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Original article

Impaired quality of life, disability and mental health in Takayasu's arteritis

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Abstract

Objective. Patient-reported outcomes (PROs) are increasingly accepted to be among the major tools for outcome assessment in rheumatic disorders. In this study we aimed to assess quality of life (QoL), disability, anxiety and depression in patients with Takayasu's arteritis (TAK).

Methods. Patients followed with the diagnosis of TAK ($n = 165$) and healthy controls (HCs) ($n = 109$) were enrolled to the study. The 36-item Short Form Health Survey (SF-36) and hospital anxiety and depression scales (HADS) were used to assess QoL and mental status together with HAQ for disability.

Results. In SF-36 subscale assessment, all items were observed to be statistically lower in TAK patients; similarly HAQ scores were also higher ($P < 0.001$) in this group. In mental assessment, anxiety was found to be more common in TAK patients [90 (54.5%) *vs* 38 (34.9%), $P = 0.001$]. Depression also tended to be higher in TAK patients [70 (66.7%) *vs* 35 (33.3%)], without reaching significance ($P = 0.086$). Most of the SF-36 subgroup parameters were lower in TAK patients with active disease. Patients having anxiety and depression or with high HAQ scores reported worse SF-36 scores. In multivariate analysis, HADS-A, HADS-D and HAQ were associated with most SF-36 subscales.

Conclusion. PROs demonstrate that not only general health but also physical and social functioning with physical role limitations and mental health parameters were impaired in TAK. Our results, especially in active disease, suggest that PROs such as SF-36 can be core domains of disease assessment in TAK, similar to ANCA-associated vasculitides.

Key words: Takayasu's arteritis, quality of life, function, mental status.

CLINICAL SCIENCE

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Introduction

Takayasu's arteritis (TAK) is a chronic, inflammatory disorder involving large vessels, especially the aorta and its main branches [1–3]. Histopathologically it is characterized by panarteritis with an inflammatory infiltrate that is predominantly lymphoblastic, with granuloma formation and giant cells involving the media and adventitia [4]. As a result of inflammation, intimal hyperplasia, vascular stenosis and rarely aneurysm formation can occur [5, 6]. Clinical presentation of TAK is varied and can occur with non-specific symptoms such as fever, myalgia, arthralgia, weight loss or ischaemia, and vessel stenosis-related symptoms (upper extremity claudication, hypertension, carotidynia, syncope, dizziness and visual symptoms) [4].

Quality of life (QoL) is increasingly accepted to be a major domain for the assessment of patients with chronic disorders. The 36-item Short Form Health Survey (SF-36) is the most frequently used generic QoL tool in rheumatic diseases [7, 8]. Recent studies have suggested that QoL parameters are impaired in small to medium vessel systemic vasculitides [9–14] and also in TAK [15, 16]. Functional status is another area of life impact in inflammatory disorders, with generic tools developed for inflammatory arthritides but rarely studied in vasculitides [11]. In addition, mood and other mental changes are also a significant problem in chronic medical conditions and may impact the QoL of vasculitis patients.

With this background, the aims of this study were to (i) evaluate QoL and functional disability in TAK patients compared with healthy controls (HCs), (ii) assess some psychometric properties and (iii) examine the role of disease activity and other predictors of QoL and mental health.

Materials and methods

Patients

One hundred and sixty-five consecutive patients (153 female, 12 male) followed with the diagnosis of TAK at the rheumatology outpatient clinics of nine university hospitals in Turkey were enrolled in this multicentre, cross-sectional study. All patients fulfilled the proposed classification criteria of the ACR for Takayasu's arteritis [17] and were subclassified according to the angiographic classification for TAK [18]. One hundred and nine age- and sex-adjusted HCs (99 female, 10 male) were randomly selected from healthy people who accompanied TAK patients attending the rheumatology outpatient clinics. Having no symptoms of any disorder and not being a member or close relative of the patient's family were the inclusion criteria for the control group. The study was approved by the Ethical Committee of Marmara University Medical School and all patients and controls gave written informed consent. Exclusion criteria were being <18 years of age, having a personal history of psychiatric disease and being unable to give written informed consent. The demographic and clinical data of the patients were recorded and TAK patients were evaluated by physician's global assessment (PGA, active/inactive) and modified Kerr activity criteria for their disease activity [19]. Active disease was defined if two of the following were positive: (i) systemic features with no other cause, (ii) elevated ESR, (iii) features of vascular ischaemia or inflammation (claudication, diminished or absent pulses, bruit, vascular pain or asymmetric blood pressure) and (iv) typical angiographic features [19].

QoL, functional status and mental assessment

QOL was evaluated with a validated Turkish translation of the SF-36 [20]. The SF-36 contains eight domains, four physical (physical functioning, physical role limitation, bodily pain and general health) and four mental (social functioning, emotional role limitation, mental health and vitality). On the basis of these separate subscales, physical and mental component summary scores can be calculated. The scales and summary scores range from 0 to 100, with higher scores indicating better QoL [15, 21, 22].

No validated tool is available for functional assessment in vasculitides. Although primarily developed for inflammatory rheumatological diseases with joint involvement such as RA, HAQ was suggested to be a useful tool for all rheumatic diseases by Pincus *et al*. [23] and was chosen for our study.

The Hospital Anxiety and Depression Scale (HADS) [24] was used to assess the mental status. HADS scores of 8–10 indicate possible, scores of 11–14 indicate probable and scores of 15–21 indicate extreme cases of depression and anxiety [11, 25].

Statistical analysis

Comparisons between groups were made by using parametric Student's *t* test in normal distributions and non-parametric Mann–Whitney *U* tests in non-normal distributions of variables.The χ^2 test was performed to compare HADS-A, HADS-D and HAQ scores between the groups. In addition associations between the PGA and Kerr activity, HADS-A and HADS-D scores were evaluated by χ^2 test. Internal consistency (reliability) of the HAQ and SF-36 were evaluated using Cronbach's α (each subscale against the HAQ total score). Correlation between HAQ scores and SF-36 physical disability scores for concurrent validity were assessed using Spearman's correlation coefficient. Interobserver reliability of SF-36 subscales was assessed with the Wilcoxon test.

Univariate linear regression analyses were used to determine the relationships between age, disease duration, ESR, CRP and SF-36 subgroups. Multivariate logistic regression models using a stepwise backward elimination approach were fitted to determine the ability of HADS-A, HADS-D, HAQ and PGA to independently predict SF-36 scores. Impaired SF-36 subgroup scores on each SF-36 subscale were defined as values lower than the mean values observed for the entire study population.

$P<0.05$ was considered statistically significant. All statistical analysis was performed by using the SPSS 11.5 statistical package programme (Chicago, IL, USA).

Results

Demographic and clinical features

Patient characteristics are shown in Table 1. The mean (± S.D.) age was 41.3 ± 12.1 and 40.4 ± 10.3 years in TAK and HC, respectively ($P > 0.05$). The mean disease duration was 8.73 ± 7.72 years. Fifty-three (31.2%) patients had type I, 28 (17%) had type II, 10 (6.1%) had type III, 11 (6.7%) had type IV and 63 (38.1%) had type V angiographic disease. While 144 (87.2%) patients were taking combination treatment with immunsuppressives and corticosteroids, 6 (3.6%) patients were taking corticosteroids only and 15 (9.1%) were followed without any medication.

Table 1 Demographic features of TAK patients

Gender, female/male	153/12
Age, years	41.3 (12.1)
Disease duration, years	8.73 (7.72)
Disease subset, *n* (%)	
Type I	53 (31.2)
Type II	28 (17)
Type III	10 (6.1)
Type IV	11 (6.7)
Type V	63 (38.1)
Treatment, *n* (%)	
MTX plus MP	75 (45.4)
AZA plus MP	51 (30.9)
CYC plus MP	5 (3)
LEF plus MP	3 (1.8)
MMF plus MP	2 (1.2)
CsA plus MP	1 (0.6)
Infliximab	7 (4.2)
Glucocorticoids alone	6 (3.6)
Without treatment	15 (9.1)
ESR, median (min–max range), mm/h	21.5 (1–110)
CRP, median (min–max range), mg/dl	0.5 (0.02–54.5)

MP: methyprednisolone; CsA: ciclosporin-A. Values are presented as mean (S.D.), unless otherwise indicated.

At the time of the study, 71 (43%) patients were accepted as having active disease according to the PGA. According to criteria defined by Kerr *et al.*, 42/165 patients were active (25.4%), with a significant association observed between Kerr scores and PGA ($P < 0.001$). The median ESR was 21.5 (1–110) mm/h and the median CRP level was 0.5 (0.02–54.5) mg/dl.

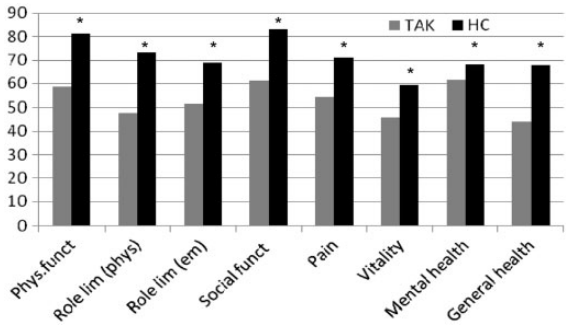
SF-36 scores

In the SF-36 assessment, all items were observed statistically lower in TAK patients than HCs ($P < 0.001$) (Fig. 1). The SF-36 subscales showed high internal consistency with a Cronbach's α value of 0.85 (range 0.82–0.85), indicating a high reliability of the measure when used in TAK patients. Inter-observer reliability was done by two observers in 13 TAK patients and a good inter-observer reliability was also observed at all SF-36 scores ($P > 0.05$).

Assessment of functional disability with HAQ

The HAQ score was $\geqslant 1$ in 21 patients (12.7%) in the TAK group, whereas all HC scores were <1 ($P < 0.001$) (mean HAQ scores were 0.49 ± 0.84 *vs* 0.08 ± 0.15, $P < 0.001$). As HAQ is mainly validated to measure physical functioning in RA and not validated as a disability measure in TAK, we assessed the reproducibility and reliability of HAQ in our patient population. Cronbach's α values ranged from 0.93 to 0.94, indicating a high reliability of the measure when used in TAK patients. Concurrent validity was evaluated by correlating the total HAQ score with the SF-36 physical functioning subscale score. There was a significant negative correlation between the two measures ($r = -0.69$, $P < 0.001$), supporting that HAQ also has a high concurrent validity in TAK patients.

Fig. 1 SF-36 subscale parameters of TAK patients and HCs.



*$P < 0.001$.

Mental health in TAK

Of the 165 TAK patients who completed the HADS, 19.3% scored as possible, 20.6% as probable and 2.4% as extreme cases of depression and 25.4% scored as possible, 20% as probable and 9% as extreme cases of anxiety. When the cut-off value was taken as 8, anxiety was found to be significantly higher in TAK patients than in HCs [90 (54.5%) *vs* 38 (34.9%), $P = 0.001$]. Depression also tended to be higher in TAK patients [70 (66.7%) *vs* 35 (33.3%)], without reaching statistical significance ($P = 0.086$) (mean anxiety scores were 8.28 ± 4.08 *vs* 6.2 ± 3.86 and mean depression scores were 6.81 ± 4.18 *vs* 5.8 ± 3.83, respectively).

Disease activity and PROs

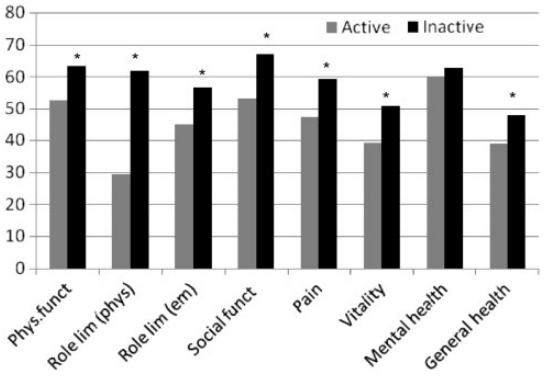
Defining active disease according to PGA, most of the SF-36 subgroup parameters, except mental health, were observed to be statistically lower in active TAK patients ($P < 0.05$) (Fig. 2, Table 2). However, the HADS-A, HADS-D and HAQ scores were not different between the active and inactive groups. Anxiety was found in 47 patients (50%) with inactive disease and in 43 patients (60.6%) with active disease ($P > 0.05$). Depression was present in 37 (39.4%) and 33 (46.5%) patients, respectively ($P > 0.05$). Patients having anxiety and depression or with high HAQ scores reported worse SF-36 scores ($P < 0.001$, $P < 0.001$ and $P < 0.05$, respectively) (Table 2).

Predictors of QoL in TAK patients

We also assessed the factors associated with QoL in TAK patients with uni- and multivariate analysis. The results of the univariate analysis are shown in Table 3 and the multivariate analysis in Table 4. There was no association between acute-phase response (ESR or CRP levels) and SF-36 scores ($P > 0.05$), except physical role limitation ($\beta = -0.16$, $P = 0.03$). Age was negatively associated with some SF-36 parameters [physical functioning ($\beta = -0.31$, $P < 0.001$), emotional role limitation ($\beta = -0.18$, $P = 0.02$)

and pain (β = −0.16, $P = 0.03$)] that were not significant in practice. When multivariate analysis was performed, HADS-A, HADS-D and HAQ were associated with most SF-36 subscales (Table 4).

FIG. 2 SF-36 subscale parameters in active and inactive patients.



*$P < 0.05$.

Discussion

In this study we showed that all aspects of SF-36, both physical and mental, were impaired in TAK patients compared with age- and sex-matched HCs. Similarly, our patients had impaired physical function and higher anxiety scores, suggesting that TAK also might affect QoL, similar to small to medium vessel vasculitides. Disease assessment in TAK has important challenges, as recently discussed [26, 27]. Being a chronic, slowly progressive, large vessel vasculitis with usually limited constitutional features, it may be difficult to determine the impact of TAK on patient QoL. Physicians following TAK patients usually focus on vascular outcomes such as narrowing or occlusion, using mainly various imaging techniques to assess vascular patency. The most cited Kerr criteria for disease activity involves constitutional features, bruits, acute-phase response and imaging as parameters of active disease. A new effort to assess activity by a composite index of clinical manifestations without imaging or acute-phase response has also been shown to have important limitations [28]. However, recent studies have demonstrated that physician and patient expectations

TABLE 2 SF-36 scores in TAK patients

	Physical functioning	Role limitation (physical)	Role limitation (emotional)	Social functioning	Pain	Vitality	Mental health	General health
Depression								
Score <8	66.2 (23.4)	61.3 (42.1)	60.0 (34.1)	69.2 (24.6)	59.8 (29.1)	55.5 (19.5)	68.2 (15.1)	51.7 (24.9)
Score ⩾8	48.6 (24.8)	28.9 (38.2)	39.8 (33.5)	49.7 (25.1)	46.4 (30.3)	32.8 (18.1)	52.0 (18.4)	33.9 (20.8)
P value	<0.001	<0.001	<0.001	<0.001	0.006	<0.001	<0.001	<0.001
Anxiety								
Score <8	67.4 (23.4)	65.2 (41.3)	65.4 (31.7)	71.4 (26.4)	64.7 (29.5)	58.6 (19.5)	72.0 (13.8)	55.9 (23.2)
Score ⩾8	51.7 (24.9)	33.3 (40.1)	40.1 (34.0)	52.6 (23.7)	45.3 (28.1)	35.3 (18.0)	52.5 (17.0)	34.4 (21.2)
P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
HAQ								
Score <1	64.0 (21.1)	53.3 (42.7)	54.9 (35.3)	65.2 (24.8)	59.0 (28.4)	48.9 (21.4)	63.3 (17.2)	47.4 (23.7)
Score ⩾1	23.1 (23.8)	9.5 (26.7)	28.3 (24.1)	33.1 (20.9)	21.3 (20.4)	25.9 (14.0)	48.7 (21.3)	22.9 (18.7)
P value	<0.001	<0.001	0.001	<0.001	<0.001	<0.001	0.003	<0.001
PGA								
Inactive	63.4 (24.3)	61.8 (42.1)	56.6 (34.2)	67.1 (25.7)	59.4 (29.0)	51.0 (21.6)	62.6 (18.3)	48.2 (22.9)
Active	52.7 (25.7)	29.2 (38.2)	44.8 (35.6)	53.2 (25.8)	47.1 (30.7)	39.2 (20.8)	59.9 (18.4)	38.8 (25.8)
P value	0.01	<0.001	0.02	0.001	0.008	0.001	0.34	0.009

All analysis were performed with Mann–Whitney *U* test. Values are presented as mean (S.D.), unless otherwise indicated.

TABLE 3 Univariate analysis [standardized regression coefficient (β)] of SF-36 scores in TAK patients

	Physical functioning	Role limitation (physical)	Role limitation (emotional)	Social functioning	Pain	Vitality	Mental health	General health
Age	−0.31*	−0.15	−0.18**	−0.14	−0.16**	−0.09	−0.01	−0.04
Disease duration	−0.13	0.02	−0.05	−0.09	−0.09	−0.15**	−0.13	−0.11
ESR	−0.11	−0.16**	−0.12	−0.13	−0.12	−0.06	0.07	−0.04
CRP	−0.003	−0.10	−0.06	0.009	−0.09	−0.06	−0.05	−0.10

*$P < 0.001$, **$P < 0.05$.

Table 4 Multivariate logistic regression of factors associated with SF-36

	β	S.E.	*P* value	Odds ratio
Physical functioning				
HAQ	2.54	0.77	0.01	12.7
Role limitation (physical)				
HADS-A	0.85	0.39	0.03	2.35
HADS-D	0.92	0.40	0.02	2.52
HAQ	1.99	0.78	0.01	7.37
PGA	1.35	0.37	<0.001	3.86
Role limitation (emotional)				
HADS-A	1.54	0.40	<0.001	4.69
HADS-D	0.79	0.40	0.04	2.20
HAQ	2.03	0.80	0.01	7.62
PGA	0.85	0.38	0.02	2.34
Social functioning				
HADS-D	1.02	0.35	0.004	2.78
HAQ	2.02	0.66	0.002	7.59
PGA	0.79	0.35	0.02	2.21
Pain				
HADS-A	1.13	0.34	0.001	3.10
HAQ	2.02	0.78	0.01	7.54
PGA	0.84	0.35	0.01	2.37
Vitality				
HADS-A	1.99	0.40	<0.001	7.30
HADS-D	1.14	0.41	0.006	3.31
PGA	1.07	0.40	0.007	2.93
Mental health				
HADS-A	1.99	0.39	<0.001	7.33
HADS-D	1.14	0.39	0.004	3.13
General health				
HADS-A	1.63	0.35	<0.001	5.13
HAQ	1.46	0.67	0.03	4.34

might differ for the outcome and treatment effects. Fatigue, for example, is commonly described by patients as the major disabling feature of inflammatory disorders, whereas it is rarely employed as a major outcome tool in routine follow-up or clinical studies. For this reason, OMERACT study groups emphasize the importance of PROs as core domains of clinical assessment in clinical trials. The OMERACT vasculitis study group recently placed SF-36 for QoL assessment among the four core domains (along with patient-reported outcomes, disease activity, damage and mortality) for disease assessment in ANCA-associated vasculitis [29].

Our results with SF-36 for QoL are similar to those of two previous studies in TAK. Akar *et al.* [15] first reported that QoL parameters are impaired in TAK patients compared with HCs, without any differences between TAK, RA and ankylosing spondylitis patients. SF-36 subscales had high internal consistency, indicating high reliability for the measurement of QoL in TAK. No significant correlation between ESR or CRP levels and SF-36 parameters was observed, similar to our study. However, in contrast to our results, no correlation was present between the disease activity and SF-36 parameters. In another study, Abularrage *et al.* [16] showed that QoL is impaired in TAK patients compared with HCs and other chronic diseases associated with peripheral vascular disease, including diabetes mellitus, hypertension and coronary artery disease. The SF-36 has also been studied for small to medium vessel vasculitis and has been shown to be impaired in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis [30–33]. Tomasson *et al.* [34] showed that improvement in the BVAS was also reflected in both the physical and mental components of the SF-36, suggesting that the SF-36 can be used to assess disease activity. However, studies on large vessel vasculitis such as GCA are limited and are controversial [35]. A major criticism for generic PRO tools is their possible lack of sensitivity to the areas of life impact that might be specific to the health condition. Hellmann *et al.* [36] studied domains of QoL important to GCA patients and found vision-related impairment described to be the most important item by patients. Similarly, compared with other vasculitides, TAK has some major different impacts associated with large-vessel involvement such as extremity claudication, and some features not covered by standard QoL instruments such as SF-36 should be assessed by focus group studies.

We chose HAQ as the tool for assessing functional status in our study, which was mainly devised for inflammatory rheumatological disorders with joint involvement. We validated HAQ in our study and significant differences were present between the patients and controls. However, as only a difference of around 0.5 units was observed (close to the minimum clinically detectable difference of 0.22 in RA) [37], HAQ might have a limited value for disease assessment in TAK. This might be associated with the nature of TAK, which usually causes very limited impairment in the activities of daily life. New tools that emphasize upper extremity claudication should be developed to use for TAK. Similarly, damage assessment through the Vasculitis Damage Index (VDI) or other disease-specific instruments might also be useful for this purpose.

To our knowledge, our study is the first to evaluate mental health in TAK. When we evaluated anxiety and depression scores with HADS, only anxiety seems to be impaired significantly. Depression was also found to be slightly higher in TAK patients, without a significant difference. These results suggest a milder impairment of psychological status in TAK compared with other inflammatory disorders such as SLE and RA, where depression is commonly observed [38, 39]. The patient-reported outcomes,resence of depression is also reported to be 22% in one study in GPA, which is unassociated with disease activity [40, 41]. However, we observed that psychological status (both anxiety and depression) is associated with the SF-36 in multivariate analysis. Anxiety seems to be a continuous feature of mental health in TAK, possibly due to long-term consequences that disturb mental status, which might be accompanied by mild depression. The mental component of the SF-36 possibly reflects this

mental status, with a general lower QoL of the patients in both remission and relapses of the disease course.

Disease activity was observed to be significantly associated with most of the SF-36 parameters, suggesting that disease activity affects QoL and mental and functional status in TAK patients. In this respect, any clinical trial for TAK in future studies should also incorporate PROs, especially the SF-36, as a major outcome parameter.

A limitation of our study is the fact that both QoL and mental status can be affected by many residual confounding factors (such as degree of fatigue, socioeconomic status, education, impact of treatment and drug compliance) that we have not analysed, which might have caused biases in our interpretation of the results. Especially for psychometric assessment, other PRO tools might be incorporated to define the mental status and associated factors better. The cross-sectional nature of our study and its hospital-based population might also have influenced our results. However, we assume that, due to its complicated clinical course and rare presence, most TAK cases are referred to specialized centres in Turkey. Finally, there can be a clinical *vs* statistical difference in our PRO measurements. Some of the observed differences might have limited value as a clinically important difference compared with controls. Disease-specific instruments developed from patient focus groups will show the real impact of our results.

In conclusion, QoL parameters are impaired in patients with TAK and remission of disease activity is associated with better QoL. As disease activity is also associated with anxiety and depression, supportive help for these domains of health seem to be important for better QoL. Finally, mild impairment of functional status with HAQ should be better assessed with new tools in TAK.

Rheumatology key messages

- QoL is impaired in TAK and is associated with active disease.
- A higher anxiety score and a mild functional impairment are also observed in TAK.

Disclosure statement: The authors have declared no conflicts of interest.

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