A new Mucocutaneous Activity Index for Behçet's disease

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ABSTRACT

Objective. *Patient-reported outcomes are increasingly accepted to be major domains in chronic disorders. The aim of this study was to develop a patient-derived disease activity index in Behçet's disease (BD).*

Methods. *One hundred and seventy-seven BD patients (M/F: 69/108) were included in the study. Data were collected by clinical examination and a questionnaire regarding a Mucocutaneous Index (MI) with genital ulcer activity (GI), erythema nodosum activity (EI) and the composite index (CI) for oral ulcers, as subscales of it. Self-reported treatment evaluation was carried out as criterion validity. Patients whose symptoms completely disappeared or decreased significantly, were categorised as "improved group", others were classified as "non-improved group".*

Results. *Among the study group, 79.7% of the patients (n=141) were active, whereas 20.3% were inactive (n=36). Scores of CI, GI, EI and MI score were 0±0 in inactive ones, whereas scores were 5.65±2.36 for CI, 0.81±2.34 for GI, 0.91±2.35 for EI and 6.25±5.1 for MI in actives (p=0.000 for all). MI score was significantly higher in "non-improved group" (65.5%) compared to "improved group" (34.5%) (p<0.0001).*

Conclusions. *The mucocutaneous activity index may help decision-making process for treatment strategies in BD patients.*

Introduction

The impact of treatment protocols on disease manifestations are mainly evaluated by objective criteria with the physician's perspective, whereas the patient's perspective, filtered through a clinician's evaluation, may give critical information in practice (1). Clinician-based scores are objective evaluation criteria in clinical practice (2). Yet, the physician's evaluation could be different from those of patients for pain and overall health (3). Therefore, modern treatment regimens might be modified according to the patients' expectations of treatment outcomes (3-5). Therefore, patient-reported outcomes reflecting patients' perception are increasingly being investigated in understanding the patient perspective concerning the effectiveness of a treatment (3, 6, 7). In this context, the use of validated patient reported outcome measures and disease activity indices are important in decision-making process, especially in chronic diseases (2).

Behçet's disease (BD) is a chronic and multisystemic vasculitic disorder characterised by recurrent oral and genital ulcers, ocular, articular, intestinal, vascular and nervous system manifestations (8). The evaluation of disease activity is difficult in BD with different organ manifestations. In addition, no specific biochemical or serological marker is available for the evaluation of disease activity in BD (4).

Global and organ-specific activity indices with different scoring procedures in BD have been published over the last 30 years. Total clinical activity index, the first published activity index in BD, is derived from observed signs and symptoms. Scores were obtained with sum of points derived from involvement (9, 10). The Iranian Behçet's disease dynamic activity measure (IBD-DAM) assess organ involvements with various scoring procedures according to severity and extent of them (11).

Behçet's Disease Current Activity Form (BDCAF), another activity index, was based on presence or absence of clinical manifestations during the last 4 weeks. (4) (12). Behçet Syndrome Activity Score (BSAS) as a global patient-derived activity index evaluates clinical activity with 10 questions covering organ involvements in BD (13, 14). In our previous study, Composite index (CI), a patient-derived organ-specific activity index, is validated for oral ulcer activity in BD and recurrent aphthous stomati-

tis. The impact of oral ulcer activity on pain and functional status of patients is evaluated by this index (15).

Single or multiple tools or organ-based measurements is previously suggested for serious organ involvements regarding ocular, vascular, neurologic and gastrointestinal in Behçet's disease, However, although mucocutaneous manifestations including oral and genital ulcers and erythema nodosum are the most common clinical conditions and affect quality of life status negatively in BD, there is no specific tool for them. Therefore, we chose to investigate this aspect of BD. Moreover, patient expectations about their treatment are not assessed in routine. Therefore, the aim of this study was to develop a disease-specific mucocutaneous activity index (MI) in BD.

Materials and methods

Patients

In the cross-sectional study, 177 consecutive BD patients (M/F: 69/108, mean age:38.2±10.7 years) classified according to ISG criteria (16) and followed in the Behçet's Disease Clinic of the Marmara University Medical School in Istanbul were included. BD patients were treated with colchicine (1.5 mg/day, n=129) or immunosuppressive/immunomodulatory medications (IS) (n=48). Clinical manifestations of BD patients were as follows: oral ulcers (100%), genital ulcers (89,8%), cutaneous (100%), arthritic (48.6%), ocular (30.5%), vascular (16.9%), neurological (5.1 %) and gastrointestinal (1.7%) involvement. Positive pathergy reaction was observed in 69.5% of the patients (Table I).

Table I. Clinical manifestations of patients with Behçet's disease.

Clinical manifestaions	n	%
Oral ulcers	177	100
Genital ulcers	159	89.8
Cutaneous involvement	177	100
Arthritic involvement	86	48.6
Ocular involvement	54	30.5
Vascular involvement	30	16.9
Neurological involvement	9	5.1
Gastrointestinal involvement	3	1.7
Positive pathergy reaction	123	69.5

Selection procedure of mucocutaneous items

Since CI has five criteria previously validated for oral ulcer by our group (15), specific activity criteria for genital ulcer and erythema nodosum were searched in the literature. Since the discrimination and specificity of folliculitis from steroid-related acne and acne vulgaris lesions might be difficult, only erythema nodosum was selected for the index. The questionnaire structure of the CI was used for other involvements. Prominent items were selected and evaluated by the expert study group. Finally, five genital ulcer-related and four erythema nodosum related items were addressed for content validity for a target patient group (n=30). Then, patients were interviewed for mucocutaneous manifestations and their impact on pain and daily functions in the outpatient clinic. In addition to these identified items, open-ended questions were also asked during the face-to-face interviews. These were as follows: "In addition to these questions, do you have any opinion to further define both genital ulcer and erythema nodosum"? and "Do these questions reflect your genital ulcer and erythema nodosum related experience'? Answers were noted in this form by the interviewer and questions of selected items were revised. In the pilot study, MI was tested whether patients were able to understand the items and the response categories in the index. Then, final form of the 14 item-MI was obtained (Fig. 1). The form was filled by patients in approximately five minutes, although variations could be seen among patients.

Subgroups and scoring procedures of the Mucocutaneous Index

The Mucocutaneous index (MI) is a patient-derived activity index in BD, composed of 3 subscale activity indices regarding genital ulcer activity index (GI), erythema nodosum activity index (EI) and the composite index (CI) for oral ulcer (15). The score of MI could be between 0 and 30 (0–10 points for each involvement).

- Presence of the lesion was coded as 1 for actives and 0 for inactives (0 *vs.* 1 point),
- Pain was evaluated by 100 mm-visual analogue scale (VAS; 0: no pain-100: severe pain) by patients. Then, the VAS score was categorised to calculate the score as follows: ≤10:0; 11–20: 1; 21–40: 2; 41–60: 3; 61–80: 4; 81 and over: 5 points.
- Functional status was evaluated by a 5-point Likert-type scale: none of the time (0 points)), little of the time: 1 point, some of the time: 2 points, most of the time: 3 points and all of the time: 4 points. Mean score was used in the index (Fig. 1).

Reliability of the Mucocutaneous Index

Reliability was evaluated in two ways: internal reliability (Cronbach's alpha) and external reliability (test-retest). Internal reliability was evaluated by Cronbach's alpha coefficient in functional disability score of CI, GI and EI since the same rating was used in all three of them. The first 10% of the BD were again contacted to evaluate intra-observer agreement. After a period of 3 hours, they completed the questionnaire again. Since mucocutaneous manifestations may occur in short-time intervals in BD, time intervals were limited to the same day. MI was applied to 10.6% of active patients (n=15) by both a dermatologist (TE) and rheumatologist (HD) in 3 hours to evaluate for inter-observer agreement. Examinations were carried out in the morning by a dermatologist (TE) and in the afternoon by a rheumatologist (HD) on the same day. Wilcoxon-rank test was used in test-retest analysis as non-normal distributions of data were used in the analysis.

Validation of the Mucocutaneous Index

The score was evaluated in patients with both active and inactive disease in the previous month for content valid-

COMPOSITE INDEX FOR ORAL ULCER ACTIVITY (Total score: 0-10)

1. Oral ulcer activity: (0-1 points)

1) The number of oral ulcers during the last month: 0= 0 point, ≥1= 1 point

2. Pain status: (0-5 points)
Please place a vertical mark on the scale below to describe how bad you felt pain due to oral ulcer during the last month.

0 ——————————————————— 100

3. Functional status: Please describe effects of oral ulcers on your oral functions in the last month? (0-4 points)

How often.....	None of the time (0)	Little of the time (1)	Some of the time (2)	Most of the time (3)	All of the time (4)
Did you feel unpleasant *taste* in your mouth due to oral ulcers?					
Did you have difficulty in *speaking* due to oral ulcers?					
Did you have difficulty in *eating/chewing/swallowing* due to oral ulcers?					

GENITAL ULCER ACTIVITY (Total score: 0-10)

1. Genital ulcer activity: (0-1 points)

1) The number of genital ulcers during the last month: 0= 0 point, ≥1= 1 point

2. Pain status: (0-5 points)
Please place a vertical mark on the scale below to describe how bad you felt pain due to genital ulcer during the last month.

0 ——————————————————— 100

3. Functional status: Please describe effects of genital ulcers on your functions in the last month? (0-4 points)

How often.....	None of the time (0)	Little of the time (1)	Some of the time (2)	Most of the time (3)	All of the tim (4)
Did you feel limitation of your *simple movements* such as sitting due to genital ulcers?					
Did you have difficulty in *your sexual life* due to genital ulcers?					
Did you have difficulty in doing your *personal care and needs* (bathroom, toilet, cleaning) due to genital ulcers?					

ERYTHEMA NODOSUM (Total score: 0-10)

1. Erythema nodosum activity: The number of ertyhema nodosum during the last month: 0= 0 point, ≥1= 1 point

2. Pain status: (0-5 points)
Please place a vertical mark on the scale below to describe how bad you felt pain due to tender nodules on your legs during the last month.

0 ——————————————————— 100

3. Functional status: Please describe effects of aching tender nodules on your legs in the last month? (0-4 points)

How often.....	None of the time (0)	Little of the time (1)	Some of the time (2)	Most of the time (3)	All of the time (4)
Did you have difficulty in doing *daily activities*?					
Did you have difficulty in doing *physical activity* (sports, walking, going up and down stairs)?					

Fig. 1. Mucocutaneous Activity Index and Its subscales in Behçet disease.

ity. Self-reported treatment evaluation for mucocutaneous symptoms and self-reported health status (excellent/very good; not good and not bad; poor) were used for criterion validity in the previous month. If symptoms of patients completely disappeared or decreased significantly, these patients were categorised as "improved group". If symptoms did not change or worsened, they were classified as "non-improved group".

The correlation between the MI score and BSAS score was assessed for construct validity. Behçet Syndrome Activity Score (BSAS) with 10 questions covering organ involvements was calculated during the last 4 weeks in BD. In the questionnaire, 10-point visual analogue scale (VAS) was used to evaluate the discomfort related with oral ulcer, genital ulcer, skin lesions and general disease activity. The other symptoms regarding eye, vascular and gastrointestinal involvements and the number of mucocutaneous manifestations were coded categorically as 0, 5 and 10 points (13, 14).

Disease severity score was calculated for BD according to objective clinical manifestations (17). This score was calculated as the sum of 1 point each for mild symptoms regarding oral and genital ulcers, arthralgia and cutaneous manifestations regarding erythema nodosum, papulopustular lesions and folliculitis, 2 points each for moderate symptoms including arthritis, deep vein thrombosis of the legs, anterior uveitis and gastrointestinal involvement and 3 points each for severe disease manifestations (posterior/panuveitis, retinal vasculitis, arterial thrombosis or aneurysms, neurologic and bowel perforation). Moreover, physician global assessment (PGA) for overall status of mucocutaneus manifestations was also evaluated by a 100 mm-VAS (0=no evidence of disease activity *vs*. 100=severe disease activity) in BD patients. The study was approved by the Ethical Committee of Marmara University Medical School and informed consent was taken from the patients before the study.

Statistical analysis

Data were analysed using the SPSS 20.0 statistic programme (SPSS Inc, Chicago, IL, USA). Unpaired *t*-test was used for the comparison of MI and subscale scores according to disease activity, self-reported treatment evaluation and gender. ANOVA test was used to evaluate the relationship between self-reported general health status and score of MI. Mann-Whitney U-test and Kruskal-Wallis tests were used in analyses when the data were not normally distributed and where few subjects were included in the analysis. Pearson's correlation test was used to evaluate the relationships between PGA and MI and subgroups. Cronbach's alpha value was used to evaluate internal reliability of the global functional disability score as same scoring procedure was applied in subscales.

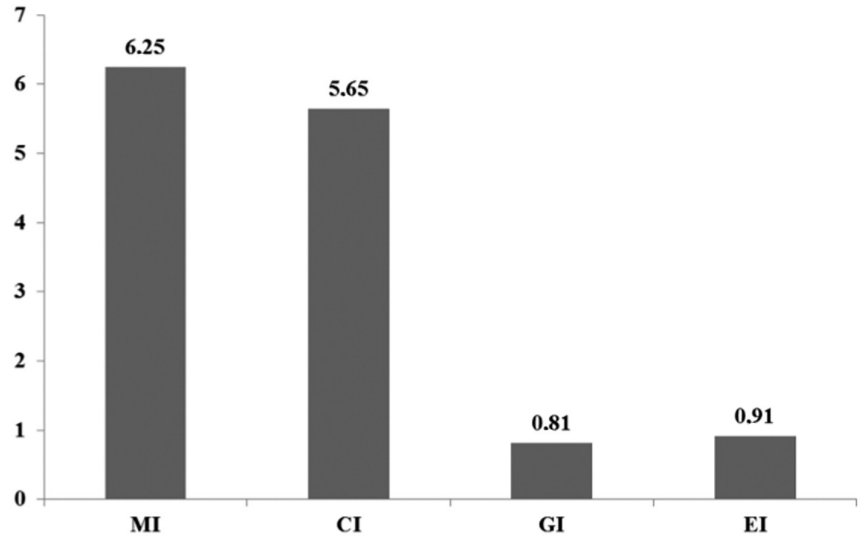

Fig. 2. Scores of MI and subgroups in active BD patients.

Table II. Scores of the Mucocutaneous Index and subscales in active patients according to gender.

Scores	Female (n=89) Mean	SD	Male (n=52) Mean	SD	*p*-value
MI	8.37	4.64	6.55	4.26	**0.020**
CI	6.04	2.31	4.7	2.52	**0.001**
GI	1.19	2.85	0.69	1.99	0.21
EI	1.14	2.62	1.09	2.5	0.90

Table III. Scores of the Mucocutaneous Index and subscales according to self-reported treatment status.

Scores	Improved group (n=61)		Non-improved group (n=116)		
	Mean	SD	Mean	SD	*p*-value
MI	1.65	2.56	8.66	4.39	**<0.0001**
CI	1.57	2.49	6.04	2.14	**<0.0001**
GI	0.01	0.04	1.24	2.8	**<0.0001**
EI	0.04	0.21	1.37	2.8	**<0.0001**

Results

In the BD group, 79.7 % (n=141) were active and 20.3 % were inactive (n=36). Scores of CI, GI, EI and MI score were 0±0 in inactive ones, whereas scores were 5.65±2.36 for CI (n=141), 0.81±2.34 for GI (n=20), 0.91±2.35 for EI (n=29) and 6.25±5.1 (n=141) for MI in actives ($p<0.0001$ for all) (Fig. 2). MI score significantly correlated with CI (r: 0.81 $p<0.0001$), GI (r: 0.46, $p=0.000$) and EI (r: 0.50,

Table IV. Scores of the Mucocutaneous Index and subscales according to self-reported health status.

Scores	Excellent/Good (n=32)		Not good and not bad (n=75)		Poor (n=70)		
	Mean	SD	Mean	SD	Mean	SD	*p*-value
MI*	3.72	4.03	7.19	3.56	12.2	5.74	<0.0001
CI**	3.01	2.87	5.85	2.76	6.01	2.28	<0.0001
GI***	0.36	1.7	0.51	1.6	3.07	4.02	<0.0001
EI****	0.35	1.41	0.77	1.97	3.12	3.98	<0.0001

*p<0.0001 among all groups, **Poor-excellent and poor-not good and not bad p<0.0001, ***and ****p=excellent- not good and not bad and excellent-poor p<0.0001.

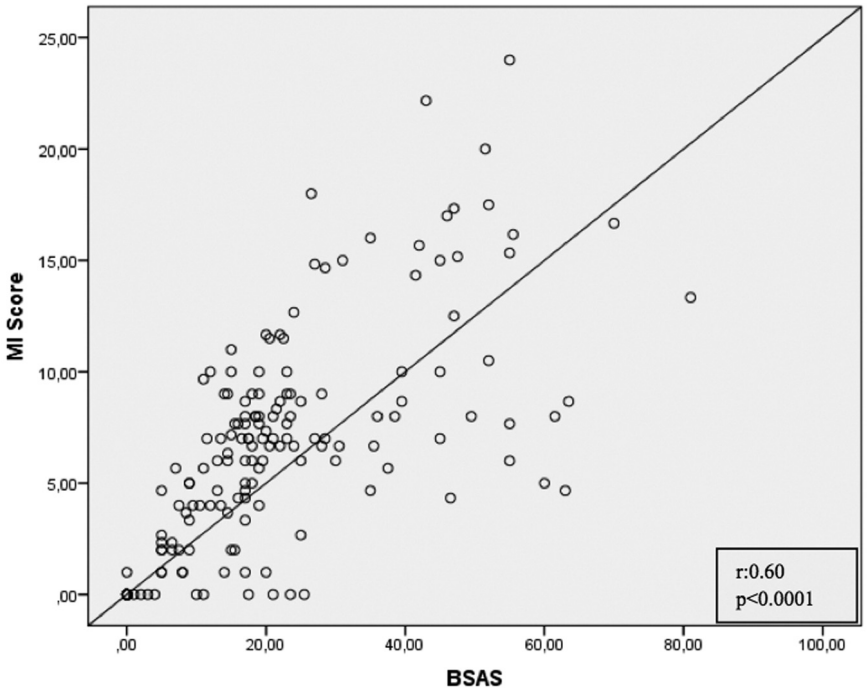

Fig. 3. The relationship between the MI score and BSAS.

p<0.0001). No floor or ceiling effects were detected in the MI score.

Over half of the active group (n=89, 63.1%) were females. Scores of MI and CI were higher in females than males in active patients (p=0.02 and p=0.001, respectively). Similar relationship was not observed in scores of GI and EI (p>0.05) (Table II).

BD patients were mainly treated with colchicine (n=129, 72.9%) and immunosuppresives (IS, n=48, 27.1%). Among active group (n=141), majority were treated with colchicine (n=109, 77.3%) whereas 55.5% (n=20) of inactive patients (n=36) were using colchicine (p=0.08). Regarding gender, 82.02% (n=73) of females (n=89) and 69.2% (n=36) of males (52) were found to be treated with colchicine in active patients (p=0.029).

In the "Improved group" (n=61, 34.5%), scores of MI, CI, GI and EI were significantly lower compared to those in non-improved group (n=116, 65.5%) (p<0.0001) (Table III). Almost all of the patients in the "Non-improved group" (n=114, 98.3%) had active mucocutaneous involvement, whereas the activity was 49.2% (n=30) in "Improved group" (p=0.000) (Table III). According to self-reported general health status, the activity ratio was 39.5% in the poor ones (n=70), 42.4% in the not good and not bad ones (n=75) and 18.1% in the excellent ones (n=32). Decrease in the MI scores was associated with excellent/very good general health status (3.72±4.03) compared to not good/not bad ones (7.19±3.56) and poor ones (12.2±5.74) (p<0.0001). Similar relations were seen in subscales (p<0.0001) (Table IV).

In the actives, BSAS score was found to be 24.69±16.10. A moderate correlation was observed between MI score and BSAS score (r=0.60, p<0.0001) (Fig. 3).

Severity score as an objective disease activity scale was as found to be 5.07±2.07 in patients with BD. A weak and negative correlation was observed between severity score and MI score (r:-0.16 p=0.032). Similarly, PGA score (33.15±27.35) was weakly correlated with MI (r: 0.15, p=0.037) in the BD patients.

Cronbach-alpha coefficients for functional status were found to be 0.888 for CI, 0.934 for GI and 0.942 for EI. Fifteen active patients were examined by both observer 1 (TE) (8.8±2.3) and observer 2 (HD) (9.1±1.3) to evaluate inter-observer difference without a significant difference (p=0.89). Moreover, no significant difference was present in intra-observer agreements (p>0.05).

Discussion

We have developed a mucocutaneous index for BD, aiming to evaluate patient reported outcomes in addition to objective assessment of disease activity, and shown this index to be sensitive to improvement after treatment and also general health status.

Assessment of disease activity in BD is fairly difficult due to the heterogeneous pattern of the disease with unpredictable flare-ups and lack of an activity biomarker. Therefore, activity indices are necessary to assess the disease course in clinical practice (18). Among the heterogeneous disease course, mucocutaneous manifestations are the most common compared to other involvements (19) and are considered as the mild spectrum of the disease (20-24). Patient's perspective in the evaluation of disease severity could be considered in treatment decisions of mucocutaneous involvement. (23), Accordingly, in our previous studies, oral ulcer activity (15) and quality of life status (25-29) were examined by patient-derived indi-

ces. The aim of the current study was to develop a standardised patient-derived MI and to assess treatments by patient's perspective in BD. Presence of any mucocutaneous manifestations, global assessment of pain and difficulty in functional status were evaluated for 3 different manifestations including oral and genital ulcers and erythema nodosum in the present study. We observed the MI score to be sensitive to changes of symptoms. Scores of inactive patients were zero and as almost all of the active patients had oral ulcers, higher MI scores which were mainly derived from the CI score. The MI score also correlated with health status with patients with excellent/very good general health having better scores.

In our group, the patients with active mucocutaneous manifestations, higher MI and CI scores were mainly females treated with colchicine and the scores of both MI and CI were significantly higher in females. This is consistent with the literature, as major organ involvement requiring more aggressive treatment is mainly seen in males (30-33).

Complete remission or significant decrease in the number mucocutaneous manifestations are common response criteria for treatment effects in clinical practice of BD, as objective criteria determined by the physician (34). In the present study, treatment was also assessed by the patients and the self-reported treatment evaluation was categorised as "improved" and "non-improved" groups. The persistence of activity or worsening of mucocutaneous lesions was associated with poor scores of MI and its subgroups compared to those of patients whose lesions disappeared or decreased significantly. Therefore, clinical activity was found to be related to "Dissatisfaction" with the treatment protocol. Moreover, patients classified their health status as excellent/good; not good and not bad; poor. The highest scores of the MI and subgroups were associated with poor self-reported health status.

Among the patient-derived activity indices, the BSAS covers all involvements from mild to major organ involvement (13, 14) whereas MI was a specific activity index for mucocutaneous involvement. The moderate correlation between MI score and BSAS score was not unexpected, since the majority of the group had active mucocutaneous lesions.

Interestingly, objective evaluations regarding disease severity score (17) and physician's global activity score were not associated with the patient-derived MI score in the study. This can be explained in two ways: first, increased disease severity score is associated with a rise in immunosuppressive usage which easily eliminates mucocutaneous activity (20, 23). Secondly, objective evaluations are based on organ involvement and physician's opinion of the morbidity or mortality risk of the patient, which may underestimate mucocutaneous findings. In contrast, patients usually suffer more because of mucocutaneous symptoms in daily life. Therefore, it is crutial to take patient needs into consideration in disease management to improve the outcome of the treatment which also gives critical information to physicians for a better understanding of the patient's perspective in BD.

The study was planned as a cross-sectional one, therefore continuous clinical data were not collected. Moreover, disease control and healthy control groups were not included in the study because disease-specific activity was the main domain. These are the main limitations of the study.

Conclusions

The new Mucocutaneous Activity Index is associated with mucocutaneous-specific clinical symptoms and treatment outcomes and may help the decision-making process in the management of BD patients with mucocutaneous involvement.

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