



# Sustainable positive effects of Ramadan intermittent fasting in rheumatoid arthritis

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## Abstract

The short-term positive effects of intermittent fasting during the month of Ramadan on rheumatic inflammatory diseases have been previously evaluated. The objective of this study was to assess the sustainability of these effects on rheumatoid arthritis (RA) activity. This prospective study included 35 patients with RA, who observed fasting during Ramadan 2019. The disease activity was assessed and compared between three time points: T1 (6 months before the beginning of Ramadan), T2 (during the month between the 7th day of fasting and the 7th day after Ramadan), and T3 (averagely 3.4 months after fasting). The disease activity score 28 (DAS28) was used to evaluate the disease activity. After a significant decrease of all disease activity parameters between T1 and T2, a gradual increase of clinical and biological outcomes was seen between T2 and T3. Except for CRP, which was significantly higher at T3 ( $p=0.02$ ), the changes of the other disease activity parameters were not statistically significant. By reference to baseline data (T1), the decrease of ESR, DAS28 CRP, and DAS28 ESR induced after Ramadan fast was maintained until T3, with statistically significant differences. We can therefore conclude that this study has been conducted at the beginning of the fading-out of the effects of Ramadan fast, and that the duration of 3 months may be the recommended interval between fasting periods to maintain the positive effects of intermittent fasting on RA activity.

## Key Points

- Intermittent fasting can induce a rapid improvement of rheumatoid arthritis activity.
- The positive effects of this model of fasting can last up to 3 months.
- The recommended interval between fasting periods may be estimated at 3 months.

**Keywords** Intermittent fasting · Positive effects · Rheumatoid arthritis

## Introduction

Since the dawn of time, people have always believed in the significant impact of dietary habits on general health status. The importance of nutrition as an integral part of the prevention and subsequently of the therapeutic management of several diseases is currently increasingly recognized [1]. In

addition to the quality of food, the quantity seems to be of paramount importance. The negative impacts of both reduced and elevated nutrient intakes have been well-established, hence the importance of achieving a proper nutrient balance [1].

In this context, several dietary manipulations have been evaluated as a potential non-pharmacological approach for inflammatory chronic conditions [2]. While the “Western diet,” classically known for its high content of sugar-sweetened drinks, seems to increase systemic inflammation, the Mediterranean, vegan, and vegetarian diets may induce a significant clinical and biological improvement of the inflammatory status [2].

Different protocols of fasting have also been studied. Indeed, it has been demonstrated that dietary restriction and fasting may have suppressive effects on various inflammatory diseases [3]. More specifically, the influence

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of intermittent fasting on rheumatic diseases has gained increasing attention over the last few years. Although this issue is still under investigation, the general opinion is that intermittent fasting has positive effects on auto-immune and inflammatory disorders such as rheumatoid arthritis (RA), spondyloarthritis (SpA), and systemic lupus erythematosus (SLE) [4–8]. Furthermore, the question might also arise in connection with the durability of these effects, and how to accurately assess the minimal effective duration of fasting and the recommended interval between fasting periods.

In this regard, our team performed relevant research that started in 2019 and showed that diurnal intermittent fasting observed by Muslims during Ramadan, the ninth month of the Islamic calendar, can induce a rapid improvement of rheumatic disease activity [6]. This short-term assessment was performed during fasting, or immediately after fasting. The aim of the present study was to evaluate the sustainability of this improvement, or in other words, to assess the long-term effect of Ramadan fast.

## Methods

### Study design

This prospective study started 6 months before starting Ramadan fasting, and continued until the next follow-up visit after Ramadan. The fasting model comprised intermittent fasting that is observed from sunrise to sunset and is alternated with moments of re-feeding. Instead of three meals eaten throughout the day, Muslims consume exclusive nocturnal meals. “Suhur” is the meal consumed before dawn and Iftar is the evening meal replacing the traditional dinner. The range of fasting hours during the month was about 15.5 to 16.5 h a day.

All study endpoints were measured at three time points:

- T1 (baseline): 6 months before the beginning of Ramadan (December 2018)
- T2: during the month between the 7th day of fasting and the 7th day after Ramadan (12 May–10 June 2019)
- T3: averagely 3.4 months after fasting (August–September 2019)

The sustainability of fasting’s effects was evaluated by comparing T3 endpoints with T1 and T2. It is worth noting that the comparison between T1 and T2 endpoints has been previously published [6] and does not form part of the present study.

All participants were informed about the aim of the study and gave their informed consent to participate. The study protocol was approved by the Ethics Committee of Kassab Institute of Orthopedics.

## Participants

A total of 57 patients, with a confirmed diagnosis of RA (according to 2010 ACR/EULAR classification criteria for RA) or SpA (according to ASAS classification criteria for SpA), initially participated in a previous study aiming at assessing the potential short-term effect of Ramadan fasting on rheumatic diseases [6]. While a significant positive effect has been demonstrated among patients with RA, this improvement was less evident in the group of SpA, hence the non-inclusion of this latter group in the present study. Exclusion criteria included pregnancy, lactation, and patients who started, stopped, or changed the dose of any drug that may affect the level of disease activity.

## Measurement of the variables

During each visit, the clinical elements were identified and recorded in a computerized file: demographic data, comorbidities, associated treatments, disease duration, visual analogue scale (VAS) pain score, morning stiffness duration, tender and swollen joint counts (TJC and SJC).

Then blood samples of patients were assessed for C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

In order to assess disease activity, the disease activity score 28 (DAS28) was used. This score includes the assessment of tender joints, swollen joints, CRP or ESR levels, and the level of pain.

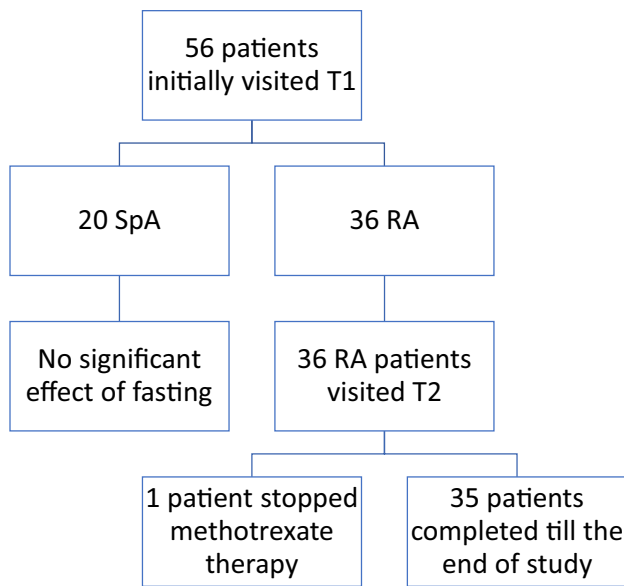
## Statistical study

Statistical analysis was performed by using SPSS version 18. The quantitative variables were expressed as means  $\pm$  standard deviation (SD) and the qualitative values as percentages. Normality in distribution of variables was checked by nonparametric one-sample Kolmogorov–Smirnov test. Student’s *t*-test for paired samples or Wilcoxon signed-rank test (depend on data distribution) was used to compare the continuous parameters before, during, and after fasting.

## Results

### Recruitment and screening

Figure 1 shows the flow of the participants throughout the study. Originally, we enrolled a group of 36 patients with RA in which a significant improvement of the disease activity has been demonstrated after fasting at least 7 days. Apart from menstrual periods for women, considered a temporary religious exemption, all patients carried



**Fig. 1** Flowchart. RA, rheumatoid arthritis; SpA, spondyloarthritis; T1 (baseline), 6 months before the beginning of Ramadan (December 2018); T2, during the month between the 7th day of fasting and the 7th day after the end of Ramadan (12 May–10 June 2019); T3, averagely 3.4 months after fasting (August–September 2019)

on fasting for the whole month. One patient dropped out of the study because she stopped methotrexate (pulmonary side

effect). The median follow-up time between T2 and T3 was  $3.4 \pm 0.8$  months [2–5].

**Participants: general data**

Thirty-five patients with RA were included in this study. The main demographic, clinical, and therapeutic features are detailed in Table 1. Participants were receiving different rheumatic medications, including conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biological disease-modifying antirheumatic drugs (bDMARDs), corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and analgesics. Immunosuppressive medications were maintained during the study.

**Long-term assessment of fasting impact on disease activity**

Table 2 shows the results of clinical and biological parameters during or immediately after Ramadan (T2) and averagely 3.4 months after Ramadan (T3). Except for CRP, which was significantly higher at T3 ( $p=0.02$ ), the other disease activity parameters remained nearly unchanged.

As detailed in Table 2, by reference to baseline data (T1), the decrease of ESR, DAS28 CRP, and DAS28 ESR induced after Ramadan fast was maintained until T3, with statistically significant differences.

**Table 1** Main characteristics of patients

Parameter			n = 35
Gender (female) n, (%)			28 (80)
Age (years ± SD) [range]			58 ± 10.8 [39–79]
Mean duration between T2 and T3 (months ± SD) [range]			3.4 ± 0.8 [2–5]
Disease duration (years ± SD) [range]			6.8 ± 3.2 [1–13]
Disease characteristics n (%)			RF (+): 17 (48.6) ACPA (+): 19 (54.3) Erosive: 26 (72)
Treatments n (%)	bDMARDs	ETN	3 (8.5)
		ADA	1 (2)
		TCZ	4 (11.4)
	csDMARDs	MTX	21 (60)
		SLZ	4 (11.4)
		LFN	4 (11.4)
	NSAID		4 (11.4)
	Corticosteroids		6 (17)

RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; +, positive; -, negative; bDMARDs, biologic disease-modifying anti-rheumatic drugs; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; TCZ, tocilizumab; ETN, etanercept; ADA, adalimumab; MTX, methotrexate; SLZ, sulfasalazine; LFN, leflunomide; NSAID, non-steroidal anti-inflammatory drugs; T1 (baseline), 6 months before the beginning of Ramadan (December 2018); T2, during the month between the 7th day of fasting and the 7th day after the end of Ramadan (12 May–10 June 2019); T3, averagely 3.4 months after fasting (August–September 2019)

**Table 2** Comparison between disease activity parameters at T3 with T2 and T1

	T1	T2	T3
VAS pain score	4.9±2.9	3.7±3.3	5.1±3
Morning stiffness duration (minutes)	21±47.3	15.6±43	19±40.1
Tender joint count	4±5	4±7.1	4.15±5.3
Swollen joint count	1.7±2.6	0.94±1.7	1.77±2.9
ESR (mm)	35.2±22.9 **	22.6±16.4	23.4±19.3
CRP (mg/dL)	7.7±16.4	4±5.2 *	8±9.8
DAS28 <sub>ESR</sub>	4.3±1.3 **	3.6±1.5	3.67±1.6
DAS28 <sub>CRP</sub>	3.4±1.2 **	2.8±1.3	2.8±1.7

VAS, visual analogue scale; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS 28, disease activity score 28; \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ ; T1 (baseline), 6 months before the beginning of Ramadan (December 2018); T2, during the month between the 7th day of fasting and the 7th day after the end of Ramadan (12 May–10 June 2019); T3, averagely 3.4 months after fasting (August–September 2019)

The overall analysis of the objective outcomes (SJC, CRP, ESR) shows a significant decrease between T1 and T2, followed by a gradual increase between T2 and T3 (Fig. 2).

## Discussion

The purpose of this study was to determine the long-term effect of Ramadan fasting on RA activity. Within the past decade, intermittent fasting has been recognized as a potential non-pharmacological treatment for RA regarding pain, and clinical and biological disease activity [7]. However, to the best of our knowledge, there is a lack of studies regarding the sustainability of this impact.

In our set of patients, subjective (VAS scale, morning stiffness) and clinical (TJC, SJC) outcomes remained nearly

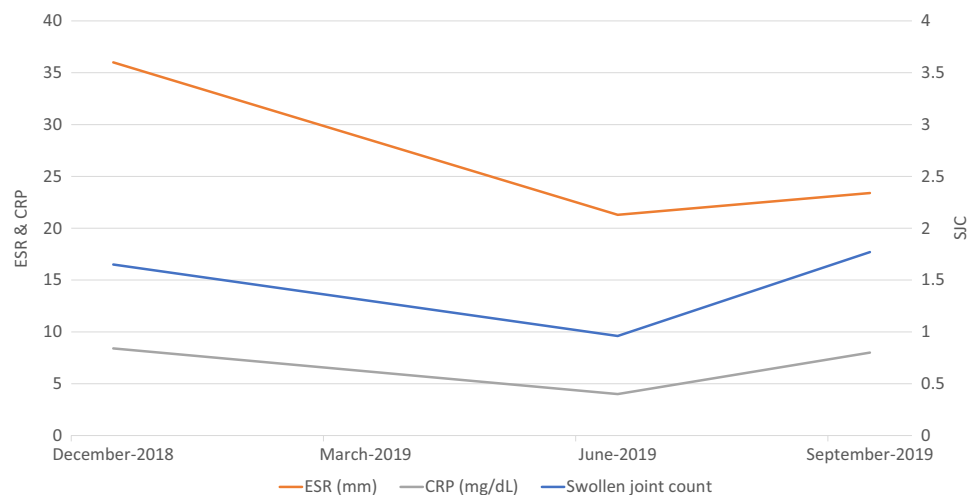
unchanged averagely 3 months after Ramadan. In fact, from a spiritual point of view, fasting goes beyond the simple aim of achieving a balanced diet. It is a source of deep inner serenity, which may account for the enhancement of subjective parameters such as pain and morning stiffness.

As for biological outcomes, a discrepancy was noted between ESR and CRP levels in our study. Unsurprisingly, the median CRP level was significantly higher at T3 than that at T2. In contrast, despite a slight increase in the ESR levels, no significant change was seen. Indeed, it is well-documented that CRP has a faster kinetic profile than other acute phase reactants such as ESR, hence providing early information about the inflammatory state [9, 10]. We can therefore conclude that this study has been conducted at the beginning of the fading-out of the effects of Ramadan fast. The above suggests that the duration of 3 months may be the recommended interval between fasting periods.

Even though the benefits of intermittent fasting on rheumatic diseases have been unanimously recognized, this non-pharmacological perspective has not yet been included in the recent recommendations. We believe that this therapeutic option will move from theory to practice only if specific protocols of fasting are suggested through randomized controlled trials. This was the key factor motivating the present study. Our practical suggestion at this stage of knowledge would be 1 month of intermittent fasting, to observe two or three times per year. Given the rate of iatrogenic illness, this option would be of particular benefit to older patients who are more vulnerable to adverse drug reactions [11].

To sum up, the benefits of intermittent fasting in RA have been demonstrated at both molecular and clinical levels [7]. The underlying mechanisms which trigger the effects of fasting are worth investigating. Faris et al. assessed the immunomodulatory effects of Ramadan intermittent fasting on 50 healthy adults [12]. Circulating proinflammatory cytokines IL-6, IL-1 $\beta$ , and TNF $\alpha$  were found to be

**Fig. 2** Comparison between objective disease activity parameters at T1, T2, and T3. ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SJC, swollen joint count



significantly decreased after 28 days of daily fasting. The levels of immune cells (lymphocytes, total leukocytes count, granulocytes, and monocytes) were also shown to be reduced but remained in the reference ranges [12]. On the other hand, circulating levels of immune complex (CIC) and immune indices were shown to be maintained after Ramadan in 120 healthy volunteers [13]. We can thus conclude that the attenuation of the inflammatory status induced by intermittent fasting does not harm the immunity.

However, intermittent fasting in the specific context of Ramadan has some distinguishing features to be taken into account. During this month, Muslims enjoy a festive atmosphere which may lead to radical changes in habits, affecting sleeping, dietary patterns, water intake, physical activity, etc. Exclusive nocturnal large meals containing high levels of saturated fats, salt, and sugar may weaken immunity and reduce the positive effects of fasting [14]. The impact of ritual and social behaviors can also include a significant qualitative and quantitative impairment of sleeping [15]. Such disturbances in sleep pattern can harm the immune system. All of this implies that intermittent fasting does not dispense in any way with a healthy lifestyle and a balanced diet.

To our knowledge, this is the first study evaluating the long-term effect of intermittent diurnal fasting on RA activity. The main limitation was the low sample size. This is partly due to the exclusion of patients with SpA in whom the short-term effect of Ramadan fasting was not firmly confirmed. A further limitation of this study is the non-availability of a control group. Considering valid exemptions for not fulfilling Ramadan fasting (physical or mental illness, weakness, pregnancy, breastfeeding), it was obvious that a non-fasting group during Ramadan would not be comparable to the fasting group. This limitation might be overcome by conducting a comparative controlled study during another period.

## Conclusion

Non-pharmacological interventions, such as dietary manipulation, physical activity, and psychosocial support, are increasingly recognized as a part of the therapeutic management of chronic inflammatory conditions. The effect of the practice of intermittent fasting on RA activity has been demonstrated by several observational studies. Randomized controlled trials are still needed to allow significant conclusions to be drawn.

## Declarations

**Informed consent** Informed consent was obtained from the patients.

**Disclosures** None

## References

- Ohlhorst SD, Russell R, Bier D et al (2013) Nutrition research to affect food and a healthy life span. *J Nutr* 143:1349–1354. <https://doi.org/10.3945/jn.113.180638>
- Dey M, Cutolo M, Nikiphorou E (2020) Beverages in rheumatoid arthritis: what to prefer or to avoid. *Nutrients* 12. <https://doi.org/10.3390/nu12103155>
- Iwashige K, Kouda K, Kouda M et al (2004) Calorie restricted diet and urinary pentosidine in patients with rheumatoid arthritis. *J Physiol Anthropol Appl Human Sci* 23:19–24. <https://doi.org/10.2114/jpa.23.19>
- Adawi M, Watad A, Brown S et al (2017) Ramadan fasting exerts immunomodulatory effects: insights from a systematic review. *Front Immunol* 8:1144. <https://doi.org/10.3389/fimmu.2017.01144>
- Adawi M, Damiani G, Bragazzi NL et al (2019) The impact of intermittent fasting (Ramadan fasting) on psoriatic arthritis disease activity, enthesitis, and dactylitis: a multicentre study. *Nutrients* 11. <https://doi.org/10.3390/nu11030601>
- Ben Nessib D, Maatallah K, Ferjani H et al (2020) Impact of Ramadan diurnal intermittent fasting on rheumatic diseases. *Clin Rheumatol* 39:2433–2440. <https://doi.org/10.1007/s10067-020-05007-5>
- Ben Nessib D, Maatallah K, Ferjani H et al (2020) The potential effect of Ramadan fasting on musculoskeletal diseases: new perspectives. *Clin Rheumatol*. <https://doi.org/10.1007/s10067-020-05297-9>
- Goharifar H, Faezi ST, Paragomi P et al (2015) The effect of Ramadan fasting on quiescent systemic lupus erythematosus (SLE) patients' disease activity, health quality of life and lipid profile: a pilot study. *Rheumatol Int* 35:1409–1414. <https://doi.org/10.1007/s00296-015-3282-5>
- Lorrot M, Fitoussi F, Faye A et al (2007) Laboratory studies in pediatric bone and joint infections. *Arch Pediatr* 14(Suppl 2):S86–90. [https://doi.org/10.1016/s0929-693x\(07\)80040-6](https://doi.org/10.1016/s0929-693x(07)80040-6)
- van Leeuwen MA, van Rijswijk MH (1994) Acute phase proteins in the monitoring of inflammatory disorders. *Baillieres Clin Rheumatol* 8:531–552. [https://doi.org/10.1016/s0950-3579\(05\)80114-1](https://doi.org/10.1016/s0950-3579(05)80114-1)
- Onder G, van der Cammen TJM, Petrovic M et al (2013) Strategies to reduce the risk of iatrogenic illness in complex older adults. *Age Ageing* 42:284–291. <https://doi.org/10.1093/ageing/af038>
- Faris MA-IE, Kacimi S, Al-Kurd RA et al (2012) Intermittent fasting during Ramadan attenuates proinflammatory cytokines and immune cells in healthy subjects. *Nutr Res* 32:947–955. <https://doi.org/10.1016/j.nutres.2012.06.021>
- Latifynia A, Vojgani M, Abofazeli T, Jafari H (2007) Circulating immune complex during Ramadan. *J Ayub Med Coll Abbotabad* 19:15–18
- Faris MA-IE, Salem ML, Jahrami HA et al (2020) Ramadan intermittent fasting and immunity: an important topic in the era of COVID-19. *Ann Thorac Med* 15:125–133. [https://doi.org/10.4103/atm.ATM\\_151\\_20](https://doi.org/10.4103/atm.ATM_151_20)
- Faris MA-IE, Jahrami HA, Alhayki FA et al (2020) Effect of diurnal fasting on sleep during Ramadan: a systematic review and meta-analysis. *Sleep Breath* 24:771–782. <https://doi.org/10.1007/s11325-019-01986-1>

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