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Effects of Intermittent Fasting on Serum Lipid Levels, Coagulation Status and Plasma Homocysteine Levels

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Key Words

Homocysteine · *D*-Dimer · High-density lipoprotein · Islamic fasting · Ramadan, meal frequency · Fasting, circadian variation

Abstract

Background: During Ramadan, Muslims fast during the daylight hours for a month. The duration of restricted food and beverage intake is approximately 12 h/day which makes Ramadan a unique model of intermittent fasting. Many physiological and psychological changes are observed during Ramadan that are probably due to the changes in eating and sleeping patterns. ***Methods:*** Serum total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), prothrombin time, activated partial thromboplastin time (aPTT), plasma fibrinogen, *D*-dimer and homocysteine levels were measured in 24 healthy fasting volunteers (12 females, 12 males) aged 21–35 years. Venous blood samples were taken 1 week before Ramadan, on the 21st day of Ramadan and 20 days after Ramadan. ***Results:*** No significant changes were observed on serum total cholesterol, triglycerides and LDL levels. HDL levels were significantly elevated during Ramadan ($p < 0.001$) and 20 days after Ramadan ($p < 0.05$). Prothrombin time, aPTT, fibrinogen and *D*-dimer levels were in the physiologic limits in all samples but *D*-dimer levels were significantly low at the end of Ramadan in comparison to pre- and post-fasting levels ($p < 0.001$). Homocysteine levels, being still in reference ranges, were low during Ramadan ($p < 0.05$) and reached the pre-fasting levels after Ramadan. ***Conclusion:*** Our results demonstrate that intermittent fasting led to some beneficial changes in serum HDL and plasma homocysteine levels, and the coagulation status. These changes may be due to omitting at least one meal when the body was particularly metabolically active and possibly had a low blood viscosity level at the same time. We conclude that intermittent fasting may have beneficial effects on hemostatic risk markers for cardiovascular diseases.

Introduction

It is well known that nutritional habits, sleeping patterns and frequency of meals have profound effects on maintaining human health. Ramadan is a religious month during which all Muslims refrain from eating and drinking during the daylight hours for a month. The duration of restricted food and beverage intake is approximately 12 h/day which makes Ramadan a unique model of intermittent fasting. Many physiological and psychological

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changes that are probably due to the changes in eating and sleeping patterns are observed during Ramadan [1, 2].

Homocysteine is a mixed amino acid, intermediary on the metabolic pathway between methionine and cysteine. Several B vitamins are cofactors in the methionine catabolic pathway. Deficiencies in folic acid, vitamin B_{12} and pyridoxine have been associated with mildly elevated homocysteine levels in healthy populations [3, 4]. The role of plasma homocysteine levels in vascular diseases and the mechanisms are still a matter of debate. Recent studies suggest that hyperhomocysteinemia may stimulate procoagulant factors or impair anticoagulant mechanisms by affecting normal endothelial functions [4].

Circulating concentrations of *D*-dimer reflect the extent of fibrin turnover in the circulation as this antigen is present in several degradation products from the cleavage of cross-linked fibrin by plasmin [5, 6]. Hence, plasma *D*-dimer levels indicate fibrin generation and fibrinolytic activity in the body. It has been shown that fibrin *D*-dimer is associated with the risk of future ischemic heart disease in individuals with and without baseline evidence of vascular disease [6–8].

Physiological changes during prolonged intermittent fasting and the possible effects of delayed or shortened periods of sleep on human metabolism are not well established. In this study we have investigated the effects of intermittent fasting and the change in sleeping pattern on serum lipid levels, coagulation status and plasma homocysteine levels.

Materials and Method

Twenty-four healthy volunteers (12 females aged 21–33, mean ± SD 29 ± 3.2, 12 males aged 22–35, mean ± SD 31 ± 2.7) participated in the study. All subjects were non-smoking, normolipidemic individuals. They were on no medication and considered to be healthy on the basis of a routine clinical and laboratory examination. Informed consent was obtained from each subject. Female subjects were not using oral contraceptive drugs and had at most one menstrual period (5 ± 2 days) during Ramadan. Islamic rules do not permit fasting during the menstrual period. Male subjects fasted during the whole month, while female subjects did not fast during their menstrual period. All the subjects completed the questionnaire on diet beginning 2 days before the blood sampling. No special nutritional regimen was applied to the subjects during the study. According to the questionnaire, during Ramadan, total energy intake was increased minimally (2,180 vs. 2,320 kcal during Ramadan) which is probably because of increased carbohydrate intake (approximately 49.7 vs. 53.6% during Ramadan).

During Ramadan the frequency of meals was reduced to two, compared to three times in the pre- and post-fasting period. In our study, according to the questionnaire, the last meal was taken at 1–2 a.m. and the main meal was taken at 5–5.17 p.m., which demonstrates that our subjects fasted for 15 h on average. The study was carried out in November.

Venous blood samples were taken 1 week before Ramadan, on the 21st day of Ramadan and 20 days after Ramadan and were frozen at –20°C before being studied. Prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen and *D*-dimer levels were studied in fresh samples. Serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), calcium, total protein, albumin, PT, aPTT, plasma fibrinogen, *D*-dimer and homocysteine levels were measured in all samples after 12 h of fasting. HDL risk factor was calculated as TC/HDL.

Several metabolic responses are shown to have occurred at the end of the first week, so the blood samples were drawn in the last week of Ramadan and 20 days after Ramadan. The body weight of all subjects was recorded during each blood sampling and also 24-hour urinary volume was obtained on each blood sampling day.

PT, aPTT and fibrinogen determinations were made by microcoagulation analyzer (Sigma Diagnostics, USA). Biochemical parameters were measured by Dimension® RxL automated analyzer (Dade Behring, USA), *D*-dimer levels were measured by a two-step enzyme immunoassay, sandwich method with a final fluorescent detection enzyme-linked fluorescent assay (VIDAS®; bioMérieux, France) and homocysteine levels were measured by fluorescence polarization immunoassay (IMX®; Abbot, USA). The results were statistically analyzed by using repeated measures ANOVA as each subject served as his own control by comparing pre- and post-fasting values with those during Ramadan fasting.

Results

No significant changes were observed on serum total protein, albumin, calcium, TG and LDL levels. HDL levels were significantly elevated during Ramadan ($p < 0.001$) and 20 days after Ramadan ($p < 0.05$). The mean HDL risk factor was decreased during Ramadan ($p < 0.05$) and remained depleted after Ramadan fasting for at least 20 days ($p < 0.05$). PT, aPTT, fibrinogen and *D*-dimer levels were in the physiologic limits in all samples but *D*-dimer levels were significantly low at the end of Ramadan in comparison to pre- and post-fasting levels ($p < 0.001$).

Homocysteine levels, being still in reference ranges, were low during Ramadan and reached the basal levels, (pre-fasting levels) after Ramadan. *D*-Dimer levels and homocysteine levels were positively correlated ($r = 0.67$), while fibrinogen and *D*-dimer levels were not correlated ($r = 0.08$). Average body weight and 24-hour urinary volumes did not change significantly. The mean ± SD values of all parameters of male subjects are shown in table 1 and of female subjects in table 2.

Table 1. Intermittent fasting data of male subjects: fasting and post-fasting levels are compared to basal (pre-fasting) levels

	Pre-fasting	Fasting	Post-fasting
Cholesterol, mg/dl	179.25 ± 47.94	174.11 ± 42.73	178.8 ± 39.68
LDL, mg/dl	115.7 ± 37.44	109.8 ± 34.85	106.1 ± 35.17
HDL, mg/dl	49 ± 15.25	56 ± 16.31**	57 ± 15.09**
Triglycerides, mg/dl	76.27 ± 29.04	76.68 ± 27.08	70.05 ± 27.8
HDL risk factor	3.85 ± 1.41	2.92 ± 1.12*	2.97 ± 1.33*
BUN, mg/dl	17 ± 2.51	18 ± 3.52	17 ± 2.12
Creatinine, mg/dl	1.0 ± 0.1	1.1 ± 0.12	1.0 ± 0.08
Total protein, g/l	7.8 ± 1.32	7.9 ± 1.23	7.7 ± 1.28
Calcium, mg/dl	9.01 ± 0.5	9.41 ± 0.23	9.46 ± 0.33
D-Dimer, ng/ml	159.3 ± 21.6	89.2 ± 27.7**	144.2 ± 11.6
Fibrinogen, mg/dl	255 ± 42	286 ± 56	278 ± 48
PT, s	12.50 ± 1.10	12.12 ± 1.02	12.46 ± 0.91
aPTT, s	32 ± 3.2	33 ± 2.15	33 ± 2.9
Homocysteine, μmol/l	10.20 ± 1.26	9.06 ± 1.22*	9.52 ± 1.03
Urine volume, ml/24 h	1,750 ± 198	1,790 ± 145	1,830 ± 142
Weight, kg	82.24 ± 5.47	82.47 ± 6.05	82.41 ± 5.21

Values are mean ± SD.
* $p < 0.05$, ** $p < 0.001$.

Table 2. Intermittent fasting data of female subjects: fasting and post-fasting levels are compared to basal (pre-fasting) levels

	Pre-fasting	Fasting	Post-fasting
Cholesterol, mg/dl	178.15 ± 67.73	182.32 ± 58.94	176.91 ± 79.65
LDL, mg/dl	107.4 ± 37.44	103.7 ± 54.67	99.4 ± 64.89
HDL, mg/dl	57.4 ± 13.63	66.5 ± 11.79**	66.9 ± 11.08**
Triglycerides, mg/dl	66.82 ± 23.53	68.66 ± 15.49	65.58 ± 26.74
HDL risk factor	3.31 ± 1.23	2.63 ± 1.02*	2.71 ± 1.47*
BUN, mg/dl	15 ± 1.46	14 ± 2.67	15 ± 2.71
Creatinine, mg/dl	0.9 ± 0.14	1.0 ± 0.24	0.9 ± 0.18
Total protein, g/l	7.3 ± 0.38	7.5 ± 0.23	7.4 ± 0.38
Calcium, mg/dl	8.9 ± 1.40	9.1 ± 1.37	9.5 ± 1.46
D-Dimer, ng/ml	167.3 ± 35.2	73.5 ± 26.7**	153.7 ± 28.4
Fibrinogen, mg/dl	258 ± 67	266 ± 43	262 ± 76
PT, s	13.15 ± 1.42	13.27 ± 1.89	13.52 ± 1.72
aPTT, s	33 ± 2.66	34 ± 1.75	32 ± 2.41
Homocysteine, μmol/l	10.77 ± 2.58	8.52 ± 1.78**	9.97 ± 2.15
Urine volume, ml/24 h	1,640 ± 178	1,580 ± 239	1,690 ± 216
Weight, kg	63.14 ± 6.22	62.69 ± 5.92	62.23 ± 6.67

Values are mean ± SD.
* $p < 0.05$, ** $p < 0.001$.

Discussion

Long-lasting modifications in the circadian distribution of the eating and sleeping schedule result in various changes in metabolism and Ramadan fasting is shown to have an impact on metabolic endocrine processes [9, 10]. In the present study our subjects had the same working hours before and during Ramadan. According to the questionnaire, their sleep was delayed 2 h on average. There were two major changes in their routine: meal timing and sleep schedule. The lack of significant change in body weight indicates that food intake from sunset to sunrise was sufficient to maintain energy balance. On the other hand, during the daylight hours, fasting subjects

must certainly be undergoing dehydration [11], but as confirmed from the body weight and the questionnaire, there was no chronic hypohydration during Ramadan among our subjects. The water balance seemed to be constant on a daily basis as the 24-hour urinary volumes did not change significantly. Consistent with our study, in another recent study using an isotopic tracer technique, it has been demonstrated that total body water content was conserved during Ramadan fasting [12].

Recent studies with human beings and animals with mild hyperhomocysteinemia provided an understanding of the mechanism that underlies between mild elevations of homocysteine and vascular disease. These studies demonstrated the possibility that the effect of elevated homocysteine is multifactorial, affecting both the vascular wall structure and blood coagulation system [3, 13]. A meta-analysis by the Homocysteine Studies Collaboration confirmed homocysteine as a risk factor for the first events of stroke and coronary heart disease (CHD) [14]. Our results demonstrate that homocysteine levels were decreased in the last week of Ramadan and returned almost to the basal values 20 days after Ramadan. None of our subjects used any kind of vitamin supplements and according to the questionnaire, consumption of food containing folic acid and other B vitamins did not change significantly during the study period. The changes in the rest-activity cycle and sleep and food patterns during Ramadan may beneficially affect the bioavailabilities or redistribution of cofactors such as B vitamins. However, mechanisms that underlie homocysteine decrease during intermittent fasting for 15 h/day for a month, as in the Ramadan fasting model, must be further investigated as some previous studies reported mild hyperhomocysteinemia under fasting conditions due to mild impairment in the methylation pathway, although in these studies the fasting conditions were different [3, 15].

In the present study there was a significant decrease in *D*-dimer levels during fasting. It has been suggested that modestly elevated circulating *D*-dimer levels reflect minor increases in blood coagulation, thrombin formation and a turnover of cross-linked intravascular fibrin which is partly intra-arterial in origin [5, 6]. These increases may be relevant to CHD as previous prospective studies suggest that CHD risk is approximately 70% greater in those having higher plasma *D*-dimer levels [5, 16, 17]. Aybak et al. [18] showed that Ramadan fasting led to a decrease in the platelet responses to different aggregating agents. On the other hand, an increase in bleeding and coagulation time (but not above the physiologic limits) had been shown by the same study. These results are in agreement with the present study. In addition, plasma factor VII coagulant activity (FVIIc) is demonstrated to be raised postprandially and remained elevated 7 h, especially following high-fat diets [19]. During Ramadan fasting at least one meal is omitted, hence a possible increase in FVIIc activity after lunch may not be seen. Moreover, associations between homocysteine and fibrin *D*-dimer are under investigation in recent studies, while in multivariate analysis the association of homocysteine and *D*-dimer is demonstrated to remain statistically significant after adjustment for indicators of chronic inflammation and fibrinogen [20, 21]. These results are consistent with our study in which we showed a significant decrease in *D*-dimer levels indicating fibrin generation in the body was decreased during intermittent fasting. Additionally, homocysteine levels were correlated with *D*-dimer levels. In combination with other as yet undetermined mechanisms, such as increased HDL levels, coagulation activation may be minimal during prolonged intermittent fasting.

Plasma fibrinogen and *D*-dimer levels were not correlated in our study. Previous studies have reported minimal correlations between plasma *D*-dimer and fibrinogen levels. This lack of correlation has been reported to have little reduction in the strength of association between high *D*-dimer levels and CHD, indicating that *D*-dimer is an independent risk factor for CHD [16, 22, 23]. On the other hand, we have measured clottable fibrinogen. Sweetnam et al. [24] reported that a heat-precipitation nephelometric assay of fibrinogen has a better performance in minimal variations and predicting CHD. To our knowledge, no other reports on plasma *D*-dimer, fibrinogen and homocysteine levels during Ramadan fasting are available.

Most of the previous studies on Ramadan fasting did not use female subjects – in the present study however, both female and male subjects were studied. The interdiction of fasting during the menstrual period (5 ± 2 days) seems to be without effect, as the data from female subjects is similar to that from male subjects. Previous studies showed that at least 10 days were necessary for the body to adapt metabolically to the changes in feeding and sleeping habits [1, 10]. Moreover, it has been shown that metabolic changes remain the same for at least 10 days after Ramadan [1, 10]. In the present study, 5 ± 2 days were possibly not enough for the metabolic shift and that may be the reason for the interruption of fasting during the menstrual period, not affecting our data.

In our study, serum HDL levels were significantly elevated and HDL risk factor was significantly decreased

during Ramadan and remained the same 20 days after Ramadan in both female and male subjects. The change in eating habits during Ramadan did not affect other lipoproteins, TC and TG levels. These results are consistent with the previous study by Adlouni et al. [1]. However, in their studies, Maislos et al. [25, 26] reported that HDL levels returned to basal values 4 weeks after the end of Ramadan. In our subjects, 20 days after Ramadan may not be enough for HDL to return to pre-fasting levels which seems to be an advantage on the risk of CHD. The principle role of HDL in lipid metabolism is the uptake and transport of cholesterol from peripheral tissues to the liver through a process known as *reverse cholesterol transport* which is proposed as a cardioprotective mechanism. Low HDL levels are associated with an increased risk of CHD [27]. On multivariate analysis it has been suggested that the best independent lipid predictor of CHD risk among populations is the TC/HDL ratio (HDL risk factor) [28, 29] and a unit increment of HDL risk factor adds an excess of 68% to both the non-fatal and fatal CHD event risk [28, 30].

In the study, non-fasting samples were taken in the morning and the fasting ones in the afternoon. This point is a limitation for the present study as some compared parameters have circadian variations. However, homocysteine, *D*-dimer, PT, aPTT, BUN, creatinine and total protein levels do not intend to change during the day. Another limitation for the study is only one measurement for the *D*-dimer levels at the end of the fasting period was made. In order to exclude a systematic error, additional series of *D*-dimer measurements could have been done.

However, our results demonstrate that although no nutritional diet regimen and no reduction in caloric intake were applied to the subjects, intermittent fasting led to some beneficial changes in serum HDL and homocysteine levels, and in the coagulation status. These changes may be due to omitting at least one meal when the body was particularly metabolically active and possibly had a low blood viscosity level at the same time. We conclude that intermittent fasting may have beneficial effects on hemostatic risk markers for cardiovascular diseases.

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