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ORIGINAL RESEARCH

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Association of time-restricted feeding, arterial age, and arterial stiffness in adults with metabolic syndrome

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Abstract

Background: Time-restricted feeding (TRF) is a kind of intermittent fasting defined as eating and drinking only during a certain number of hours in a day. It has been suggested that intermittent fasting may improve cardiovascular risk factors. This study evaluated the association of TRF and arterial stiffness, using pulse wave velocity (PWV), pulse wave analysis, and arterial age in metabolic syndrome participants.

Methods: A cohort study was carried out among metabolic syndrome adults who were followed over the Ramadan fasting period (used as a model of TRF since food was only allowed for about 8 h/day). The subjects were divided into Ramadan fasting and Ramadan nonfasting groups. The aortic PWV and central aortic pressure waveform were measured. Central systolic pressure, central pulse pressure, and indices of arterial compliance, such as augmentation pressure and augmentation index (AIx), were determined from waveform analysis.

Results: Ninety-five adults (31.57% female, age: 45.46 ± 9.10 years) with metabolic syndrome (based on the International Diabetes Federation definition) participated in this study. Ramadan fasting and Ramadan nonfasting groups were including 80 and 15 individuals respectively. A significant reduction was seen in PWV (0.29 m/s), central systolic pressure (4.03 mmHg), central pulse pressure (2.43 mmHg), central augmentation pressure (1.88 mmHg), and central AIx (2.47) in the Ramadan fasting group ($p = 0.014$, $p < 0.001$, $p = 0.001$, $p = 0.003$, and $p = 0.036$ respectively). There were no significant changes in these indices among the Ramadan nonfasting group.

Conclusions: This study suggested that TRF reduces arterial age and improves arterial stiffness among people with metabolic syndrome. This might be considered a beneficial nutrition strategy for extending healthspan (and perhaps longevity).

KEYWORDS

arterial age, arterial stiffness, metabolic syndrome, pulse wave velocity, time-restricted feeding

1 | INTRODUCTION

As the world's population grows older, human aging and age-associated diseases become the most significant challenges and burdens for developing and developed countries.[1] Ischemic heart disease and stroke have remained the most common cause of death during the past decade, with 32% of all global deaths and 38% of premature deaths due to cardiovascular diseases (CVDs) in 2019.[2] It has been shown that substantial lifespan extension is related to delayed or reduced morbidity in most cases,[3] and should first focus on treating age-related conditions and diseases (not specifically aging).[4]

It has been established that metabolic syndrome (defined as the combination of metabolic risk factors, including hypertension, insulin resistance, abdominal obesity, low HDL cholesterol, and hypertriglyceridemia[5]) increases the risk of atherosclerosis,[6,7] and all-cause mortality.[7] Another risk factor for CVD is vascular aging, associated with mechanical and structural changes in the vascular walls, leading to increase arterial stiffness,[8] which is independently predictive of cardiovascular events, coronary artery disease, and stroke.[8,9] Also, high arterial stiffness decreases the compliance of arteries, increases systolic blood pressure and pulse pressure, as well as reduced diastolic blood pressure which leads to adverse cardiovascular outcomes.[10]

Pulse wave velocity (PWV) measurement is the gold standard method for assessing arterial stiffness in clinical practice, because of its high reproducibility, low cost, and ease to use.[11] It is also one of the earliest indicators of increased CVD risk and can be considered a good predictor of the development of subclinical cardiovascular dysfunction. Arterial stiffness is a significant prognostic factor influencing cardiovascular risk, which dietary habits can modify.[12–15] Perivascular adipose tissue is a fat depot not widely studied yet and has direct and profound effects on arterial stiffening.[16–18]

Furthermore, it has been shown that aortic (central) pulse pressure is a better cardiovascular events predictor than brachial pulse pressure.[19,20]

Lifestyle modifications have been suggested for arterial stiffness prevention and treatment.[21] Fasting, described as a total or partial abstention from all foods or selected prohibited foods over some time,[22] has been suggested as a dietary intervention to slow aging in humans,[4] also cardiovascular risk improvement in metabolic syndrome patients.[22] Ramadan model of Time-restricted feeding (TRF) is a type of intermittent fasting that comprises eating and drinking on average only for 8–16 h, each day.[22,23] Previous studies showed that Ramadan fasting has a beneficial effect on cardiovascular risk factors in moderate and high-risk populations[24] and no adverse effect on ambulatory blood pressure monitoring in treated hypertensive

TABLE 1 Criteria for clinical diagnosis of metabolic syndrome in Iranian adults.[2,29]

Measure	Categorical cut-off points
Waist circumference	>95 cm (men and women)
Raised triglycerides	>150 mg/dL (1·7 mmol/L)
OR Specific treatment for this lipid abnormality	
Reduced HDL-cholesterol	<40 mg/dL (1·03 mmol/L) in men
OR Specific treatment for this lipid abnormality	<50 mg/dL (1·29 mmol/L) in women
Raised blood pressure	Systolic ≥ 130 mmHg
OR Treatment of previously diagnosed hypertension	Diastolic ≥ 85 mmHg
Raised fasting plasma glucose	≥100 mg/dL (5·6 mmol/L)
Fasting plasma glucose	
OR Previously diagnosed type 2 diabetes	

TABLE 2 Descriptive statistics of gender, age and number of fasting days ($N = 95$).

	Fasted group ($N = 80$)	Not fasted group ($N = 15$)	p Value
Female (number)	25 (31.3)	5 (33.3)	0.873[a]
Male (number)	55 (68.8)	10 (66.7)	
Mean age (year)	45.6 ± 8.9	44.7 ± 10.2	0.737[b]
Number of fasting days during Ramadan	26.5 ± 6	2.7 ± 3	<0.001[b]

Note: Data was expressed as mean ± sd and *n* (%).

[a]Chi-square test;

[b]Independent sample *t* test.

TABLE 3 Effect of intermittent fasting on body weight and body weight changes before and after Ramadan ($n = 95$).

	Fasted ($N = 80$)			Not fasted ($N = 15$)			
	Before mean ± SD	After mean ± SD	p Value[a]	Before mean ± SD	After Mean ± SD	p Value[a]	p Value[b]
Weight (kg)	85.5 ± 13	84.0 ± 13	<0.001	88.2 ± 16	87.5 ± 16	0.112	0.028
Body mass index (kg/m^2)	30.7 ± 4	30.1 ± 4	<0.001	30.5 ± 4	30.3 ± 4	0.106	0.014
Visceral fat area (cm^2)	145.5 ± 50	139.8 ± 50	<0.001	144.1 ± 52	139.9 ± 53	0.026	0.416

[a]Paired Sample *t*-test.

[b]ANCOVA was used for comparison between groups and before Ramadan measurements considered as covariate.

volunteers.[25,26] There is not conclusive evidence regarding the association between Ramadan model of TRF and arterial stiffness indices.[27,28]

This study aimed to evaluate the association of the Ramadan model of TRF and arterial stiffness indices including PWV, pulse wave analysis (PWA) indices, brachial and central blood pressures, and arterial age in volunteers with metabolic syndrome with the hypothesis that arterial stiffness indices and arterial age may be improved after Ramadan fasting.

2 | METHODS

A cohort study was conducted in adults with metabolic syndrome from May to June 2017 in Mashhad, Iran. Patient recruitment was done based on Public announcements in offices and clinics of Mashhad University of Medical Sciences. The clinical diagnosis of metabolic syndrome in this study was based on the definition of the International Diabetes Federation and Iranian adults' specific waist cut-off values (Table 1).[5,30] Exclusion criteria were patients with a history of cardiac arrhythmias, carotid or aortic valve stenosis, peripheral artery disease, and hypotension.

Ramadan is the 9th month of the Islamic calendar and Ramadan fasting means abstention from eating, drinking, smoking, and sexual activity from down to sunset.[22,23]

Subjects were categorized into Ramadan fasting and Ramadan nonfasting groups retrospectively (at the end of Ramadan, based on self-declaration of the number of fasting days). Fasting for 10 days was considered the minimum acceptable number for the Ramadan fasting group. Individuals who fasted for less than 10 days were considered the Ramadan nonfasting group. The aortic PWV was measured noninvasively from the right carotid and femoral artery pulses using SphygmoCor XCEL System (AtCor Medical). Participants were asked to abstain from eating, drinking, and consuming alcohol, caffeine, or smoking 6 h before the study. Measurements were done after a 15 min rest in a lying position, in a quiet, dry, and thermally comfortable room.[29] Mean arterial age was calculated based on an individual's cfPWV or augmentation index (AIx).[31]

Visceral fat area was measured using assessed using bioelectrical impedance analysis (InBody770; Biospace). Measurements were taken 6 days before and 4 days after Ramadan.

The Kolmogorov–Smirnov test was performed to test the normality of the distribution of the outcome measures. The paired sample *t*-test was used to assess the differences between the normally distributed variables before and after Ramadan in the Ramadan fasting and Ramadan nonfasting groups. ANCOVA was used for comparison between groups and before Ramadan measurements considered as covariate.

A p-value of <0.05 was considered statistically significant. All analyses were conducted in SPSS statistical software (version 16, SPSS Inc.).

TABLE 4 Effect of intermittent fasting on arterial stiffness in adults with metabolic syndrome (*N* = 95).

	Fasted group (*N* = 80)				Not fasted group (*N* = 15)			
	Before mean ± SD	After mean ± SD	Change mean ± SD	*p* Value[a]	Before mean ± SD	After mean ± SD	Change mean ± SD	*p* Value[a]	*p* Value[b]
Mean pulse wave velocity (m/s)	8.45 ± 1.23	8.16 ± 1.11	−0.29 ± 1.02	0.014	8.00 ± 1.19	8.23 ± 0.96	0.23 ± 1.33	0.507	0.233
Arterial age (year)	60.54 ± 17.88	53.73 ± 19.60	−6.80 ± 17.46	0.001	56.27 ± 17.98	59.53 ± 20.15	3.26 ± 14.80	0.407	0.061
Central augmentation index (%)	132.89 ± 11.57	130.42 ± 11.11	−2.47 ± 10.19	0.036	129.23 ± 10.98	131.87 ± 12.27	2.63 ± 10.62	0.371	0.183
Central augmentation pressure (mmHg)	12.06 ± 5.90	10.18 ± 5.71	−1.88 ± 5.40	0.003	10.95 ± 7.04	12.34 ± 7.80	1.39 ± 5.57	0.351	0.043

[a]Paired Sample *t*-test.
[b]ANCOVA was used for comparison between groups and before Ramadan measurements considered as covariate.

3 | RESULTS

Overall 102 adults were recruited for the study and seven withdrew because of personal reasons. So, 95 metabolic syndrome volunteers (68% male, mean age of 45.4 ± 9 years) participated in this study, and the average duration of daily fasting was about 16.5 h. Baseline characteristics of patients before and after the Ramadan period are reported in Tables 2 and 3.

There was a significant reduction in PWV (0.29 ± 1.02 m/s), arterial age (6.8 ± 17.46 years), central AIx (2.47 ± 10.19), and central augmentation pressure (1.88 ± 5.40 mmHg) after the intermittent fasting period in the Ramadan fasting group ($p = 0.014$, $p = 0.001$, $p = 0.036$, and $p = 0.003$ respectively) (Table 4, Figure 1). The Ramadan nonfasting group did not significantly change PWV, arterial age, central AIx, and central augmentation pressure ($p = 0.50$, $p = 0.40$, $p = 0.37$, and $p = 0.35$, respectively) (Table 4).

There was a significant difference between the Ramadan fasting and Ramadan nonfasting groups regarding arterial age and central augmentation pressure changes ($p = 0.039$ and $p = 0.036$, respectively). However, there was no significant difference between groups in PWV and central AIx changes after Ramadan fasting ($p = 0.334$ and $p = 0.100$, respectively).

A significant reduction in central systolic (−4.03 ± 9.18 mmHg) and diastolic blood pressures (−1.6 ± 6.21 mmHg), central mean blood pressure (−2.85 ± 7.43 mmHg), and central pulse pressure (−2.4 ± 6.41 mmHg) were seen in the Ramadan fasting group ($p < 0.001$, $p = 0.024$, $p = 0.001$, and $p = 0.001$ respectively) (Table 5).

Brachial systolic (−4.35 ± 9.69 mmHg) and diastolic blood pressures (1.67 ± 6.06 mmHg), brachial mean blood pressure (−2.5 ± 6.60 mmHg) and brachial pulse pressure (−2.7 ± 7.35 mmHg) decreased significantly in the Ramadan fasting group (Table 5).

There was a significant difference between the Ramadan fasting and Ramadan nonfasting groups in brachial mean blood pressure changes ($p < 0.001$), but no significant differences were seen in other central and brachial blood pressure parameters.

4 | DISCUSSION

This study showed a significant improvement in arterial stiffness parameters, including PWV, arterial age, AP, AIx, brachial and central pressures in adults with metabolic syndrome after an average of 26.5 days of Ramadan model TRF. It has been reported that each 1 m/s increase in aortic PWV corresponds to an adjusted risk increase of 14% in total cardiovascular events, 15% in cardiovascular mortality, and 15% in all-cause mortality.[32] This infers that a significant reduction (−0.29 m/s) in PWV after an average of 26.5 days of Ramadan fasting may suggest a 5% improvement in cardiovascular events, cardiovascular mortality, and all-cause mortality in metabolic syndrome patients. In our study, an average of 26.5 days of Ramadan fasting reduced arterial age by 7 years, suggesting a 1.8% decrease in the Framingham risk score for CVDs.[33] Seven years of reduction in arterial age regarding Ramadan fasting equals 1 month low, subtherapeutic doses of Fluvastatin or Valsartan therapy to decrease arterial age.[34] Also, it has been reported that for each 10% increase in the AIx, the risk of cardiovascular mortality and all-cause mortality increases by about 50%,[35] thus the improvement of 3.25% in the central AIx seen in the current study is also suggestive of a reduction

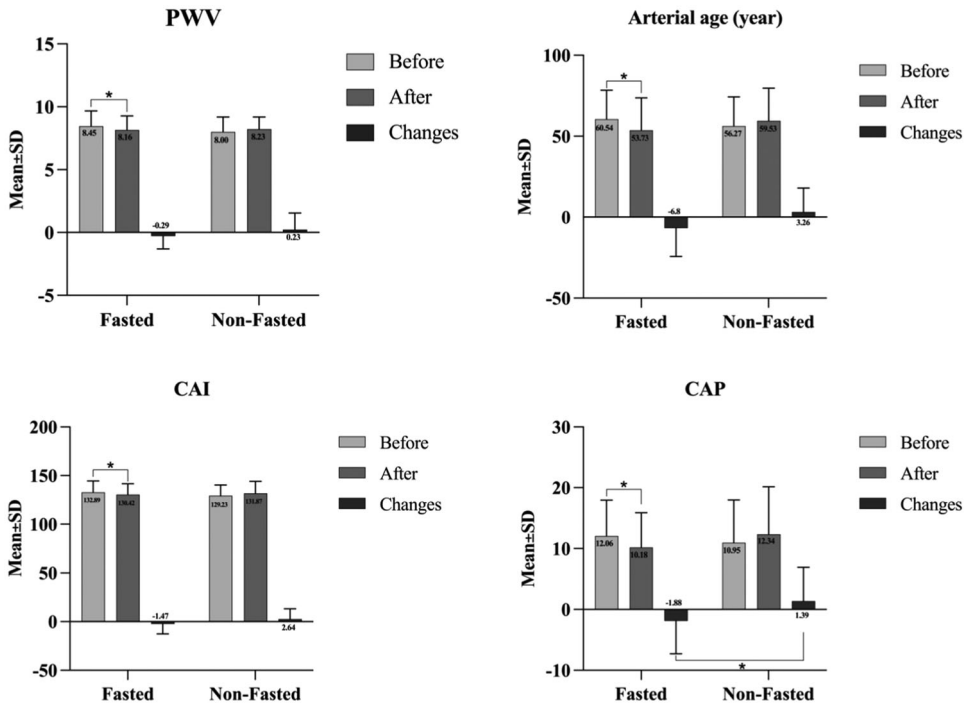

FIGURE 1 Effect of intermittent fasting on arterial stiffness in adults with metabolic syndrome ($N = 95$).

TABLE 5 Effect of intermittent fasting on central and brachial blood pressures in adults with metabolic syndrome ($N = 95$).

	Fasted ($N = 80$)				Not fasted ($N = 15$)				
	Before mean ± SD	After mean ± SD	Change mean ± SD	*p* Value[a]	Before mean ± SD	After mean ± SD	Change mean ± SD	*p* Value[a]	*p* Value[b]
Central systolic blood pressure (mmHg)	116.07 ± 13.99	112.04 ± 11.47	−4.03 ± 9.18	<0.001	114.48 ± 11.31	114.49 ± 9.81	0.005 ± 6.48	0.998	0.096
Central diastolic blood pressure (mmHg)	78.27 ± 10.32	76.67 ± 8.97	−1.59 ± 6.21	0.024	78.88 ± 8.48	78.48 ± 8.56	−0.40 ± 4.39	0.730	0.358
Central mean pressure (mmHg)	93.34 ± 12.16	90.49 ± 10.06	−2.85 ± 7.43	0.001	93.39 ± 10.14	93.07 ± 9.62	−0.31 ± 5.29	0.822	0.136
Central pulse pressure (mmHg)	37.79 ± 7.56	35.36 ± 7.25	−2.43 ± 6.41	0.001	35.60 ± 7.64	36.00 ± 6.46	0.40 ± 5.24	0.770	0.211
Brachial systolic blood pressure (mmHg)	126.05 ± 14.68	121.70 ± 12.44	−4.35 ± 9.69	<0.001	124.53 ± 11.97	123.87 ± 9.65	−0.66 ± 7.61	0.740	0.163
Brachial diastolic blood pressure (mmHg)	77.28 ± 10.28	75.61 ± 8.81	−1.67 ± 6.06	0.016	77.86 ± 8.08	77.26 ± 8.37	−0.60 ± 4.03	0.574	0.389
Brachial mean pressure (mmHg)	93.47 ± 11.33	90.97 ± 9.50	−2.50 ± 6.60	0.001	93.33 ± 8.86	92.67 ± 8.38	−0.66 ± 5.15	0.624	0.248
Brachial pulse pressure (mmHg)	48.76 ± 8.65	46.08 ± 8.31	−2.67 ± 7.35	0.002	46.66 ± 7.85	46.60 ± 6.43	−0.06 ± 5.16	0.961	0.316
Heart rate (beat/minute)	65.95 ± 9.08	64.67 ± 9.91	−1.28 ± 6.19	0.070	71.46 ± 11.68	68.23 ± 8.39	−3.23 ± 5.16	0.044	0.587

[a]Paired Sample *t*-test.
[b]ANCOVA was used for comparison between groups and before Ramadan measurements considered as covariate.

in cardiovascular and all-cause mortality. Moreover, the 4.35 mmHg reduction in central systolic blood pressure due to the Ramadan model of TRF can be considered equivalent to a 10.44% reduction in the risk of stroke.[36]

There is scarce evidence regarding arterial stiffness and fasting, particularly in the Ramadan model of TRF. A previous study has demonstrated that Ramadan fasting improves AIx, central systolic, and diastolic blood pressures, but not PWV in hypertensive patients without CKD.[27] Another study showed no significant change in arterial stiffness parameters (including PWV and PWA indices) among 100 healthy overweight and obese men.[28]

One previous study assessing central pulse pressure after a fasting period in young, overweight, and obese men reported no significant change.[28] Moreover, previous studies assessing Ramadan fasting and brachial blood pressure reported a considerable reduction or no significant difference in brachial systolic and diastolic blood pressures.[25,26]

Although there are no randomized control trials regarding Ramadan fasting and cardiovascular outcomes, previous studies have reported a significant improvement in traditional cardiovascular risk factors and Framingham risk score after the Ramadan model of TRF among metabolic syndrome and high-risk cardiovascular patients.[24]

Several mechanisms may explain the improvements seen in arterial stiffness parameters in the current study. These may be driven by aortic blood pressure decline,[31,37] calorie restriction,[38,39] weight loss,[40,41] and visceral fat loss[41,42] that were seen in our study population.

It has been reported that increased blood pressure (as a consequence of cellular changes due to increased BP-related wall stress) has acute and long-term effects on arterial stiffness.[37] In the fasted group, significant aortic blood pressure decline (−4.03 and −1.59 mmHg for systolic and diastolic blood pressures, respectively) may be a major hemodynamic factor, directly affecting arterial stiffness.

As we previously reported, the Ramadan model of TRF resulted in a 23% restriction in energy intake and a reduction in total physical activity scores during the fasting period, leading to 1.81% weight loss and 3.93% visceral fat loss in our study population.[43] Calorie restriction itself has protective effects on arterial stiffness, preserves endothelial function and collagen–elastin balance,[44] reduces arterial oxidative stress and inflammation,[44–46] and increases nitric oxide bioavailability.[45,46] It has been reported that a 30% reduction in calorie intake for 12 weeks, without any increase in physical activity, improves artery endothelium-dependent dilatation[47] and recurrence of vascular stiffness[41] in overweight and obese adults. the improvement in endothelial function in these studies was independent of age[47] and associated with the rate of abdominal adiposity reduction.[41]

Changes in the elastic content of the arterial wall,[41] improved nitric oxide bioavailability, decreased sympathetic neuronal activity, and improvements in arterial stiffness-associated factors have been observed following weight loss.[38]

Reduction of visceral fat by using lifestyle modification has been introduced as a practical strategy to improve obesity-associated cardiovascular risk factors[48–50] and prevention of acute cardiovascular

events[48,49] in patients with metabolic syndrome. Visceral fat reduction (3.93%) in the current study can lead to improvements in the pathological role of abdominal fat,[51] including dysfunctional adipocytes,[49] hypoadiponectinemia,[49] predisposing factors of Insulin resistance, proinflammatory metabolites, and other hormones and metabolites associated with hypertension and fibrinolysis disorders,[52] consequently improvement in arterial stiffness indices. This diet also has an influence on gut microbiota leading to beneficial effects on obesity prevention.[53]

The results of this study can help to better understand the effects of Ramadan fasting as a lifestyle modification on atherosclerosis indicators in people with metabolic syndrome. The results of this study and previous studies[23,24] (with the improvement of cardiovascular risk factors after Ramadan fasting) can help patients and clinicians evaluate Ramadan fasting's benefits and drawbacks to make decisions about it.

This study has several strengths and limitations. This is the first study to assess the effects of the Ramadan modal of TRF on detailed arterial stiffness indices, arterial age, or central blood pressure changes among metabolic syndrome patients. The inclusion of a Ramadan nonfasting group is a further strength of this study. This study is limited due to the small number of individuals in the Ramadan nonfasting group. It was impossible to randomize subjects into Ramadan fasting and not fasting groups due to ethical and religious reasons. So, any causality cannot be determined due to the study design. Although the groups were classified retrospectively, based on self-declaration of the number of fasting days, there was a difference in the male-to-female ratio between the two groups. The outcomes evaluated are outcomes surrogated from clinical outcomes so that ideally future studies should evaluate clinical outcomes. A change at the end of Ramadan does not imply that this change will be maintained over time and will have an impact on clinical outcomes.

5 | CONCLUSIONS

This study suggested that the Ramadan model of TRF may be considered a lifestyle strategy for improving arterial stiffness, arterial age, and blood pressure in people with metabolic syndrome. Also, it can be suggested that this strategy with less weight loss (compared to calorie restriction interventions) can be associated with arterial stiffness improvements.

Further studies are needed, however, preferably randomized controlled trials, to confirm these findings.

AUTHOR CONTRIBUTIONS

Maryam Alinezhad-Namaghi: Conceptualization; data curation; formal analysis; investigation; project administration; writing—original draft; writing—review and editing. **Saeid Eslami**: Conceptualization; formal analysis; methodology; software; supervision; writing—review and editing. **Mohsen Nematy**: Conceptualization; methodology; writing—review and editing. **Reza Rezvani**: Conceptualization; investigation; writing—review and editing. **Adeleh Khoshnasab**: Investigation; writing—review and editing. **Shokoofeh Bonakdaran**: Methodology; writing—review and editing. **Elena Philippou**: Conceptualization; writing—review and editing. **Abdolreza Norouzy**: Conceptualization; funding acquisition; project administration; resources; supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

This study was conducted following the guidelines laid down in the Helsinki Declaration. The Research Ethics Committee of Mashhad University of Medical Sciences approved all procedures on human volunteers (approval code of IR.MUMS.fm.REC.1395.494). All subjects completed the written informed consent before the study.

TRANSPARENCY STATEMENT

The lead author Abdolreza Norouzy affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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