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Original Article

Is it possible to objectively determine morning stiffness in rheumatoid arthritis?

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ABSTRACT

Objectives: This study aimed to objectively and quantitatively exhibit morning stiffness by using electrophysiological methods.

Patients and methods: The prospective, controlled study was conducted with 52 participants between February 2013 and February 2014. Of the participants, 26 were recruited among RA patients (3 males, 23 females; mean age: 55.9±11.2 years; range, 24 to 74 years) followed at the rheumatology clinic, and 26 were healthy subjects (4 males, 22 females; mean age: 54.9±8.3 years; range, 41 to 70 years) for the control group. Duration and severity of morning stiffness were recorded for all participants. Activity of disease and functional status were evaluated by the Disease Activity Score 28 and Health Assessment Questionnaire (HAQ), respectively. Electrophysiological reaction times, severity of pain (Visual Analog Scale), HAQ, and grip strength were measured for each participant twice in 24 h in the morning (08:00-09:00 am) and afternoon (03:00-05:00 pm).

Results: In the RA group, motor reaction and response times and severity of pain values were significantly lower in the afternoon compared to the morning (p=0.030, p=0.031, and p=0.002, respectively), and hand grip strengths were significantly higher in the afternoon (p=0.007). In the control group, no change was observed between morning and afternoon measurements in the strength and reaction time variables.

Conclusion: Our hypothesis that stiffness would slow down the movements in the morning in RA was supported by the prolonged motor and response times in the morning compared to the afternoon. However, in the control group (no morning stiffness), there was no difference in reaction time variables between the morning and afternoon, objectively demonstrating the concept of morning stiffness in this study.

Keywords: Morning stiffness, reaction time, rheumatoid arthritis.

Morning stiffness is one of the most salient complaints in rheumatoid arthritis (RA). Individuals with RA suffer from stiffness and related functional limitations in the early morning hours. Stiffness around joints may continue for hours, easing with motion. Pain and reduction in muscle strength can accompany morning stiffness leading to functional limitations[1,2] and a negative impact on work life, influencing early retirement.[3]

Definition of joint stiffness is not clear. The presence of morning stiffness is assumed by the subjective definition of the patient and not determined by objective methods, and this symptom has not been in composite indexes, such as the Disease Activity Score 28 (DAS28), clinical disease activity index, and simplified disease activity index, used in clinical trials; however, patients reported that morning stiffness is still an important issue affecting their life.[4]

The etiology of morning stiffness has not been understood yet. It is suggested that higher levels of cytokines, such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α), secreted at night cannot be adequately suppressed by endogen steroids.[5] Morning symptoms are associated with

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circadian secretion of IL-6.[6] Strong inhibition of these proinflammatory cytokines by low-dose modified-release prednisone or nonsteroidal anti-inflammatory drugs administered at night is believed to decrease morning stiffness in RA.[7-11]

Gelling phenomenon in joints after long rest periods might be another explanation for morning stiffness.[12] However, the absence of stiffness in healthy individuals after prolonged rest reveals that this cannot be the sole factor for joint stiffness.

Morning stiffness was included in the 1987 American College of Rheumatology (ACR) criteria.[13] However, the 2010 ACR/European Alliance of Associations for Rheumatology (EULAR) criteria did not include morning stiffness due to problems related to specificity, sensitivity, definition, and measurement.[14] Nowadays, disease activity indexes involving more objective components are highly preferred. Although disease activity evaluated by traditional methods such as DAS28 indicates remission in some patients, persisting morning stiffness might have detrimental effects on quality of life, working life, productivity,[15,16] and even some radiologic progression.[1] Furthermore, it was shown that duration of morning stiffness predicts development of erosive disease in early undifferentiated arthritis.[17]

Morning stiffness might reflect different aspects of disease activity that DAS28 cannot. In early RA, severity of morning stiffness reflects pain and functional loss better than conventional inflammation markers, such as number of tender/swollen joints, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).[18]

Assessment of morning stiffness is mainly subjective; duration and severity of morning stiffness are usually measured in minutes or Visual Analog Scale (VAS), respectively.[19] Duration is the parameter usually preferred in studies, and severity is evaluated in a few studies.[19] However, there is no objective method assessing morning stiffness. Hence, there is a need of an objective method to measure morning stiffness periodically. This study aimed to objectively demonstrate the concept of morning stiffness.

PATIENTS AND METHODS

The prospective, controlled study was conducted with 52 participants at the Gazi University Faculty of Medicine Division of Rheumatology between February 2013 and February 2014. Of the participants, 26 were recruited among RA patients (3 males, 23 females; mean age: 55.9±11.2 years; range, 24 to 74 years) followed at the rheumatology clinic, and 26 were healthy subjects (4 males, 22 females; mean age: 54.9±8.3 years; range, 41 to 70 years) for the control group. The inclusion criteria were diagnosis of RA according to the 2010 ACR/EULAR classification and an age over 18 years. Subjects with neurologic, psychiatric, or cognitive problems that may interfere with the measurement of reaction time and subjects with a pacemaker were excluded from the study. Figure 1 demonstrates the flow chart of the study.

Demographic and clinical features, including age, sex, duration of disease, duration and severity of morning stiffness, and medications, were recorded for all participants. Activity of the disease and functional status were evaluated by DAS28 and the Health Assessment Questionnaire (HAQ), respectively. Laboratory investigations consisting of ESR and CRP were performed to measure the level of inflammation and disease activity.

Electrophysiological reaction time and grip strength were measured in each participant twice in the morning (08:00-09:00 am) and afternoon hours (03:00-05:00 pm) within 24 h. The first measurement was performed either in the morning or in the afternoon to exclude learning effect. The order of measurements was set according to the availability of the participants, investigator, or laboratory.

The grip strength of the dominant hand was measured by a vigorimeter (Dynatest; Rudolph Riester GmbH, Jungingen, Germany) before the measurements of reaction time in both the morning and afternoon. Measurements of grip strength were repeated three times, and the best value was recorded. The intensity of pain was assessed by VAS.

Electrophysiological measurement was performed in the electrophysiology laboratory by an eight-channel electromyography (EMG) device (MEB-5508K; Nihon Kohden Corporation, Tokyo, Japan). High and low filters of the EMG device were calibrated at 3 kHz and 2 Hz. Analysis time and sensitivity were 0.5 sec/division and 0.5 mV/division, respectively. Participants sat on a chair with their back supported and forearms on their lap. A button was located on a vertical platform placed in their front at arm's length. With a surface stimulation electrode, a painless electrical stimulus of 5 mA was applied over the shoulder of the nondominant side. The active recording surface electrode was placed

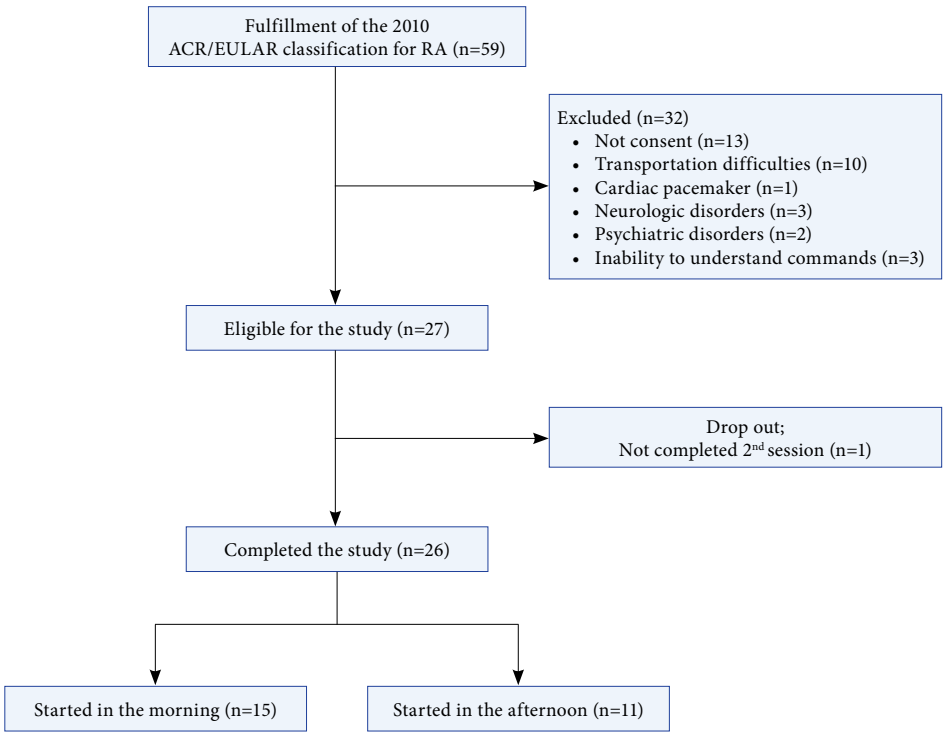

Figure 1. Flowchart of the study.

on the anterior portion of the deltoid muscle of the dominant upper extremity. The reference electrode was placed on the acromion of the dominant upper extremity. The participant was asked to press the button in response to the stimulus (Figure 2).

To familiarize each participant to the experimental setup and the study protocol, sufficient number of trials was performed in the first session, either in the morning or afternoon sessions. After familiarization, 10 test trials were performed, and the mean of the 10 trials was recorded. The means of morning and afternoon measurements were recorded separately.

Premotor reaction time is defined as the interval between the stimulation and the beginning of muscle activation. Motor reaction time is defined as the interval between the beginning of muscle activation to perform a prespecified task and fulfillment of that task.[20] Response time is the sum of premotor and motor reaction times.

Premotor reaction, motor reaction, and response times were electrophysiologically measured in this study. Premotor reaction time was measured as the interval between the electrical stimulus to the nondominant shoulder and the beginning of deltoid muscle activation on the dominant side. Motor reaction time was measured as the interval between the beginning of the deltoid muscle activation and pressing the button. Response time was regarded as the time taken to press the button in response to the electrical stimulus (Figure 3).

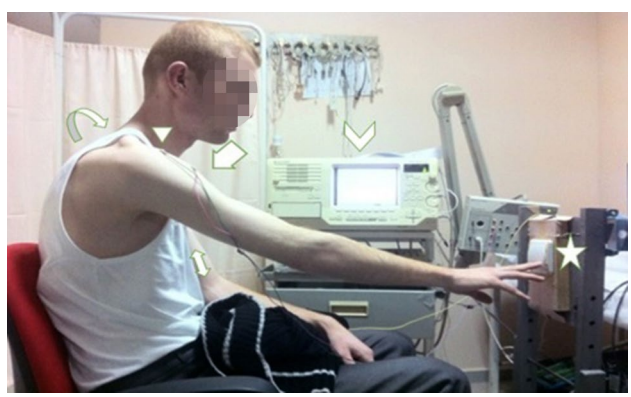

Figure 2. Experimental setup for the measurement of reaction time (arrow: active recording surface electrode placed on the anterior portion of deltoid muscle of the dominant upper extremity, triangle: reference electrode placed on the acromion of the dominant upper extremity, star: button located on the vertical platform, curved arrow: non-dominant shoulder where stimulation was performed with the surface electrode, double-headed arrow: non-dominant upper extremity, chevron arrow: stimulating [electromyography] device).

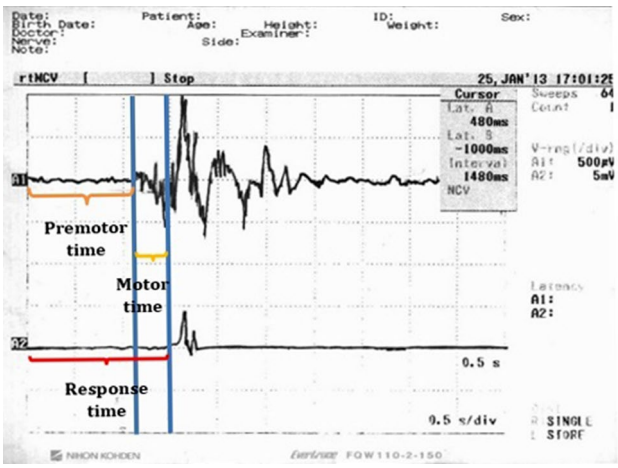

Figure 3. Measurements of premotor, motor, and response times.

Statistical analysis

The sample size was calculated as 26, with 80% power, 5% type 1 error, and 0.69 effect size, using the G*Power version 3.1.9.6 software (Heinrich-Heine Universität Düsseldorf, Düsseldorf, Germany), where there was a difference of 25 msec in motion time between the control group and the RA group.[21]

Data were analyzed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were applied for the demographic and clinical features of the participants. Categorical variables were compared using the chi-square test. Continuous variables with a normal distribution were presented as mean ± standard deviation (SD). Median (min-max) values were reported for the nonnormally distributed variables. For testing the distribution pattern, the Kolmogorov-Smirnov normality test was performed. A paired t-test was used for the comparison of variables with normal distribution in the same groups. The Wilcoxon test was used for the comparison of variabilities without normal distribution in the same groups. Two independent groups were compared by Student's t-test or its nonparametric equivalent, the Mann-Whitney U test, according to whether the data were normally distributed or not, respectively. Pearson's correlation test or the Spearman correlation test were performed to determine the interrelationships. A p-value <0.05 was considered statistically significant.

RESULTS

Demographic and clinical features of participants with RA and controls are demonstrated in Table 1. Age and sex did not differ between the two groups. There were 11 (42%) subjects reporting morning stiffness lasting 30 min or longer among participants with RA. Fifteen participants reported morning stiffness shorter than 30 min.

Premotor and motor reaction times, response times, and hand grip strength results are given in Table 2. In the RA group, motor reaction and response time and severity of pain values were significantly lower in the afternoon compared to the morning (p=0.030, p=0.031, and p=0.002, respectively), and

TABLE 1
Demographic and clinical variables of rheumatoid arthritis and control groups

	RA group (n=26)			Control group (n=26)			
	n	%	Mean±SD	n	%	Mean±SD	p
Age (year)			55.9±11.2			54.9±8.3	0.725[a]
Sex							
Female	23	88.5		22	84.6		0.685[b]
Duration of disease (year)			12.8±10.5			NA	-
Duration of morning stiffness (min)			56.9±78.6			NA	-
Severity of morning stiffness-VAS			4.0±3.0			NA	-
Disease activity score-DAS28			3.8±1.4			NA	-
Health assessment questionnaire-HAQ			0.8±0.7			NA	-
Erythrocyte sedimentation rate (mm/h)			35.7±21.5			NA	-
C-reactive protein (mg/L)			18.9±19.3			NA	-

RA: Rheumatoid arthritis; SD: Standard deviation; VAS: Visual Analog Scale; DAS28: Disease Activity Score-28; HAQ: Health Assessment Questionnaire; NA: Not applicable; a: Student's t-test; b: Chi-square test.

TABLE 2
Measurements of reaction time, handgrip strength and severity of pain in the morning and in the afternoon

	Morning		Afternoon			Between group	Within group
	Median	Min-Max	Mean±SD	Median	Min-Max	*p**	*p*
Premotor reaction time (msec)							
RA	1182.5	1014-1595		1160.5	1083-1393	0.017[a]	0.218[b]
Control	1124	1039-1275		1145.5	1082-1314		0.101[b]
Motor reaction time (msec)							
RA	459	161-1548		426.5	166-774	0.170[a]	**0.030**[b]
Control	420.5	223-587	413.7±119.9				0.751[c]
Response time (msec)							
RA	1626.5	1345-3130		1574.5	1342-2014	**0.039**[a]	**0.031**[b]
Control	1562.5	1336-1774		1567.5	1286-2040		0.939[b]
Hand grip strength (bar)							
RA	0.22	0.09-0.75		0.28	0.11-0.81	**<0.001**[a]	**0.007**[b]
Control	0.45	0.30-0.98		0.45	0.20-1.0		0.536[b]
VAS-pain							
RA	6	0-10		4	0-10		**0.002**[b]
Control	NA	NA		NA	NA		-

SD: Standard deviation; RA: Rheumatoid arthritis; VAS: Visual Analog Scale; NA: Not applicable; a: Mann-Whitney-U test; b: Wilcoxon test; c: Paired T-test; *: Comparison of morning measurements between RA and control group.

TABLE 3
Correlations among DAS28, VAS, HAQ scores, morning stiffness, and hand grip strength

	DAS28	Duration of morning stiffness	Severity of morning stiffness	VAS morning	VAS afternoon	HAQ morning	HAQ afternoon	Hand grip strength (morning)	Hand grip strength (afternoon)
DAS28									
r	1	0.448	0.639	0.541	0.248	0.583	0.442	-0.293	-0.189
p		**0.019**	**<0.001**	**0.004**	0.213	**0.001**	**0.021**	0.139	0.346
Duration of morning stiffness									
r	0.448	1	0.683	0.525	0.086	0.721	0.566	-0.295	-0.350
p	**0.019**		**<0.001**	**0.005**	0.669	**<0.001**	**0.002**	0.135	0.074
Severity of morning stiffness									
r	0.639	0.683	1	0.699	0.077	0.768	0.455	-0.525	-0.465
p	**<0.001**	**<0.001**		**<0.001**	0.704	**<0.001**	**0.017**	**0.005**	**0.015**
VAS morning									
r	0.541	0.525	0.699	1	0.552	0.581	0.346	-0.335	-0.386
p	**0.004**	**0.005**	**<0.001**		**0.003**	**0.001**	**0.077**	0.087	**0.047**
VAS afternoon									
r	0.248	0.086	0.077	0.552	1	0.107	0.259	-0.082	-0.139
p	0.213	0.669	0.704	**0.003**		0.594	**0.193**	0.683	0.491
HAQ morning									
r	0.583	0.721	0.768	0.581	0.107	1	0.789	-0.514	-0.515
p	**0.001**	**<0.001**	**<0.001**	**0.001**	0.594		**<0.001**	**0.006**	**0.006**
HAQ afternoon									
r	0.442	0.566	0.455	0.346	0.259	0.789	1	-0.428	-0.454
p	**0.021**	**0.002**	**0.017**	**0.077**	0.193	**<0.001**		**0.026**	**0.018**
Hand grip strength (morning)									
r	-0.293	-0.295	-0.525	-0.335	-0.082	-0.514	-0.428	1	0.918
p	0.139	0.135	**0.005**	0.087	0.683	**0.006**	**0.026**		**<0.001**
Hand grip strength (afternoon)									
r	-0.189	-0.350	-0.465	-0.386	-0.139	-0.515	-0.454	0.918	1
p	0.346	0.074	**0.015**	**0.047**	0.491	**0.006**	**0.018**	**<0.001**	

DAS28: Disease Activity Score-28; VAS: Visual Analog Scale; HAQ: Health assessment questionnaire.

hand grip strengths were significantly higher in the afternoon (p=0.007). In the control group, no change was observed between morning and afternoon measurements in the strength and reaction time variables.

Correlations between disease activity (DAS28), morning stiffness (duration and severity), pain levels (VAS), health and quality of life (HAQ) scores, and hand grip strengths in the morning and afternoon are summarized in Table 3. Disease Activity Score 28 scores were associated with duration and severity of morning stiffness, VAS (morning), and HAQ (morning and afternoon; p<0.05). The duration of morning stiffness was associated with severity of morning stiffness, VAS (morning), and HAQ (morning and afternoon; p<0.05). Severity of morning stiffness was associated with VAS (morning), HAQ (morning and afternoon), and hand grip strengths (morning and afternoon; p<0.05). Morning VAS scores were associated with VAS afternoon, HAQ (morning and afternoon), and hand grip strength (afternoon; p<0.05). Health Assessment Questionnaire (morning) scores were associated with HAQ (afternoon) and hand grip strengths (morning and afternoon; p<0.05). Health Assessment Questionnaire afternoon scores were associated with hand grip strengths (morning and afternoon; p<0.05). Hand grip strength (morning) was associated with hand grip strength (afternoon; p<0.05). Correlations of all variables were positively associated, except for hand grip strengths. The premotor and response time values were significantly higher in the RA group compared to the control group (p<0.05). Moreover, motor time was higher in RA patients; however, the difference did not reach statistical significance (Table 2). Hand grip strengths were significantly lower in the RA group (p<0.05).

DISCUSSION

In this study, the hypothesis that stiffness would slow down the movements in the morning in RA was supported by the prolonged motor and response times in the morning compared to the afternoon. Motor and response times reflect the motor performance of reaction time. Motor ability of RA patients was adversely affected in the morning. In the present study, it was demonstrated that pain, muscle strength, and morning stiffness improved significantly in the afternoon compared to the morning measurements. These results were compatible with the circadian rhythm of morning stiffness, pain, reduction in strength, and functional impairment demonstrated in RA.[11] Morning stiffness and functional impairment reach their maximum level at 6:00 am, and pain peaks at 8:00 am in RA patients. The lowest grip strengths are measured at 6:00-8:00 am.[5] The evaluation of changing symptoms parallel to the circadian rhythm is important regarding the assessment and follow-up of patients, optimizing the management strategy and designing medical studies.[3]

In the current study, EMG study was conducted to demonstrate joint stiffness. For morning measurements, the time interval between 08:00-09:00 am was preferred to invite patients to the electrophysiology laboratory to increase their possibility of transportation. Since morning stiffness reaches its peak at 6:00 am,[5] if the measurements were performed earlier in the morning, joint stiffness would be demonstrated more accurately, and the reduction in motor and response times between morning and afternoon would be greater in the RA group.

In future studies, novel methods to measure response times at home can provide patients the opportunity to perform their own measurements. Objectively monitoring morning stiffness in the follow-up of the patients may help to assess disease activity more accurately. Although the method used in our study was very accurate and objective, it was not practical for both the patient and the examiner. This method necessitates an EMG device, time for assessment, and area for the device at outpatient clinics. Additionally, patients should come to the hospital for the measurements. Instead of this electromyographic method, computer-based programs developed for reaction time measurement may also be used. Patients record their own measures and show them to their physician during their periodical examination. In a study to determine stiffness in hand joints, Conolly et al.[22] developed a special glove with sensors that collects data in accordance with the motions of metacarpophalangeal and proximal interphalangeal joints and measured the angles and velocities of these joints. However, this method is sophisticated, expensive, and not user-friendly.

The results of the present study revealed that DAS28 was positively correlated with both the duration and severity of morning stiffness. Similarly, Khan et al.[17] demonstrated a moderate correlation between duration of morning stiffness and DAS28, as well as HAQ. Correlation between disease activity and severity of morning stiffness was higher compared to duration of stiffness in our study (r=0.639 and r=0.448, respectively). This finding is in accordance with a recent meta-analysis, which concluded that severity

of morning stiffness was superior in the evaluation of treatment response and was also more reliable than the duration of morning stiffness.[23] Similarly, Hazes et al.[24] observed that severity of morning stiffness was a more effective parameter for discrimination of active or inactive disease compared to duration of stiffness.

The results of this study demonstrated that the higher the duration and severity of morning stiffness, the higher the HAQ scores, which is similar to the study of Jansen et al.[25]

The limitation of this study is that CRP,[26] serum levels of cytokine,[5,27] or cortisol,[6,8] showing circadian variation, were not measured. Future studies might provide additional information about the relationship among functional variables and immunologic, hormonal, and biochemical parameters.

In conclusion, morning stiffness is a symptom accompanying inflammatory conditions such as RA. However, there is still no standard method to measure morning stiffness. We demonstrated this issue with an electrophysiological technique. Future studies can exhibit new methods on this subject. Objective quantification of morning stiffness can help clinicians provide important gains in the management of inflammatory disorders.

Ethics Committee Approval: The study protocol was approved by the Gazi University Clinical Research Ethics Committee (date: 26.12.2012, no: 404). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Concept, design: G.M., F.G., M.B.; Design: G.M., F.G., M.B.; Supervision, data colleciton, processing, references and fundings: G.M, F.G, M.B, Ö.Ö.T.; Analysis and interpretation: G.M., F.G., M.B., Ö.Ö.T., H.A.; Literature review, critical review: G.M., F.G., M.B., Ö.Ö.T., H.A.; Writing the article: G.M., M.B., Ö.Ö.T., H.A.; Materials: G.M., M.B., Ö.Ö.T.

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