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Lipid profile and comorbidities in patients with psoriasis vulgaris

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Abstract: *Background and Aim: Psoriasis is an inflammatory skin disorder with important influence on the lipid profile, insulin resistance and cardiovascular disease. The aim of this study is to compare the lipid profile of classical therapy versus anti-TNFs patients and asses the associated diseases.*
Methods: We conducted a prospective study. Patients' data were collected from two Romanian Dermatology Clinics, during the period January 2015 – June 2016. The patients were divided into two groups: study group (on TNF inhibitors) and control group (on classical treatment).
Results: The subjects in the study group had more associated diseases and much more patients suffered from dyslipidemia. There were not statistically significant differences in the lipid profile between the two groups. But eliminating patients treated with Acitretin and Methotrexate, a p-value of 0.0259 (significant statistically) was observed when comparing the values of triglycerides in the two groups.
Conclusions: We did not observe a beneficial effect of the TNF inhibitors therapy in psoriatic patients on the lipid profile. Subjects on biological treatment suffer from a more severe form of psoriasis vulgaris and associate much more comorbidities.

Keywords: *lipid profile, comorbidities, anti-TNF agents.*

INTRODUCTION

Psoriasis is a chronic, inflammatory skin disorder [1]. The inflammation predisposes to a pro-atherogenic lipoprotein profile, large vessel inflammation, and adipokine dysregulation [1] thus leading to insulin resistance and cardiovascular diseases [2]. There is a strong link between psoriasis and risk factors for metabolic syndrome (central obesity, insulin resistance [3], abnormal lipid metabolism [4], hypertension [5]. Patients with psoriasis have a more increased risk of developing atherosclerosis due to inflammation and dyslipidemia [4]. Moreover, lipid abnormalities may play an important role in the development of psoriasis [4].

The inflammation mediated changes at lipids and lipoproteins levels have more likely a role in protecting the host. The treatment of psoriasis was shown to lead to a normalization of the lipid levels [6]. TNF induces a reduction in cholesterols (especially HDL) by interfering with LDL receptors, Apolipoprotein A and B, and 7A1 and 7B1 cytochromes with no changes in HMG-Co reductase action [7].

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In Romania, however, the inclusion criteria for biological therapies require previous two systemic non-biological therapies (retinoids, systemic glucocorticoids, methotrexate, PUVA, UVB narrow band).

Moreover, most of these therapies are known as lipid modifiers [4].

The aim of this study was to examine two groups of patients (biological versus non-biological therapy psoriatic patients) in terms of comorbidities and lipid profile.

MATERIAL AND METHODS

Study design

We carried out a prospective study. Patients' data were collected from two Romanian Dermatology Clinics: Dermatology Department, Carol Davila Emergency Military Hospital, Bucharest, (January – June 2016) and Dermatology Department, Mureş County Clinical Hospital, (January – December 2015).

All subjects had a physical examination. Body max index (BMI) was calculated as weight (kg)/height (cm^2) (normal weight: 18.5–24, 9; overweight: 25–29, 9; class I obesity: 30–34, 9; class II obesity: 35–39, 9; class III obesity: ≥ 40). Each patient completed a DLQI form and a dermatologist filled the PASI form.

The data collected included (i) patients' demographic characteristics: date of birth, gender, weight, height, BMI; (ii) psoriasis-related data: type of psoriasis, current therapies (topical treatment, Methotrexate/ MTX, Acitretin, PUVA, UVB TL01, anti-TNFs: Infliximab original and biosimilar, Adalimumab, Etanercept); (iii) comorbidities, with an accent on metabolic syndrome (hypertension, diabetes mellitus, obesity); (iv) cholesterol/cho and triglycerides/TG levels.

Patients were divided into two groups: study group (biological therapy) and control group (topical treatment, Methotrexate, Acitretin, PUVA, UVB TL01).

All participants gave written informed consent.

Statistical analysis

Data were analyzed using 2017 GraphPad Software.

RESULTS

At the end of the follow-up period, 102 subjects were included for the analysis: study group – 53 patients: 39 males (73.58%) and 14 females (26.42%) and control group – 49 patients: 25 females (51.02%) and 24 males (48.98%).

The biological therapy patients were distributed as follows: Infliximab (9, 16.98%), Infliximab biosimilars (4, 7.54%), Entanercept (17, 32.07%), Adalimumab (23, 43.39%). Four subjects had a switch of anti-TNF therapy, two changed Infliximab for Etanercept, the other two switched Infliximab for Adalimumab. Only 16 (15.68%) patients out of the 102 achieved both PASI and DLQI equal to zero during the study.

Biological patients were screened for associated diseases. Table 1 includes the number/(%) and comorbidities.

Table 1: Comorbidities of biological patients

Associated diseases	Number of patients /(%)
HTA	10/(18.86%)
Diabetes mellitus type 2	3/(5.66%)
Obesity	40/(77.35%)
Latent tuberculosis	5/(9.43%)
Hepatitis VHB	1/(1.88%)
Herpes zoster	1/(1.88%)
BPOC	1/(1.88%)
Chronic bronchitis	2/(3.77%)
Hepatic steatosis	1/(1.88%)
Glaucoma	1/(1.88%)
Arthropathy	15/(28.3%)
Synovitis right knee	1/(1.88%)
Disc hernia	1/(1.88%)
Anemia	1/(1.88%)
Allergy to penicillin and erythromycin	1/(1.88%)
Renal litiasis	1/(1.88%)
Hidradenitis suppurativa	3/(5.66%)
Bipolar disorder	1/(1.88%)
Amputation of right police	1/(1.88%)
Thyroid nodule operation	1/(1.88%)
Cholecystectomy	3/(5.66%)
Appendectomy	2/(3.77%)

The subjects with criteria of metabolic syndrome were

41 (77.35%) with obesity, 3 (5.66%) had diabetes mellitus type 2, 10 (18.86%) with hypertension. Other comorbidities were previous surgery (cholecystectomy, thyroid nodule operation, appendectomy), infection (latent tuberculosis, hepatitis VHB, herpes zoster), accidents (amputation of right police), pulmonary disease (BPOC, chronic bronchitis), inflammatory disease (hidradenitis suppurativa), hepatic disease (hepatic steatosis), renal disease (renal litiasis), ocular disorder (glaucoma), skeletal problems (arthropathy, synovitis right knee, disc hernia), hematological disease (anemia), psychiatric disorder (bipolar disease), allergy to drugs (allergy to penicillin and erythromycin).

The classical therapy patients associated obesity – 20 (40.81%), diabetes mellitus type 2 – 3 (6.12%), hypertension – 4 (8.16%). Other associated diseases were: hematological (anemia, thalassemia), skin cancer, arthropathy, osteoporosis, Cushing disease, venous disease, operated pituitary gland (table 2).

Table 2: Associated diseases of control group

Associated diseases	Number of patients
HTA	4
Diabetes mellitus type 2	3
Obesity	20
Anemia	1
Thalassemia	1
Skin cancer	2
Arthropathy	9
Osteoporosis	1
Cushing disease	1
Operated pituitary gland tumor	1
Chronic venous insufficiency	1

Patients with psoriasis have an important weight problem. The normal weight patients in the study group represented 12 (22.64%) versus 16 (32.65%) control group patients. Increased BMI was found in 74 (72.54%) psoriatic patients. (Table 3)

Some patients on anti-TNFs required additional drugs for disease control. 10 (18.86%) biological therapy patients used only topical treatment versus the majority of control group – 45 (91.83%).

Table 3: BMI for the two groups

BMI	Study group	Control group
Normal weight	12	16
Overweight	20	20
Obesity class I	15	13
Obesity class II	5	-
Obesity class III	1	-

Methotrexate was prescribed to 6 (11.3%) patients in the study group and to 4 (8.16%) patients on classical therapy.

Retinoid (Acitretin) was used only in 1 (1.88%) biological patient versus 2 (4.08%) patients in the control group. (Tables 4, 5)

Table 4: Additional therapy of anti-TNFs patients

Patient	Additional therapy
1	Acitretin
2	Methotrexate
3	Methotrexate
4	Methotrexate
5	Calcipotriol and betamethasone gel
6	Clobetasol propionate 0.0525% ointment
7	Calcipotriol and Betamethasone gel
8	Calcipotriol and Betamethasone gel
9	Methotrexate
10	Calcipotriol and Betamethasone gel
11	Calcipotriol and Betamethasone gel
12	Calcipotriol and Betamethasone gel
13	Keratolytic creams, Dermatocorticoids
14	Calcipotriol and Betamethasone gel
15	Calcipotriol and Betamethasone gel
16	Dermatocorticoids, Methotrexate
17	Methotrexate
18	Methotrexate

Table 5: Therapies of patients in the control group

Patient	Therapy
1	calcipotriol and betamethasone gel, 15% urea cream, UVB TL01
2	0.1% mometasone furoate cream, vitamin A, emollient, cream with salicylic acid, UVB TL01
3	topical corticosteroid, calcipotriol and betame-thasone gel, keratolytics, emollient cream, Methotrexate, UVB TL01
4	clobetasol propionate 0.0525% cream, Methotrexate, PUVA
5	0.1% mometasone furoate cream, calcipotriol and betamethasone gel, PUVA
6	0.1% mometasone furoate cream, UVB TL01
7	0.1% mometasone furoate cream, calcipotriol and betamethasone gel, UVB TL01
8	0.1% mometasone furoate cream, Methotrexate
9	betamethasone dipropionate and salicylic acid cream, clobetasol propionate 0.0525% cream, vitamin A, vitamin E,UVB TL01
10	15% urea cream
11	0.1% mometasone furoate cream, calcipotriol and betamethasone gel, 15% urea, vitamin A, vitamin E, PUVA
12	0.1% mometasone furoate cream, emollient cream, keratolytic cream, UVB TL01
13	clobetasol propionate 0.0525% cream, betamethasone dipropionate and salicylic acid cream, Vitamin E, PUVA
14	topical corticosteroid, UVB TL01
15	clobetasol propionate 0.0525% cream, betamethasone dipropionate and salicylic acid cream, Vitamin E, PUVA
16	clobetasol propionate 0.0525% cream, calcipotriol and betamethasone gel, Vitamin E, Vitamin A, salicylic acid cream, PUVA
17	clobetasol propionate 0.0525% cream, Vitamin E, Vitamin A, UVB TL01
18	0.1% mometasone furoate cream, emollient cream, betamethasone dipropionate and salicylic acid cream, UVB TL01
19	0.1% mometasone furoate cream, emollient cream
20	clobetasol propionate 0.0525% cream, Vitamin E, Vitamin A, UVB TL01
21	calcipotriol and betamethasone gel, Vitamin E, Vitamin A
22	clobetasol propionate 0.0525% cream, betamethasone dipropionate and salicylic acid cream, emollient cream, Vitamin E, Vitamin A, PUVA
23	vitamin E, 30% urea cream
24	clobetasol propionate 0.0525% cream, emollient cream, UVB TL01
25	calcipotriol and betamethasone gel, 15% urea cream, PUVA
26	calcipotriene hydrate and betamethasone solution, 0.1% mometasone furoate cream, Vitamin A, Vitamin E, Methotrexate, PUVA
27	0.1% mometasone furoate cream, Desloratadine cp, UVB TL01
28	0.1% mometasone furoate cream, clobetasol propionate 0.0525% cream, Desloratadine cp, PUVA
29	clobetasol propionate 0.0525% cream, emollient cream, vitamin A, vitamin E, PUVA
30	0.1% mometasone furoate cream, emollient cream, Methotrexate
31	0.1% mometasone furoate cream, emollient cream, salicylic acid cream, Clarithromycin
32	0.1% mometasone furoate cream, emollient cream, UVBTL01
33	clobetasol propionate 0.0525% cream, Ciprofloxacin cp, UVB TL01
34	clobetasol propionate 0.0525% cream, salicylic acid cream, UVB TL01

35	calcipotriol and betamethasone gel, vitamin E, Vitamin A, UVB TL01
36	0.1% mometasone furoate cream, UVB TL01
37	0.1% mometasone furoate cream, calcipotriol and betamethasone gel, vitamin A, vitamin E, PUVA
38	clobetasol propionate 0.0525% cream, betamethasone dipropionate and salicylic acid cream, vitamin A, vitamin E, UVB TL01
39	clobetasol propionate 0.0525% cream, betamethasone dipropionate and salicylic acid cream, silver nitrate solution, vitamin A, vitamin E, UVB TL01
40	UVB TL01
41	Methotrexate
42	0.1% mometasone furoate cream, calcipotriol and betamethasone gel
43	0.1% mometasone furoate cream, Desloratadine cp, UVB TL01
44	clobetasol propionate 0.0525% cream, UVB TL01
45	0.1% mometasone furoate cream, UVB TL01
46	calcipotriol and betamethasone gel
47	0.1% mometasone furoate cream, 15% urea cream, emollient cream, Methotrexate
48	0.1% mometasone furoate cream, 15% urea cream, emollient cream, Methotrexate
49	calcipotriol and betamethasone gel, 15% urea cream, vitamin A, vitamin E, Methotrexate, PUVA

The lipid profile was screened in both groups of patients. But there was no difference between the two groups of patients. The p-value comparing the two groups of cholesterol (study vs. control) was 0.8674, and for the triglycerides groups (study vs. control) was 0.218. On the other hand, a significant statistically p-value of 0.0259 was observed when comparing the values of triglycerides in the 2 groups, but after eliminating the patients on Acitretin and Methotrexate.

We compared the cholesterol and triglycerides values from each group for patients treated only Methotrexate or Acitretin and the ones on anti-TNFs and Methotrexate or Acitretin, but no significant p-values were found.

We observed high triglycerides values in patients treated with Infliximab – 7 (58.33%) followed by Etanercept – 5 (35.71%) and Adalimumab – 4 (22.22%). The highest levels of cholesterol were observed in the Etanercept and Adalimumab subgroup 11 (78.57%). The others subgroups contained only small samples of patients. (Table 6)

The study group was divided into subgroups of years on biological therapy and the levels of cholesterol and triglycerides were compared.

Table 6: Patients with high lipid values divided into systemic therapies

Therapy	High cholesterol No/(%)	High triglycerides No/(%)
Infliximab (original + biosimilar)	2 (16%)	7 (58.33%)
Etanercept	11 (78.57%)	5 (35.71%)
Adalimumab	11 (61.11%)	4 (22.22%)
Adalimumab + Methotrexate	3 (75%)	3 (75%)
Etanercept + Methotrexate	2 (100%)	0 (0%)
Adalimumab + Acitretin	1 (100%)	0 (0%)
Methotrexate	2 (50%)	3 (75%)
Acitretin	0 (0%)	0 (0%)

The subgroup 4-6 years had the highest level of dyslipidemia as it can be observed in Table 7.

DISCUSSION

Analyzing the two groups, the patients on biological therapy seemed to have more associated comorbidities than the control group. Cardiovascular events appear more often in patients with severe (8) and therapy resistant psoriasis like the ones treated

with anti-TNFs.

The two groups showed a difference in the frequency of hypertension (study group – 18 (86%) vs. control group – 8 (16%)). Even though, in normotensive and rheumatoid arthritis individuals, Infliximab reduced blood pressure levels, we observed in our study that the anti-TNFs do not improve alone the blood pressure values in psoriatic hypertensive patients [9].

Table 7: Levels of cholesterol and triglycerides divided into subgroup of years of anti-TNF therapy

Years of biological therapy	High cholesterol	High triglycerides	Cholesterol %	Triglycerides %
≤ 3.5 years	7	4	13.20	7.54
4-6 years	22	15	41.50	28.30
7-8 years	2	2	3.70	3.70

Many studies observed that high blood pressure is more often noted in patients with psoriasis compared to the non-psoriatic population [10], especially psoriatic patients who were male, middle-aged and elderly people [11] as our study group (39 males (73.58%) versus 14 females (26.42%)). Men are more predispose to severe forms of psoriasis [12].

High blood pressure is independent associated with psoriasis [8].

Apparently, in psoriasis the pathophysiologic mechanisms for high blood pressure are related to the underlying autonomic nervous system dysfunction [13], elevated plasma renin activity, elevated angiotensin converting enzyme activity, and elevated endothelin-1, TNFG308A polymorphism [14].

Psoriasis is thought to promote insulin resistance by overproduction of Th1 cytokines [10]. An association can be observed between high levels of TNFα, IL6, IL17, leptin, and C-reactive protein, and increases in BMI, which contribute to alterations in insulin biochemical pathways, leading to insulin resistance, type II diabetes [15]. Our patients are overweight, dyslipidemic and topical corticosteroid users for long periods of time, more over they have an inflammatory disease which is pro-atherogenic. Although only 6 patients out of 103 were diagnosed with diabetes mellitus type 2, the screening is continuous, because psoriasis is an independent risk factor for type 2 DM, the risk being greater in severe disease. (Marius Irimie, 2015).

Most of our patients with psoriasis vulgaris are above normal weight (72.54%). It has been reported that psoriasis favors weight increase and obesity [15]. In obesity there is an unbalanced production of pro- and anti-inflammatory adipokines in obesity, leading to a chronic low-grade inflammation state, which seems to favor worsening of psoriasis lesion and a poorer response to treatment [16].

Although we did not evaluate the weight gain before and after anti-TNF treatment, several studies have reported an increase in weight and body mass index (BMI) with the use of anti-TNF agents (adalimumab, etanercept and infliximab) [9, 17]. Most of our patients in the study group are overweight (77.35%).

On the other hand, weight loss (greater than or equal to 5% of the initial weight) is associated with a higher success rate in achieving control of disease activity in patients with overweight or obesity with psoriatic arthritis treated with anti-TNF-α [9]. A study with patients on low-energy diet lost weight which led to significant reductions of several cardiovascular risk-associated factors, moreover the weight loss improved HbA1c levels by 0.7%, equivalent to reductions achieved by treatment with an anti-diabetic drug [18]. Moreover, the psoriatic patients with the lowest monounsaturated fatty acid (MUFA) intake presented the highest values of PASI score and inflammation marker [19].

The mean age of psoriasis patients in our study was 52.07 years similar to international studies, thus confirming the average age of type 2 psoriasis patients worldwide [20]. Moreover the biological patients are the ones that do not respond to classical therapy

suggesting the severe form. The equal distribution in the classical therapy group can be due only to a mild form of disease.

Between the two groups there were not statistically significant differences in the lipid profile. Our results are similar with those of [21], their psoriatic patients treated with etanercept, adalimumab, or infliximab (each patient serving as their own control), did not present a significant change in total cholesterol, LDL and triglycerides. On the other hand, a p-value of 0.0259 (significant statistically) was observed when comparing the values of triglycerides in the two groups (eliminating the patients on Acitretin and Methotrexate).

We discovered that patients with 4-6 years of anti-TNF therapy were the majority group with dyslipidemia. However, the study of Ehsani et al. demonstrated an insignificant 5% increase in LDL and triglycerides after 24 weeks of treatment with anti – TNF agents [7], but all the changes in lipid profile by biological therapy are temporary, and the negative feedback will balance these changes over time [7]. Others have proven that patients with long term psoriasis have an increase in the serum total cholesterol levels and triglyceride levels [22]. Several authors found increased cholesterol levels (more than 5 years), but the lipid profile changes from the early stage to the late chronic stage of the disease. In contrast, Jorge Santos-Juanes et al. did not find a relationship between lipid levels and disease duration [23]. Maybe lipid profile abnormalities might be genetically determined rather than acquired [8].

Comparing only patients on MTX or Acitretin versus patients on anti-TNFs and MTX or Acitretin we did not observe a significant statistically important difference. But in similar studies there was a significant increase in triglycerides in patients treated with TNF inhibitors + MTX compared with patients treated with MTX alone. In our study, the highest triglycerides levels had patients on Infliximab – 7 (58.33%), followed by Etanercept – 5 (35.71%) and Adalimumab – 4 (22.22%). Concerning cholesterol levels were higher in Adalimumab and Etanercept – 11 subjects (61.11%; 78.57%). The patients on systemic classical treatment (Methotrexate or Acitretin) or on anti-TNF + MTX/ Acitretin were too few to have statistical significance [21].

Our control group (excluding MTX and Acitretin) showed increased cholesterol (26/53.06%) versus triglycerides levels (6/12.24%). Other studies showed that TG levels were significantly higher in psoriatic subjects than control groups [24].

We did not exclude patients on Methotrexate and Acitretin.

These may cause or influence the dyslipidemia. Recent studies proved that retinoid acid treatment could produce unsaturated fatty acids and induce triglyceride breakdown, bile acid secretion, lipolysis, and retinoids elimination. But, retinoid x receptor α deficiency might induce the synthesis of saturated fatty acids, triglyceride, cholesterol, bile acids, and retinoids [25]. Retinoids, especially Acitretin increase triglycerides levels [26], but also a mild and transient reduction in HDL levels and insulin sensitivity [27].

Regarding MTX, there are conflicting studies on the effect of Methotrexate on the lipid metabolism. The HDL profile function is favorable influenced by Methotrexate [28], Methotrexate has an anti-atherogenic potential [29] with cardioprotective properties [30]: tendency to decrease the risk of heart failure [9], a lower incidence of vascular disease (cardiovascular, cerebrovascular and arteriosclerosis) [17]. But it has been proven that cholesterol, LDL cholesterol and HDL cholesterol are increased short-termed after the initiation of Methotrexate therapy [31].

CONCLUSION

Our study did not show a positive effect of anti-TNF therapy in psoriatic patients on the lipid profile. Most likely, the abnormalities of the lipids are due to genetically inherited mechanisms. Our patients on biological therapy have a more severe form of psoriasis vulgaris, with many comorbidities.

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