskeletal manifestations of PsA, c) Objective evidence of inflammatory activity, namely clinical signs, elevated acute phase reactants and/or imaging findings suggestive of inflammation. For criterion 3, we used CRP > 0.5 or DAPSA28 > 15. Finally, we assessed criteria 2 and 3 during the course of the last b/tsDMARD treatment of each patient to document that consistently met these criteria at the final three available follow-ups.

Obesity was defined as BMI > 30 Kg/m^2, and a patient was classified as ever smoker if he/she was current/former smoker. Based on the comorbidities documented by treating rheumatologists, the Rheumatic Disease Comorbidity Index (RDCI) was calculated.[18,19] Since only patients on b/tsDMARDs are included in our registry, the present analysis focused only in PsA patients treated with ≥ 1 b/tsDMARDs.

Statistical analysis. All patient characteristics were summarized using descriptive statistics. Univariate comparisons were performed to compare characteristics between D2M versus non-D2M PsA patients. For categorical variables Pearson’s chi-square tests were used. For continuous variables independent samples T-Tests and one way ANOVA were used in cases where data were normally distributed and the non-parametric Mann-Whitney Tests in cases of non-normally distributed data.

To identify which baseline factors may predict D2M development, we performed multivariate logistic regression analysis with D2M status (yes/no) as the dependent variable and independent variables were those identified as significant at a univariate level upon checking for model stability. We excluded variables that were highly correlated (|r|≥0.7) and had a Variance Inflation Factor (VIF) > 5. The independent variables that were used in the final model were presence of axial disease (yes/no), patient’s age at initiation of 1st biologic (in years), the time from disease onset to the initiation of the 1st b/ts treatment (months), fibromyalgia (yes/no), osteoarthritis of any type (yes/no), osteoporosis with/without fracture (yes/no), obesity (yes/no), hypothyroidism (yes/no) and depression (yes/no).

In order to identify the presence of any comorbidity clusters (multimorbidity) which might contribute to patients becoming D2M, we first performed a K-means cluster analysis on binary indicators of the most prevalent chronic illnesses. We included all chronic illnesses with a minimum frequency ≥ 5% in the total population. The number of comorbidity clusters was identified using the elbow method in the plot of the WCSS (Within-Cluster Sum of Squares) and the number of hypothesized clusters. We identified two comorbidity clusters within our patients (see Results). We then performed two separate multivariate logistic regression models with dependent variable patient being D2M (yes/no) in each one. Independent variable was cluster membership (yes/no) adjusted for age and gender. We presented the adjusted odds ratios (AORs) for each model in a single table.

The total person-time was calculated for each patient by subtracting the date of the last follow-up minus the date of the 1st b/tsDMARD initiation. The incidence rates of adverse events (AEs) were calculated for the D2M group and the non-D2M group of patients $IR = \frac{\text{number of AEs}}{\text{total person}-\text{time}}$. P-values for the comparison of incidence rates of AEs between D2M and non-D2M were computed using the normal approximation to the log-rate ratio using STATA iri command. For the evolution of DAPSA28 scores, HAQ scores and psoriatic area (%) we performed linear mixed models with dependent variables the above measures and independent variable: patient being D2M (yes/no). We then plotted the scores for 66 months of observation at 6-month intervals. The level of statistical significance was set to α = 0.05. The statistical software used was IBM SPSS version 26 and STATA version 18.

Results

Baseline patients' characteristics and comparisons between D2M and non-D2M groups. For the present study we analyzed 350 PsA patients from the UCRCR [58.9% females, mean age at inclusion 50.8 (SD 12.1) years], corresponding to 767 treatment courses of b/tsDMARDs, prospectively followed for 1630 patient/years (median follow-up time of 3.4 years). From the total cohort, seventy-four patients (21.1%) had failure of ≥ 2 classes of b/tsDMARDs with different mechanisms of action, in 113 (32.3%) the management was perceived as problematic by the patient or the physician and 178 (50.9%) had objective evidence of inflammatory activity (see Methods, Definitions). Ultimately, 46 out of 350 PsA patients (13.1%) satisfied all three criteria and were classified as D2M (Suppl. Figure 1). Of note, 416 of treatment discontinuations (of the total 767 cohorts of b/tsDMARDs in follow-up) were due to failure to control arthritis, while only 27 of the treatment discontinuations were due to failure to control psoriasis. Sequential patients' drug exposure of the 5 different lines of b/tsDMARDs are given in Suppl. Figure 2.

Comparison of baseline characteristics showed that D2M PsA patients were more often female compared to non-D2M patients ($p \leq 0.0001$) while the rest of demographics were comparable (Table 1). Focusing on disease characteristics, D2M patients had higher functional compromise assessed by HAQ (p=0.024) as well as they perceived a higher disease burden based on patient global VAS (p = 0.043), while a trend for higher disease activity based on the DAPSA28 index was found [34.8 (SD 14.5) vs 28.7 (SD 17) (p = 0.098)]. Interestingly, early at 6 months after treatment initiation of the 1st targeted agent, patients with D2M PsA still had higher disease activity (p<0.0001), showed no improvement in DAPSA28

and had a smaller ΔDAPSA28 as compared to non-D2M patients (p=0.0001), as well as they continued to score higher in functional disability assessed by HAQ (p = 0.0001) (Table 1).

Table 1
Basic demographic and disease's characteristics in the total cohort and comparisons of non-D2M vs D2M PsA patients.

Gender	**Total**	**Non-D2M**	**D2M**	**p-value**
	N = 350	**304 (86.9%)**	**46 (13.1%)**	
				< 0.0001
Female	206 (58.9%)	166 (80.6%)	40 (19.4%)	
Male	144 (41.1%)	138 (95.8%)	6 (4.2%)	
Age at inclusion (years)	50.8 (12.1)	51.0 (12.3)	49.7 (11.0)	0.529
Axial disease (yes)	70 (20.0%)	58 (19.1%)	12 (26.1%)	0.268
Ever smoker (yes)	147 (62.6%)	123 (63.4%)	24 (58.5%)	0.559
Time before biologic start Median (95% CI) (months)	18 (0, 479; 74)	18 (0, 479; 80)	16 (0, 240; 53)	0.551
Eye involvement	11 (3.2%)	9 (2.9%)	2 (4.4%)	0.564
Crohn's or other colitis	3 (0.9%)	2 (0.7%)	1 (2.2%)	0.346
Psoriatic area at baseline (% BSA)	1.5	2.0	1.0	0.180
Median (min,max;IQR)	(0.0, 50.0 ;4.0)	(0.0, 50.0; 5.0)	(0.0; 50.0; 3.0)	
Psoriatic area at 6 months	0.0	0.0	0.0	0.919
Median (min,max;IQR)	(0.0, 20.0; 2.0)	(0.0, 20.0; 2.0)	(0.0, 5.0; 2.0)	
DAPSA28 at baseline				
mean (SD)	31.4 (15.8)	28.7 (17.0)	34.8 (14.5)	0.098
DAPSA28 at 6 months				
mean (SD)	20.4 (17.2)	16.8 (14.7)	37.5 (18.7)	< 0.0001
ΔDAPSA28 0–6 months	10.0 (16.3)	12.4 (15.2)	-2.93 (16.2)	< 0.0001
Mean (SD)				
VAS patient global baseline mean (SD)	69.4 (18.6)	68.2 (19.4)	76.1 (11.3)	0.043
VAS patient global 6 months mean (SD)	50.3 (28.1)	45.3 (27.3)	75.9 (16.0)	< 0.0001

D2M: difficult-to-manage; PsA: Psoriatic arthritis; BSA: body surface area; DAPSA28: disease activity in psoriatic arthritis; ΔDAPSA28: difference of DAPSA; VAS: Visual Analogue Score; HAQ:Health Assessment Questionnaire.

Gender	Total	Non-D2M	D2M	p-value
	N = 350	**304 (86.9%)**	**46 (13.1%)**	
				< 0.0001
HAQ baseline mean (SD)	0.79 (0.53)	0.75 (0.51)	1.12 (0.62)	0.024
HAQ 6 months mean (SD)	0.64 (0.55)	0.54 (0.50)	1.14 (0.53)	< 0.0001

D2M: difficult-to-manage; PsA: Psoriatic arthritis; BSA: body surface area; DAPSA28: disease activity in psoriatic arthritis; ΔDAPSA28: difference of DAPSA; VAS: Visual Analogue Score; HAQ:Health Assessment Questionnaire.

Presence of comorbid diseases. Baseline prevalence of comorbid diseases was compared between the 2 groups, and it was shown that among metabolic diseases only obesity was more prevalent in D2M patients ($p < 0.002$) (Table 2). Additionally, fibromyalgia ($p < 0.0001$), depression ($p = 0.014$), osteoarthritis ($p = 0.032$) and hypothyroidism ($p = 0.007$) were all significantly more prevalent in the D2M group compared to non-D2M group. Despite the above differences, the burden of rheumatic disease-associated comorbidities assessed by the RDCI was comparable between the two groups. Thus, about a third of the patients in both groups had at least one and 13%-14% had > 2 comorbid diseases included in the RDCI (Table 2).

Table 2
Frequency of the most prevalent chronic illnesses for the total cohort and comparison between non-D2M and D2M PsA patients.

Obesity	**Total**	**Non-D2M**	**D2M**	**p-value**
	N = 350	**304 (86.9%)**	**46 (13.1%)**	
	119 (34.0%)	**94 (30.9%)**	**25 (54.3%)**	**0.002**
Dyslipidemia	117 (33.4%)	100 (32.9%)	17 (37.0%)	0.586
Hypertension	76 (21.7%)	68 (22.4%)	8 (17.4%)	0.445
Diabetes	56 (16.0%)	49 (16.2%)	7 (15.2%)	0.877
CHD	18 (5.1%)	17 (5.6%)	1 (2.2%)	0.328
OA (any)	105 (30.0%)	85 (28.0%)	20 (43.5%)	0.032
Osteoporosis any	29 (8.3%)	22 (7.2%)	7 (15.2%)	0.082
Fibromyalgia	84 (24.0%)	59 (19.4%)	25 (54.3%)	< 0.0001
Depression (any)	19 (5.4%)	13 (4.3%)	6 (13.0%)	0.014
Anxiety disorder	14 (4.0%)	12 (3.9)	2 (4.3%)	0.897
Hypothyroidism	58 (16.6%)	44 (14.5%)	14 (30.4%)	0.007
Latent TB	44 (12.6%)	39 (12.8%)	5 (10.9%)	0.709
Gout	6 (1.7%)	6 (2.0%)	0 (0.0%)	0.725
Viral hepatitis	7 (2.0%)	6 (2.0%)	1 (2.2%)	0.928
RDCI	1.53	1.54	1.43	0.611
Mean (95% CI)	(1.43–1.62)	(1.44–1.64)	(1.22–1.65)	
RDCI > 1 (yes)	116 (33.1%)	102 (33.6%)	14 (30.4%)	0.675
RDCI > 2 (yes)	50 (14.3%)	44 (14.5%)	6 (13.0%)	0.796

PsA: psoriatic arthritis; CHD: Coronary heart disease; OA: Osteoarthritis; RDCI: Rheumatic disease comorbidity index

Table 3a. Multiple logistic regression model predicting the odds of the total cohort of psoriatic arthritis patients becoming D2M (yes/no)

Predictor	OR	95% CI	p-value
Axial disease (yes)	0.899	0.368–2.080	0.803
Age at 1st biologic	0.980	0.947–1.015	0.267
Time to biologic start	0.994	0.988–0.999	0.036
Fibromyalgia	4.634	2.174–9.877	< 0.0001
Osteoarthritis	1.390	0.623–3.100	0.421
Osteoporosis	1.649	0.580–4.690	0.348
Obesity	2.265	1.092–4.699	0.028
Hypothyroidism	1.526	0.681–3.420	0.305
Depression	0.570	0.147–2.2156	0.417

R^2=0.200, Chi-square 36.593 on d.f. 9; p < 0.0001; VIF index < 1.188 for all included variables

Table 3b. Multiple logistic regression model predicting the odds of the total cohort of SpA patients becoming D2M (yes/no)

Predictor	AOR	95% CI	p-value
Cluster 1 membership (yes)	1.390	0.380 to 5.102	0.619
Cluster 2 membership (yes)	0.416	0.195 to 0.887	0.023

Adjusted for age at 1st cohort initiation and gender

Predictors of developing D2M. We next assessed for baseline predictors at 1st b/tsDMARD initiation for D2M PsA development. Multiple logistic regression (as described in Methods) showed that the presence of fibromyalgia (OR 4.634; p = 0.0001) and obesity (OR 2.265; p < 0.028) were significant predictors for D2M PsA development, while a shorter period of disease duration before the initiation of 1st b/tsDMARD protected from D2M development (Table 3a).

We additionally performed multiple logistic regression analysis assessing for the contribution of comorbidity clusters (multimorbidity) (described in Methods) to predict D2M evolution. Two clusters were identified in the analysis; patients in Cluster 1 (Metabolic Cluster) were characterized by the coexistence (clustering) of hypertension, dyslipidemia, obesity [n = 31/350 patients (8.9%)], and Cluster 2 (Comorbidities' Free) with no clustering of comorbidities [n = 208/350 patients (59.4%)]. Interestingly, adjusted (for age and gender) multiple logistic regression analysis showed that patients in Cluster 2 were at significantly lower odds to develop D2M phenotype (AOR 0.416, p = 0.023, Table 3b).

Long-term outcomes of D2M as compared to non-D2M. Real life data for the long-term outcome of D2M SpA patients are not available. Aiming to assess whether the outcome of D2M PsA group is different to that of non-D2M, we compared disease-associated evolution and rate of adverse events between the two groups for a total period of 6 years. As expected, the cumulative inflammatory articular burden of disease assessed by longitudinal DAPSA28 scores was higher in the D2M compared to non-D2M group (Fig. 1), while the evolution of skin psoriasis (assessed by psoriatic area involved) was comparable (data not shown). Interestingly, D2M group had significantly higher compromised functional status during the follow-up as compared to non-D2M counterparts assessed by HAQ (Fig. 2). Finally and further supporting the clinical value of the criteria for subgrouping of PsA patients, as shown in Table 4 the incidence rate of serious AE/hospitalizations was significantly higher in D2M patients compared to non-D2M ones ($p < 0.0008$).

Table 4
Long-term outcomes in the total cohort and comparisons of non-D2M psoriatic arthritis patient vs D2M.

Incidence rate of moderate AEs*	**Total**	**Non D2M**	**D2M**	**p-value**
	N = 350	**304 (86.9%)**	**46 (13.1%)**	
	33.4	**32.8**	**37.6**	**0.2072**
	(31.1 to 36.8)	**(30.0 to 36.2)**	**(31.4 to 44.9)**	
Incidence rate* of serious AEs/ hospitalizations	5.70	5.18	7.82	0.0008
	(4.66 to 6.99)	(4.09 to 6.58)	(5.29 to 11.6)	
Incidence rate* of all infections	24.1	23.6	26.3	0.373
	(21.8 to 26.6)	(21.1 to 26.4)	(21.2 to 32.6)	
Incidence rate* of serious infections	1.53	1.29	2.50	0.140
	(1.04 to 2.27)	(0.81 to 2.09)	(1.25 to 5.00)	
* Incidence per 100 patient-years of observation				
AE: Adverse events				

Discussion

Although the concept of D2M PsA is present in clinical research from 2022, it has only recently been clearly defined.[4,10] In the present study we applied the recently EULAR proposed definition of D2M PsA in order to assess prevalence, predictors and outcome of D2M PsA in a prospective cohort. We found that 13.1% of the patients evolved into D2M and they had an adverse long-term outcome based on the functional status, cumulative incidence of serious AE and hospitalizations. Interestingly, patients

initiating earlier b/tsDMARDs and those with no presence of multimorbidity had a lower risk of developing D2M disease.

As it has been stated in the recent EULAR proposed definition for D2M PsA and shown by the relevant literature review, the evidence in the field is limited, extremely heterogeneous and generally of low to moderate quality.[4,20] Adopting a common set of criteria to define the D2M population is a first step towards studying homogeneous populations to increase the quality of the literature in the field. In the present study we applied the recently proposed EULAR definition and we found that 13.1% of the PsA patients starting b/tsDMARDs may become D2M. Of note, our analysis is the first one to adopt the EULAR proposed criteria and study D2M PsA in a large, longitudinally followed prospective cohort with a track record on registry studies.[3,12,13,15,21] In earlier studies, adopting comparable to the EULAR proposed criteria, the prevalence of D2M PsA ranges between 33.9% (36/106) and 19.8% (75/378).[10,11,22] In a multicenter Greek study applying only the 2 first of the EULAR criteria, 16.5% (77/467) patients were D2M.[8] Differences in methodology, patients' characteristics as well as in criteria for D2M characterization applied, may account for the above-mentioned differences in D2M prevalence reported. It is important to comment that all the above-mentioned studies were cross-sectional studies of cohorts formed recently (January 2021 up-to November 2023) followed for rather limited periods of time (1-1.5 years), while we analyzed patients from a long-term, prospective registry-based study, extracting data from 01/01/2009 until 01/01/2025. Additionally, patients' characteristics (higher age and longer disease duration in the aforementioned studies compared to our) could account for the higher prevalence of D2M in these cohorts compared to ours. The present data showed the prevalence of D2M in PsA of 13.1% to fall between the respective prevalences for D2T RA and D2M axSpA (19.9% and 11.5% respectively) that we have recently reported based in the analysis of the UCRCR registry, in which we prospectively follow patients by the same protocol.[15,21]

Baseline demographics were rather comparable between D2M and non-D2M apart from female gender which was more prevalent in D2M, comparable to data from other studies (Table 1). Interestingly, disease related characteristics were also comparable concerning disease "phenotype", while patients' functional status and their overall assessment of disease burden was higher in D2M as compared to non-D2M groups ($p < 0.05$ for both). The fact that all patients at baseline had active disease leading to the initiation of the 1st b/tsDMARD may explain the marginal difference of disease activity assessed by DAPSA28 ($p = 0.098$). It is important to mention that early at 6 months of treatment initiation of the 1st biologic, the two groups differentiated clinically given that D2M patients did not improve neither disease activity nor functional status and respective levels were statistically significant different between groups ($p < 0.0001$ for both at 6 months, Table 1). These findings are comparable to what we have reported for the early disease evolution in D2T RA and D2M axSpA.[15,21] Unfortunately, no prospective data for D2M PsA cohorts are available to compare.

About half of the cohort had at least one comorbid disease (obesity, gout and smoking), and 1/3 had at least one rheumatic disease associated comorbidity included in RDCI. Interestingly, RDCI-associated

burden was comparable between the groups (Table 2). Nevertheless, chronic pain-related syndromes like osteoarthritis and fibromyalgia were significantly more common in D2M group, comparable to what it has been reported by some of the above-mentioned “D2M” studies, further supporting their contribution to D2M disease development. Comorbid fibromyalgia has been shown to be a negative predictor of achieving MDA and remission in PsA patients on biologics, while drug survival is markedly shorter, driven by apparent inefficacy rather than adverse events.[23–25] Moreover, the impact of coexisting fibromyalgia or other pain syndromes in the development of D2M/D2T diseases, has been reported for RA and axSpA.[15,21,26] It is supported that the co-existence of fibromyalgia may impact the assessment of patient’s estimation of disease’s activity /pain and thus the respective composite indexes (DAPSA, ASDAS or DAS28) which are partially based on patient’s estimation, and contribute to an overestimation of disease burden and eventually D2M evolution.[23]

It is clinically useful to predict at b/tsDMARD initiation those patients who may develop D2M phenotype. The multivariate analysis showed that fibromyalgia (OR 4.634, $p < 0.0001$) and obesity (OR 2.265, $p < 0.028$) were significantly contributors for D2M group (Table 3a). It has been shown that for PsA patients treated with TNFis, obesity is a robust negative predictor of achieving clinical responses and drug survival.[27,28] For IL-17 inhibitors, the effect of obesity may be attenuated although high-BMI patients still have lower rates of achieving stringent composite treatment targets in phase 3 trials.[29] We have also reported a differential effect of obesity in drug survival between biologics, showing a favorable effect of secukinumab as compared to TNF inhibitors.[3] In our cohort the majority of the patients were treated with TNF inhibitors (Suppl. Figure 2) and this may explain the contribution of obesity in D2M PsA in our study.

It has been proposed that assessing the constellation of multiple chronic diseases in a patient (multimorbidity), it is a better way to understand the contribution of comorbidities in patient’s outcome.[30,31] Multimorbidity patterns in patients with PsA remain understudied. Given the above-mentioned findings for the significance of comorbidities in D2M development, we performed a clustering analysis of comorbid diseases (multimorbidity) and assessed their contribution to D2M PsA development. Interestingly we found only two comorbidity clusters, the “Metabolic Cluster” [coexistence of hypertension, dyslipidemia, obesity, n = 31/350 (8.9%)], and the “Comorbidities Free” [n = 208/350 (59.4%)]. We have previously reported on the contribution of multimorbidity in D2T RA evolution.[15] Demographic differences (more males, lower age), disease-related differences and the smaller size of the present cohort as compared to the RA D2T cohort we have reported, may explain the differences in clustering between the two studies. We found that Cluster 2 (Comorbidities’ Free) protected against developing the D2M phenotype, further supporting their contribution in a more difficult phenotype (AOR 0.416, $p = 0.023$, Table 3b). It is not clear whether comorbidities contribute only via increasing the inflammatory burden or that they may also affect patients’ perception of disease’s status and rheumatologist’s treatment decisions strategies. Nevertheless, and irrespective of the specific mechanism, they should be taken into consideration in clinical practice towards a combined therapeutic approach targeting both the inflammatory burden as well as the control of comorbidities.

As it has been clearly stated, the field of clinical research in D2M PsA should be enriched with data focused in predictors and in the outcome of D2M cohorts.[4,32] Aiming to assess the long-term outcome, we compared functional evolution and rate of adverse events. It was found that indeed D2M patients accumulate more serious AE and hospitalizations [(5.18 vs 7.82), p = 0.0008] while they also have lower functional status (Fig. 2). Unfortunately, we do not obtain regular imaging data and thus we cannot estimate whether D2M patients accumulate higher structural damage during the follow-up. These are the first data on the clinical outcome of PsA D2M group, and together with the novelty of the information concerning D2M PsA outcome, they may be interpreted as a “validation” exercise of the proposed by the EULAR criteria in real-world cohorts.

We consider that the data presented herein represent a valuable contribution as the first study to apply the newly published EULAR D2M PsA criteria in a long-term registry setting (2009–2025, 1630 patient-years). However, several limitations deserve attention. The single-center design limits generalizability of the results, and underlines that the low D2M prevalence (13.1%) could partially reflects patient specific demographics rather than criteria stringency alone. No radiographic outcome data were collected, leaving structural progression unaddressed.

Conclusions

In conclusion, 13.1% of PsA patients initiating b/tsDMARDs developed a D2M phenotype. Obesity and fibromyalgia were independent predictors of this progression, whereas absence of multimorbidity and shorter disease duration before b/tsDMARD initiation were protective factors. If confirmed in other cohorts, these findings may support the development of targeted management strategies for D2M PsA.

Abbreviations

PsA
psoriatic arthritis
LDA
low disease activity
bDMARDs
biologic disease modifying antirheumatic drugs
RA
rheumatoid arthritis
axSpA
axial spondyloarthritis
D2M
difficult-to-manage
TR
treatment refractory
tsDMARDs

targeted synthetic DMARDs
UCRCR
University of Crete Rheumatology Clinic Registry
EULAR
European Alliance of Associations for Rheumatology
CASPAR
Classification Criteria for Psoriatic Arthritis
VAS
visual analogue scale
BMI
body mass index
CRP
C-reactive protein
DAPSA28
28-joint Disease Activity Index for Psoriatic Arthritis
RDCI
Rheumatic Disease Comorbidity Index
ANOVA
Analysis of Variance
WCSS
Within-Cluster Sum of Squares
AE
adverse events
AORs
adjusted odds ratios
HAQ
Health Assessment Questionnaire
OR
odds ratio
MDA
medium disease activity

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Institutional Review-Board of the University Hospital of Heraklion, Crete (decision-number:1476/20-03-2012). All participants provided written informed consents.

Consent for publication:

Not applicable

Competing interests

The authors declare no conflicts of interest relevant to this article.

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Author Contribution

IF, PS, GB: conceptualization, methodology, formal analysis, manuscript drafting, approval of final version; AR: investigation, resources, manuscript drafting; AB: formal analysis, software, manuscript drafting; NA, SP, EK, SP, EE: investigation, resources, manuscript proofreading and approval.

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Data Availability

The data and analytic methods that support the findings of this study are available to qualified investigators upon request to the corresponding author.

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Figures

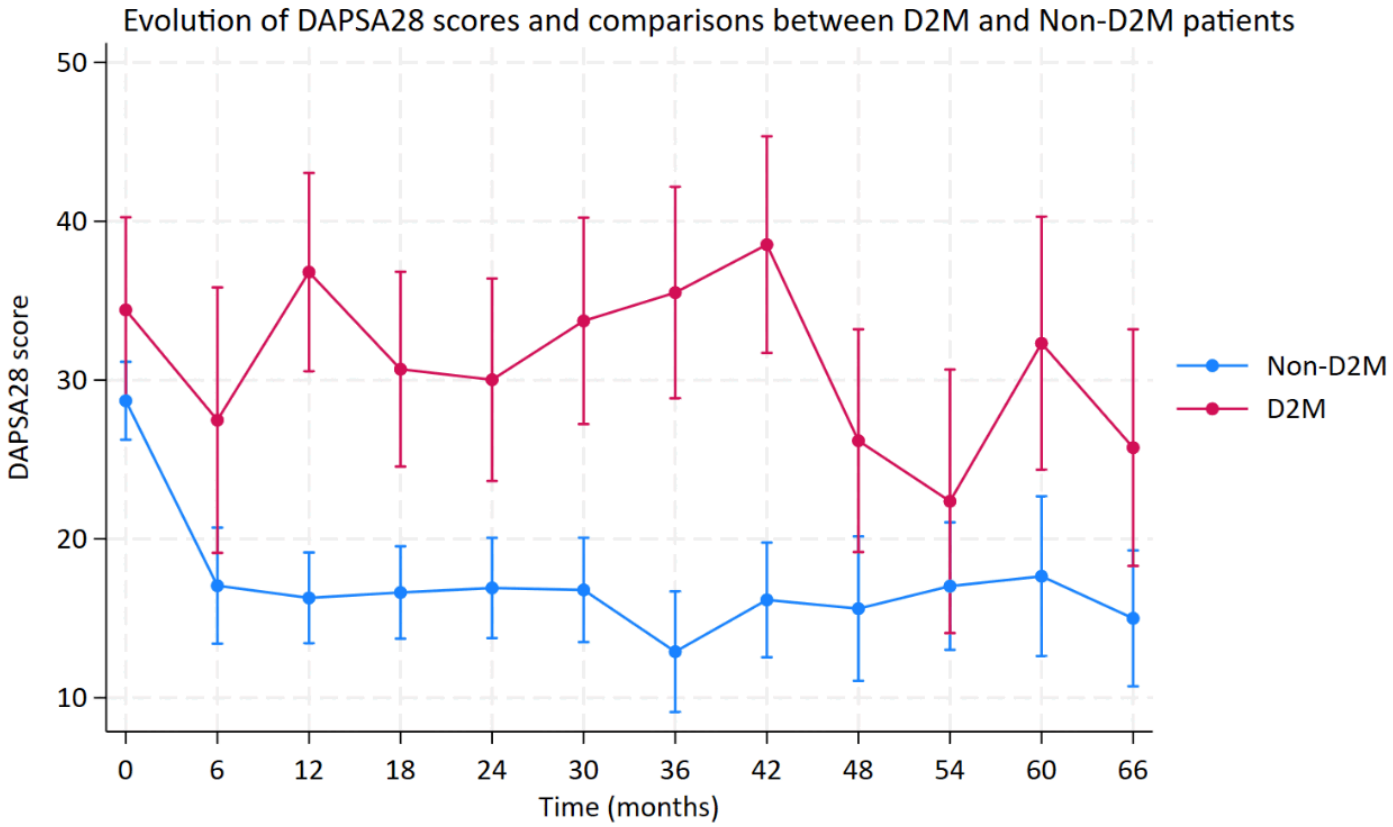


Figure 1

Linear mixed models plot of DAPSA28 evolution over time and comparison between D2M and non-D2M patients

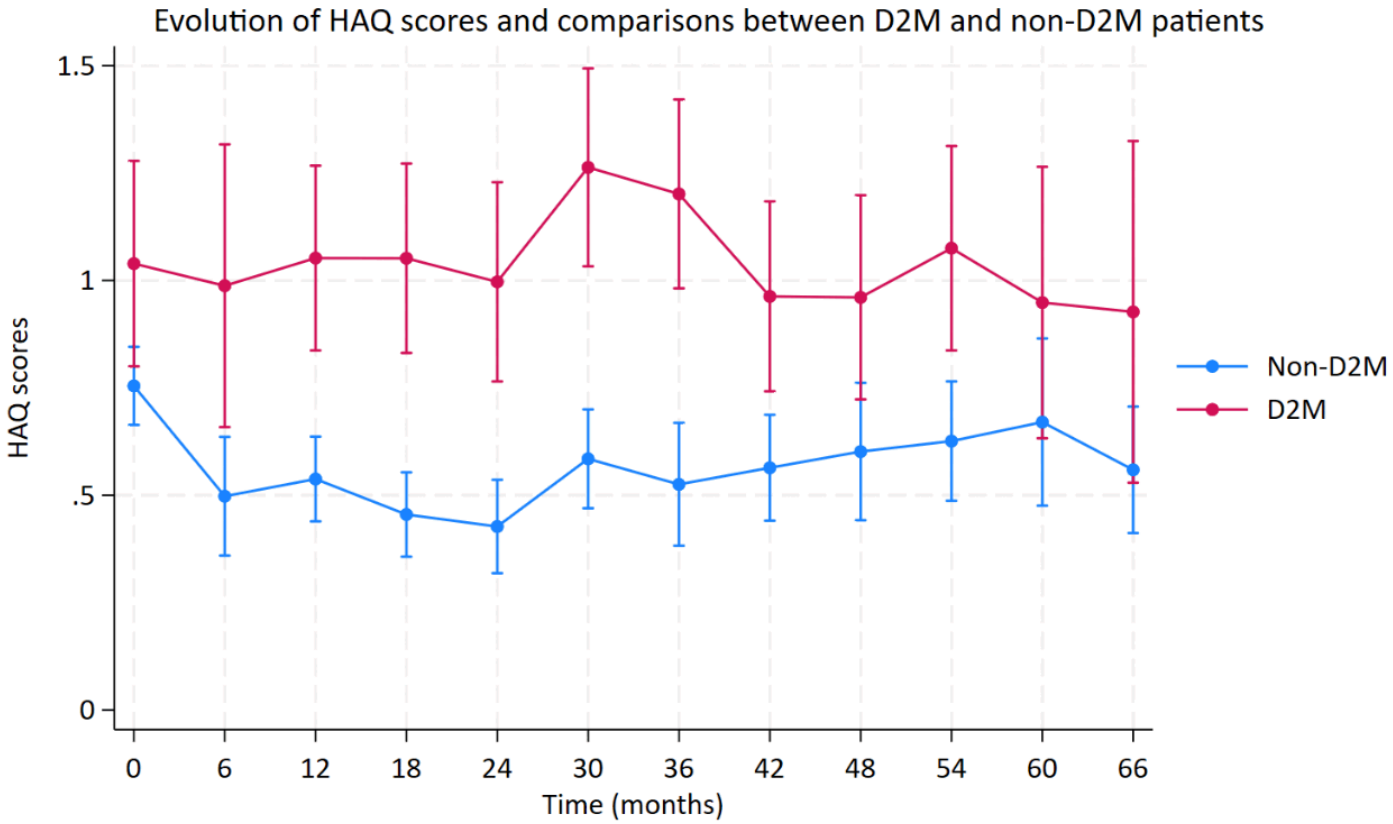


Figure 2

Linear mixed models plot of HAQ evolution over time and comparison between D2M and non-D2M patients

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