

Obesity Associated With Active, But Preserved Joints in Rheumatoid Arthritis: Results From our National Registry

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ABSTRACT

Objectives: This study aims to investigate the prevalence of obesity in patients with rheumatoid arthritis (RA) and associations with disease outcomes.

Patients and methods: The study population comprised of 1,038 patients with RA (198 males, 840 females; mean age 56.1±12.6 years; range 19 to 94 years) who had been included in National RA-Registry. RA disease activity measures, physical function, quality of life, joint destruction, laboratory tests, as well as pain, fatigue, general health, and patient and physician global health assessments on a visual analog scale were collected.

Results: Our patients had established RA with mean disease duration of 10.2±8.8 years and moderate disease activity (disease activity score in 28 joints: mean 3.7±1.6). According to the body mass index (BMI), 70% of the patients were overweight (n=362, 34.9%) or obese (n=364, 35.1%). These patients had higher disease activity scores in 28 joints, visual analog scale-pain and visual analog scale-patient global scores, and higher levels of fasting blood glucose; however, they had lower radiographic scores than normal-BMI patients (p<0.05). Regression analyses showed that the BMI was independently and inversely associated with disease activity scores in 28 joints and Sharp/van der Heijde scores after the adjustments for biologic and treatment-related factors (p<0.05).

Conclusion: Our findings indicate that obesity is more common in patients with RA than the general population. High disease activity and low radiographic damage were associated with high BMI in this National RA-Registry.

Keywords: Body mass index; disease activity; obesity; radiographic damage; rheumatoid arthritis.

Rheumatoid arthritis (RA) is a rare, heterogeneous, chronic, systemic, inflammatory and rheumatic disease, with patients presenting with various degrees of disease activity, structural damage, and

disability. Many well-known prognostic markers of disease activity have been identified; however, influence of obesity and body composition on the disease activity is rarely mentioned in the literature.

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Obesity is a common metabolic/endocrine, inflammatory and disabling disease with increased comorbidities such as diabetes, hypertension, coronary artery disease, and osteoarthritis. Obesity is thought to be a risk and a severity factor for various disorders including autoimmune chronic inflammatory diseases. The role of obesity on the development and progression of RA is poorly understood.¹⁻⁵ The influence of body mass index (BMI) on disease outcomes in RA is also unclear.

Due to the close association of obesity with activation of pro-inflammatory pathways, obese RA patients may have more active and severe disease. It has been shown that white adipose tissue is a source of specific adipocytokines (e.g., leptin, resistin, adiponectin, and visfatin) that are increased in RA patients and are able to increase the expression of cytokines such as tumor necrosis factor alpha and interleukin-6.¹ Some studies reported that obesity might slow down the radiographic progression of the disease in the early phase of RA,^{3,6,7} whereas in advanced disease, obesity increases disease activity.^{4,5,8}

Interestingly, the prevalence of obesity in RA appears to be subject to geographical variation.⁹⁻¹⁴ Therefore, national registries are important to estimate and compare RA statistics with possible associations of disease outcomes worldwide. Unfortunately, there are limited numbers of registry studies that investigated the effects of obesity in patients with RA despite its importance.¹⁵⁻¹⁷ Some studies have shown that obesity is associated with improved radiographic outcomes and higher disease activity at baseline and follow-up,¹⁵ higher levels of inflammatory markers,⁴ and higher levels of self-reported disability.^{5,15}

Our hypothesis was that obese patients with RA have more active and severe disease than normal-weight controls, based on the inflammatory nature of both diseases. Therefore, in this study, we aimed to investigate the prevalence of obesity in patients with RA and associations with disease outcomes.

PATIENTS AND METHODS

The Turkish League Against Rheumatism-Follow up Program registry consists of web-based patient

data from 36 centers in different regions of Turkey, and was first started between September 2007 and March 2011. This cross-sectional multi-center study included 1,038 patients with RA (198 males, 840 females; mean age 56.1±12.6 years; range 19 to 94 years) who were participants in National RA-Registry of Turkish League Against Rheumatism-Follow-up Program (TLAR-FP). An online tool was used to record data of the RA patients. The patient follow-up program is a web-based questionnaire, which contains sections on sociodemographic data, physical examination, laboratory and imaging data, and treatment plan.

The study was nested within the TLAR-FP registry. Thus, patients were identified from eleven outpatient clinics attending to TLAR-FP registry. Patients were diagnosed according to the American College of Rheumatology criteria.¹⁸ The study protocol was approved by the Ankara University, Faculty of Medicine Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Self-reported-disability status was evaluated by using the validated Turkish version of the Health Assessment Questionnaire (HAQ; scores range from 0 to 3, with higher scores reflecting greater limitations).¹⁹ The parameters of patient-experienced pain, fatigue, general health, patient and physician global health assessments were shown on a visual analog scale (VAS; range from 0 to 10 cm; 0= no complaint and 10= severe complaint).

Rheumatoid arthritis disease activity was assessed with the disease activity score in 28 joints (DAS28) [DAS28 including erythrocyte sedimentation rate (ESR), tender joint counts, swollen joint counts, and VAS-global health], clinical disease activity index, and simplified disease activity index at the same visit.²⁰⁻²² Sharp/van der Heijde scores²³ obtained from hand and feet joints were also collected. Levels of ESR, C-reactive protein, immunoglobulin M rheumatoid factor, anti-cyclic citrullinated peptide antibody, complete blood count, fasting glucose, liver function tests, kidney function tests, and lipids were recorded at the same visit. All patients have been treated with consensus recommendations of TLAR.²⁴

Table 1. Distribution (%) of groups according to sex and body mass index

	Rheumatoid arthritis (n=1.038)			Controls (n=12.160)		
	Men	Women	Total	Men	Women	Total
Underweight	0.5	1.4	1.2	2.7	5.1	3.9
Normal	34.5	27	28.2	44.7	43.6	44.2
Overweight	40.2	33.9	34.9	39.0	30.4	34.8
Obese	24.7	37.7	35.1	13.7	20.9	17.2

Obesity frequency was compared with 12,160 individuals of Health Survey statistics.²⁵ Sociodemographic variables, smoking, alcohol, and exercise habits, and history of cancer and menopause were noted. Blood pressure was measured while the subjects were seated.

Height was measured with a wall-mounted ruler. Weight was measured with subjects wearing no shoes using digital bathroom scale. BMI was calculated as weight (kg) divided by height (m²). Body composition classification was stratified into BMI categories as per World Health Organization cut-offs as objective variable:

- Underweight: <18.5
- Normal: 18.5-24.9
- Overweight: 25.0-29.9
- Obese \geq 30

Mono or combined disease-modifying anti-rheumatic drug therapy was started to the patients in accordance with the recommended treatment strategy in Turkey.²⁴

Statistical analysis

Continuous data are shown as the mean \pm standard deviation and categorical data are shown as frequency (percentage). Chi-square test was used to assess the association between categorical variables. Differences among groups were analyzed with the multiple comparisons of analysis of variance, or Kruskal-Wallis, where appropriate. Tukey-b multiple comparisons test was used after the analysis of variance or Kruskal Wallis test.

After the Pearson correlation tests, linear regression (for continuous outcomes: DAS28, HAQ, and VAS scores of pain, fatigue, general health, patient and physician global health assessments) was tested to examine the association of BMI with the study outcomes. To correct

possible confounding effects, multiple linear regression models were then developed with adjustments for variables considered significant in univariate regressions. The level of statistical significance was accepted as an alpha level less than 0.05.

RESULTS

Patients' disease duration was 10.2 ± 8.8 years (range 1 to 53 years) and mean DAS28 score was 3.7 ± 1.6 (range 0.4 to 7.9). Mean BMI was 28.4 ± 5.5 (range 15.2 to 47.4). According to the BMI, 1.3% (n=13) of patients was underweight, 28.2% (n=293) was in normal limits, 34.9% (n=362) was overweight, and 35.1% (n=364) was obese. The diagnosis of obesity was more common in female RA patients than males (p=0.003).

Obesity frequency was statistically significantly different when compared with 12,160 individuals of Health Survey statistics with 3.9% underweight,

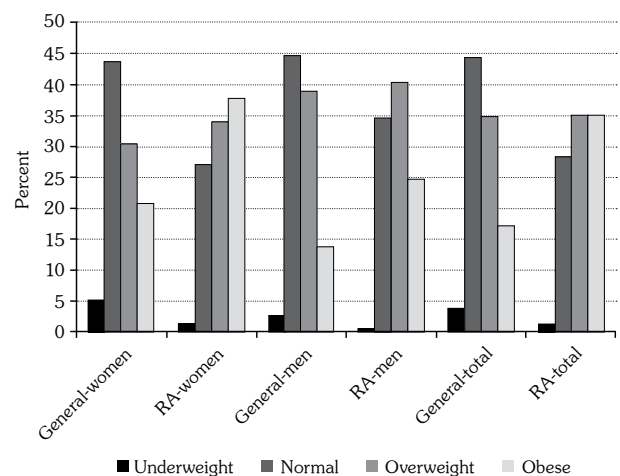


Figure 1. Prevalence of obesity by sex in the Turkish League Against Rheumatism/rheumatoid arthritis-registry and general population.

44.2% normal-BMI, 34.8% overweight, and 17.2% obese individuals. Obesity was two-fold more common in the RA group of this study compared to the general population (35% vs. 17.2%) (Table 1 and Figure 1).

Majority of the patients (n=943, 90.8%) used synthetic disease-modifying anti-rheumatic drugs including methotrexate (n=669, 64.4%), sulfasalazine (n=345, 33.2%), leflunomide (n=212, 20.4%), and hydroxychloroquine (n=163, 15.7%). The remaining patients (n=109, 10.5%) used biologic disease-modifying anti-rheumatic drugs including anti-tumor necrosis factor alpha (n=98, 9.4%) and other biologics (n=11, 1.1%). Half of the patients used corticosteroids (n=523, 50.4%).

Significant differences were detected among normal and obese groups in parameters of age, age of RA onset, sex, DAS28, pain-VAS, patient's global-VAS, Sharp/van der Heijde scores, diastolic blood pressure, and fasting blood levels of glucose ($p < 0.05$). The frequencies of smokers, alcohol consumers, exercisers, cancer patients and postmenopausal patients were not different among groups (all $p > 0.05$). Multiple comparisons for the four BMI categories were shown in Table 2 and Table 3.

Disease activity scores in 28 joints of obese patients were higher than normal-weight patients in multiple comparisons ($p = 0.019$). Sharp/van der Heijde scores of overweight and obese patients were lower than normal-weight patients in multiple comparisons ($p = 0.045$ and $p = 0.039$, respectively).

Body mass index was weakly associated with higher scores of DAS28 ($r = 0.212$), lower scores of Sharp/van der Heijde ($r = -0.158$), higher scores of patients' global ($r = 0.094$) and pain ($r = 0.085$) assessments; older age ($r = 0.135$), RA onset at older age ($r = 0.116$), female sex ($r = 0.104$); laboratory parameters including higher levels of low-density lipoprotein ($r = 0.201$), fasting blood glucose ($r = 0.187$), triglyceride ($r = 0.152$), alanine aminotransferase ($r = 0.115$), and ESR ($r = 0.087$); and higher values of diastolic blood pressure ($r = 0.175$), (all $p < 0.01$) in Pearson correlation analyses.

Body mass index was also weakly correlated with higher values of systolic blood pressure ($r = 0.126$), higher levels of total cholesterol

($r = 0.122$), state of postmenopausal period ($r = 0.120$), higher scores of HAQ ($r = 0.097$), and scores of fatigue ($r = 0.079$) and general-health ($r = 0.066$) (all $p < 0.05$).

Using univariate linear regression, the significant factors were identified. Then, the effect of BMI was examined by multiple linear regression. BMI determinants including biologic factors such as age, sex, duration of disease, and post-menopausal states were adjusted. After the adjustments, it was found that BMI was independently associated with severe disease activity according to DAS28 scores (Beta: 0.212, t: 2.989, $p = 0.003$, 95% confidence interval: 0.020-0.099) and better level of joint destruction assessed with Sharp/van der Heijde scores (Beta: -0.158, t: -2.360, $p = 0.009$, 95% confidence interval: -2.736- -0.394).

DISCUSSION

We have demonstrated that increased BMI was associated with higher disease activity scores. When individual DAS28 components were examined, obesity was associated with high VAS-pain and ESR, but not increased swollen and tender 28 joint counts. Obesity was also associated with high levels of self-reported disability and but not with impaired quality of life.

The prevalence of obesity in this cohort was two-fold higher than the wider population reported in the National Health Survey 2012.²⁵ Obese patients were older, with female predominance, higher DAS28 and lower radiographic scores in the present study. As reported in some previous studies, we also showed that BMI was independently associated with severe disease activity^{4,15} and less joint destruction.^{3,6,7} Strikingly, the association between obesity and less joint destruction has been reported only in patients who were positive for rheumatoid factor or anti-cyclic citrullinated peptide in some studies.^{3,6}

Unfortunately, over the past years, obesity has become an epidemic in many countries.²⁵⁻²⁹ Obesity may be associated with RA, whose onset and outcomes are affected by obesity.^{15,30} Hotamisligil et al.³¹ first discovered the inflammation of adipose tissue and its possible role in obesity by demonstrating the secretion of tumor necrosis

Table 2. Comparison of demographic and clinical characteristics of patients (n=1,038)

	All (n=1.038)		Underweigh (n=13)		Normal (n=362)		Overweight (n=293)		Obese (n=364)		p
	%	Mean±SD	%	Mean±SD	%	Mean±SD	%	Mean±SD	%	Mean±SD	
Age (years)		56.1±12.6		48.6±17.9		53.1±14.3*†		57.2±12.3*		57.6±10.6†	0.0001*†
Age of onset (years)		41.4±13.5		35.2±16.8		38.4±15.1*†		42.7±13.5*		42.7±11.4†	0.0001*†
RA duration (years)		10.2± 8.8		8.6±5.0		10.0±9.3		10.0±8.8		10.4±8.5	0.882
Female	81.0		92.3		62.4†		77.1‡		86.8†‡		0.008† 0.002‡
Menopause	34.7		46.2		27.3		33.7		41.5		0.113
Smoker	16.8		15.4		25.6		17.4		9.3		0.999
Drinker	2.1		7.7		3.4		1.9		1.1		0.999
Exercise	12.4		15.4		13.3		13.8		10.4		0.830
Cancer	1.3	-	1.7		1.4		1.1				0.792
Systolic blood pressure (mmHg)		124.3±19.7		113.3±11.5		126.4±20.1		120.6±14.2		125.9±22.9	0.108
Diastolic blood pressure (mmHg)		77.9±11.7		70.0±5.0		77.9±10.6†		76.0±8.1		80.0±14.1†	0.039†
Pain-VAS		4.3±2.8		5.2±2.2		4.0±2.8†		4.2±2.9		4.7±3.0†	0.023†
Patient's global-VAS		4.0±2.8		5.5±2.2		3.7±2.7†		3.7±2.7‡		4.5±2.8†‡	0.005† 0.004‡
Physician's global-VAS		2.9±2.5		4.9±2.3§¶		2.7±2.3§		2.9±2.6¶		3.0±2.5f	0.022§ 0.007¶ 0.03
Fatigue-VAS		4.6±3.2		4.8±2.1		4.4±3.0		4.4±3.1		4.9±3.3	0.141
General Health-VAS		3.6±2.6		4.9±2.1		3.2±2.5		3.5±2.7‡		3.9±2.7‡	0.007‡
DAS28		3.7±1.6		3.2±0.8		3.6±1.6†		3.3±1.5		4.1±1.5†	0.019†
SDAI		6.1±7.5		6.4±4.1		6.0±7.9		5.7±6.7		6.6±7.8	0.558
CDAI		13.3±10.8		16.5±11.7		13.3±11.1		12±10.7		14.4±10.7	0.549
HAQ		1±0.7		1.2±0.6		1.0±0.7		0.9±0.7		1.1±0.7	0.073
RA QoL		12.3±10.1		21±4.2		12.6±10.3		10.9±10.3		12.4±10.0	0.524
Sharp van der Heijde		26.3±5		62.1±85.1		20.0±41.1*†		40.7±77.0*		18.3±29.7†	0.045* 0.039†

SD: Standard deviation; RA: Rheumatoid arthritis; VAS: Visual analog scale; DAS28: Disease activity score in 28 joints; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; HAQ: Health Assessment Questionnaire; QoL: Quality of life; * Statistically significant differences between normal and overweight patients; † Statistically significant differences between normal and obese patients; ‡ Statistically significant differences between overweight and obese patients; § Statistically significant differences between normal and underweight patients; ¶ Statistically significant differences between underweight and overweight patients; || Statistically significant differences between underweight and obese patients.

Table 3. Laboratory characteristics of patients (n=1,038)

	All	Underweight (n=13)	Normal (n=362)	Overweight (n=293)	Obese (n=364)	p
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Hemoglobin (g/dL)	12.8±3.8	12.3±1.8	13.0±6.7	12.8±1.6	12.6±1.4	0.706
ESR (mm/hr)	30.7±21.8	26.3±15.8	29.3±21.3	29.0±23.6	33.4±20.8	0.064
C-reactive protein (mg/dL)	6.7±11.8	13.1±22.7	6.1±11.0	6.1±11.0	7.5±12.5	0.151
Rheumatoid factor-latex (IU/mL)	112.8±226.7	49.7±56.0	131.9±329.6	97.1±160.1	116.1±186.1	0.454
Glucose (mg/dL)	91.2±37.1	88.1±13.3	89.9±33.9*	84.5±29.8	98.1±44.6*	0.001*
Triglycerid (mg/dL)	116.1±72.5	84.1±43.2	105.4±73.1	112.2±75.5	128.2±68.7	0.104
Total cholesterol (mg/dL)	171.7±80.5	207.5±57.3	164.8±81.5	162.8±80.5	184.0±79.1	0.194
HDL-cholesterol (mg/dL)	47.3±20.8	66±36.8	44.7±21.2	48.0±22.1	48.9±19.1	0.482
LDL-cholesterol (mg/dL)	111.3±55.2	103.9±38.2	103.3±56.8	108.8±60.6	120.3±91.1	0.185
VLDL-cholesterol (mg/dL)	26.3±9.8	30.8±5.4	28.0±8.4	22.8±6.3	26.9±21.7	0.817
ALT (IU/L)	21.7±14.0	15.5±7.1	20.2±12.4	21.5±14.7	23.3±14.4	0.06
AST (IU/L)	21.0±9.6	19.2±4.5	21.0±9.4	20.6±9.2	21.6±10.2	0.614
LDH (IU/L)	287.6±114.2	249.0±58.0	261.7±115.7	288.8±115.8	312.5±108.5	0.05
BUN (mg/dL)	24.3±12.5	24.4±13.7	24.0±12.3	24.3±12.2	24.4±12.9	0.977
Creatinine (mg/dL)	2.1±9.3	0.7±0.2	1.5±5.6	2.3±9.8	2.5±11.1	0.629

SD: Standard deviation; ESR: Erythrocyte sedimentation rate; * Statistically significant differences between normal and obese patients; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; VLDL: Very-low-density lipoprotein; ALT: Alanine transaminase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; BUN: Blood urea nitrogen.

factor by the adipose tissue. The inflammatory process underlying in obesity and RA may be mediated by adipocytokines, a heterogeneous group of soluble proteins mainly secreted by the adipocytes that are mainly produced by white adipose tissue.^{1,26} These adipocytokines may have strong pro-inflammatory and anti-inflammatory potential for RA.²⁹ It is well known that obesity and increased central adiposity is common in RA and may be associated with insulin resistance.^{32,33}

To our best knowledge, this is the first registry study investigating the influence of obesity on RA outcomes such as disease activity, disability, quality of life, and radiographic damage. Interestingly, obesity appears to influence Sharp/van der Heijde scores in RA in the opposite direction to DAS28 score.

We have hypothesized that the increased adiposity of obesity might influence disease activity and, therefore, outcomes such as disease activity or disability or radiographic damage. However, we only demonstrated that obesity may increase disease activity and may decrease radiographic damage in regression analysis. This may be because obesity has been associated with chronic inflammation;¹ adipose tissue is metabolically active, secreting a range of adipocytokines, and therefore, may modulate disease activity. It is also possible that the tenderness of periarticular adipose tissue may overestimate the tender joint

count in RA patients. Moreover, increased BMI has been associated with more bodily pain, as a part of disease activity.³⁴ However, it has been found that swollen joint count, as another part of disease activity, was not associated with BMI.³⁵ We showed that obesity was associated with high VAS-pain and ESR, but not increased swollen and tender 28 joint counts.

The mechanisms of radiographically preserved joints in obese RA patients remain unclear. The mechanisms underlying less joint damage in obese/overweight patients with RA were another issue.^{3,4,6,7,35} Periarticular adipose tissue may act as a barrier for microtraumas of daily repetitive activities of hands and feet. Or some other adipocytokines may protect the erosion and joint space narrowing in these patients. For instance, adiponectins may be protective for joint damage in RA. Hence, Rho et al.³⁶ reported that visfatin is associated with increased, and leptin with reduced radiographic joint damage.

There are also some conflicting results from studies of different countries about obesity and disease outcomes. Some of them reported positive relationships for BMI and disease outcomes such as DAS28,^{4,15,37-39} HAQ,^{4,15,17,37,39} rheumatoid factor⁷ and/or Sharp total score,³⁹ while another study reported no relationship between obesity and DAS28 or HAQ, but demonstrated an association with modified Sharp/van der Heijde score.⁴⁰ It has

been reported that obesity significantly decreases the chance of achieving good disease control of RA.^{16,38}

The strengths of our study are the large number of participants and disease outcomes such as disease activity, disability, quality of life, structural damage, and real-life experience within the scope of National Registry. To the best of our knowledge, this is the first obesity study of Middle East along with measures of RA such as disease activity, radiographic damage, quality of life, and disability. We showed that obesity is twice more common in RA patients than in general population.²⁵ On the contrary, a worldwide study reported 18% of RA patients as obese,¹¹ while a UK-based study showed a higher prevalence of 31%.¹² Interestingly, these results are comparable with those of the general UK population where ~35% are overweight and ~25% obese.¹²⁻¹⁴ However, similar to our findings, studies of Dao et al.³⁷ and Ibn Yacoub et al.³⁹ showed that increased prevalence of obesity was associated with disease activity in patients with RA.

Recently, it was reported that obesity in RA was associated with increased DAS28 and HAQ scores and with lower radiographic joint damage, in parallel to our results.⁴¹ Vidal et al.⁴¹ commented that these associations mainly resulted from an increase of subjective components of the DAS28, such as total joint count and global health assessment, in obese patients and also reported conflicting results concerning C-reactive protein and erythrocyte sedimentation rate in their systematic review. Similarly, we found that BMI was weakly associated with patient's global scores and ESR in Turkey's National RA-Registry.

There are some limitations to this study. First of all, there was one-entry for BMI in our database. Therefore, we planned a cross-sectional study instead of a longitudinal study. Unfortunately, cross-sectional studies cannot establish causality, only associations. Therefore, our study is limited by its cross-sectional nature while longitudinal studies are required to examine in closer detail the temporal and causal relationship between adiposity, and outcomes on the RA. Secondly, BMI is not an optimal measure of obesity. Unfortunately, use of more optimal approaches, such as bio-impedance measurement, was not

available for this large cohort. Lastly, advanced imaging modalities, such as musculoskeletal ultrasound, may improve the assessment of true synovitis or active joints instead of the number of tender or swollen joint counts for disease activity. It is important to note, however, that many of our findings confirm the work of earlier investigators.

Obese RA patients are more likely to have higher DAS28. This increase in DAS28 may result from adipose tissue driven inflammation, despite treatment. If DAS28 is used to direct therapy using drug regimes, obese patients may be treated more intensively than non-obese RA patients. This may explain the more favorable radiographic outcomes observed in obese RA patients.

In conclusion, we have shown that RA population has two-fold obese individuals than the general population and BMI is associated with high disease activity, increasing pain scores and ESR level. Interestingly, higher BMI may be associated with less radiographic damage. The exact mechanisms responsible for this apparent dissociation need to be elucidated. A better understanding of the mechanisms underlying this observation may shed light on the unmet needs of obese RA patients to RA drugs.

Declaration of conflicting interests

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