

Metabolic effects of Ramadan fasting in patients at high risk of cardiovascular diseases

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Background and aim: The effects of Ramadan fasting on health are a little controversial. The present study is aimed at evaluating the metabolic effects on a group of 517 patients with ≥ 2 cardiovascular risk factors over a period running from 2012 to 2014.

Methods: Each patient was assessed at three visits: before, during, and after Ramadan. Demographical, clinical and biological tests were performed at each visit.

Results: Metabolically, we noted a significant and discrete rise in blood glucose level (+1.2 mmol/L), triglycerides (+0.3 mmol/L), cholesterol (+0.12 mmol/L) and creatinine (+3 μ mol/L) during Ramadan. These disturbances decreased significantly after Ramadan. The same variations were observed among diabetics (n=323). However, there was a significant decrease in HbA1c after Ramadan (9.0% vs 7.6%, $p < 0.001$). Our findings also revealed there was no significant correlation between variations of metabolic parameters and dietary intake. No acute metabolic incidents were reported during the study period.

Conclusion: The current study showed that Ramadan is responsible for a transient but well tolerated disturbance of metabolic parameters followed by a significant post-Ramadan improvement. These changes did not seem to be directly related to dietary intake.

Keywords: Ramadan, fasting, metabolic parameters

Introduction

Ramadan fasting (R) represents one of the five pillars of Islam.^{1,2} It has great repercussions on the rhythm of life affecting mainly dietary habits, sleep and working hours with some biological and physiological consequences that remain controversial.^{3,4}

Some people think fasting is healthy,^{5,6} but others think it is a great test especially for those with chronic diseases or cardiovascular risk factors.^{6,7} Although patients with serious illnesses are exempted from this religious duty, many persist with fasting for social, cultural and religious reasons.^{6,7} The metabolic effects of Ramadan fasting have been previously studied thoroughly. However, the findings remain very controversial and very little information about the effects of Ramadan fasting on patients at high risk of cardiovascular disease is available.

Furthermore, very few studies have dealt with the possible role of dietary changes during Ramadan. Our work is aimed at studying the effect of Ramadan fasting on blood glucose level and lipid profile in 517 subjects at high risk of cardiovascular disease.

Materials and methods

Inclusion criteria

This is a prospective study conducted over three periods in the years 2012, 2013 and 2014. Patients who fast Ramadan regularly and who have at least two cardiovascular risk factors according to Framingham classification were enrolled in the study.⁸ All patients gave Informed and written consent. The study was approved by the Hospital Ethics Committee (Fattouma Bourguiba University Hospital Monastir, 5000, Tunisia) and was subscribed in the clinical trials registry at ClinicalTrials.gov (NCT02720133). Any patient not fasting Ramadan or missing one visit was excluded from the study.

Conduct of the study

Patients in stable condition were recruited from different local health centers of the governorate and hospital outpatient clinics (cardiology, endocrinology). For each patient, the study period took three months and included three visits:

- A first inclusion visit: during the month preceding Ramadan.
- Two follow up visits: one visit during the last week of Ramadan and another one thirty days after it is over.

During each visit, the clinical elements (demographic data, medical history, associated treatments, physical examination, and evaluation of cardiovascular high risk factors according to Framingham criteria) were identified and recorded in a computerized file.

All patients underwent a biological examination that included a complete lipid test (total cholesterol, triglyceride, LDL-c and HDL-c), blood glucose, HbA_{1c}, insulin level, renal checkup (creatinine and uric acid), serum electrolytes (sodium, potassium and chloride levels), albuminaemia, blood bilirubin and a blood count. The LDL-c was calculated using the Friedwald formula.⁹

Creatinine clearance was calculated by means of the simplified MDRD formula (Modification of the Diet in Renal Disease).¹⁰ In order to determine insulin resistance, the HOMA-IR index (Homeostasis Model Assessment of Insulin resistance) was measured.¹¹ There is insulin resistance when HOMA-IR > 2.4.

The caloric intake was measured during the three visits using the 24 hr recall method based on the intake of the

day prior to the interview.¹² We examined chronologically from morning to evening (plus the night) nutritional intake during or outside the meals of the day before. Food amounts are most often evaluated using domestic measures (plates, glass, slice, cup, spoons ... etc).

A nutritionist was assigned this evaluation using the Nutritional Facts Table of the food products and meals to measure the energy value and content of the main nutrients. All samples were taken on an empty stomach between 8 and 11 in the morning. During the whole study period, the number of hypoglycemic incidents and hyperglycemic exacerbations requiring an emergency consultation were noted.

Statistical analysis

The study data were collected, recorded and analysed by the SPSS statistical software (version 18.0). The quantitative variables were expressed by their means with the estimation of their confidence intervals at 95%.

The general linear model with repeated measurements was used to estimate and compare the marginal means of dependent Gaussian quantitative variables before, during and after Ramadan (Bonferroni test).

A non parametric test (Friedman test) was used to compare non Gaussian quantitative variables before, during and after Ramadan. Cochran Q Test was performed to compare dependent binary variables before, during and after Ramadan. The correlation coefficient (r) between the different caloric intakes (carbohydrates, lipids and proteins) and the metabolic parameters was investigated using the partial correlation. All tests were considered significant when the threshold value was 5%.

Results

In total, 517 patients (241 females and 276 males) were included. The mean age was 59.8±10.5 years (29 to 92 years). A total of 323 patients gave a history of diabetes, 328 had dyslipidemia, and 200 were on Aspirin and 100 on clopidogrel. The basic clinical characteristics of the whole population are presented in Table 1.

The total caloric intake decreased significantly (−22%) during Ramadan then increased after Ramadan compared with the basic state (Table 2). However, as shown in Table 3, the amount of carbohydrates and lipids did not undergo any significant modifications.

Some significant modifications were observed during Ramadan compared with the basic state concerning blood glucose level, lipid profile, kidney function as well as

Table 1 Demographic and clinical characteristics of the overall population (n=517)

	n (%)
Gender	
Males	276 (53.4)
Age (years)	
>50	414 (80)
Body mass index (kg/m²)	
<25	57 (11)
25–30	228 (44.1)
>30	232 (44.9)
Previous medical history	
Hypertension	395 (76.4)
Smoking	85 (16.4)
Dyslipidemia	328 (63.4)
Diabetes	323 (62.5)
Heart failure	258 (49.9)
Coronary disease	165 (31.9)
Stroke	17 (3.3)
Number of cardiovascular risk factors	
2	326 (63.1)
3	165 (31.9)
≥4	26 (5.0)
Ongoing treatment	
Aspirin	200 (38.7)
Clopidogrel	109 (21.1)
Converting enzyme inhibitors	299 (57.8)
β-blockers	129 (25.0)
Diuretics	128 (24.8)
Oral antidiabetic agents	263 (50.9)
Statins	241 (46.6)

plasma bilirubin. These variables subside during monitoring after Ramadan.

During Ramadan, we noted a significant increase in blood glucose level (8.25 mmol/L vs 9.09 mmol/L; $p<0.001$), triglyceride (1.59 mmol/L vs 1.84 mmol/L; $p<0.001$), cholesterol (4.55 mmol/L vs 4.67 mmol/L; $p=0.008$) and serum creatinine (96.6 μmol/L vs 99.4 μmol/L; $p<0.001$) whereas creatinine clearance decreased (Table 3).

If only diabetic patients were considered (n=323), we noted the same variations observed in the overall population with a significant decrease in HbA1c after Ramadan (9.0% vs 7.6%; $p=0.000$). The HOMA-IR index rose significantly during Ramadan compared with the basic state (3.15 vs 4.25 in non diabetics and 5.26 vs 9.20 in diabetic patients ($p<0.001$). After Ramadan, a return to the basic state was observed (Figure 1). The percentage of hypoglycemic events

among diabetic patients was similar during the three study periods (Table 4). No diabetic patient was admitted to the Emergency Department for hyperglycemia exacerbation during the study period. We did not find any correlation between these variations of metabolic parameters and food intake (Table 5) and particularly between the total caloric intake and glycemia on the one hand ($r=0.065$; $p=0.182$) and between the total caloric intake and the total cholesterol ratio/HDL-C ($r=-0.053$; $p=0.282$) on the other (Figure 2).

Discussion

Many works have studied the metabolic and physiological effects of fasting during Ramadan. However, the most pertinent studies have been conducted recently.¹³ In fact, this topic has drawn the attention of many scientists, and despite the lack of financial support, some interesting findings have been generated and several studies are even talking about the benefits of fasting, a practice which could be adapted to all “excess” pathologies such as diabetes and obesity. However, it is difficult to draw final conclusions with the help of available data as the methods used are different, the number of included subjects is often modest and in most cases the enrolled subjects are healthy.

Our work studied for the first time the effect of this holy month on a consistent and homogeneous sample of patients having at least two cardiovascular risk factors. The findings revealed some significant biochemical modifications with regard to blood glucose and lipid profile. Thus, we showed a significant and transient increase in glucose level and insulin resistance during Ramadan. This increase was associated with a significant decrease in HbA1c after the holy month.

Furthermore, a simultaneous disturbance of the profile was noticed during Ramadan followed by an improvement that manifested as a rise in HDL-C and a decrease in triglycerides after Ramadan. The same modifications were present in the diabetic sub-group and did not seem to correlate with food intake. Finally no acute clinical events and particularly no hypoglycemia events neither hyperglycemia exacerbation requiring admission to the Emergency Department were reported during the study.

The rise in the blood glucose level during Ramadan was noted in several previous works.^{14–16} Other studies, however, found Ramadan fasting did not have any effects on blood glucose level,^{18,21,22} or even involve any decrease in this parameter.^{2,17–20}

Nevertheless, the disturbance of blood glucose level has often been associated with a decrease in HbA1c after

Table 2 Caloric intake variation and proportions of carbohydrates, lipids, and protids during the three study periods (before, during, and after Ramadan)

	Before Ramadan	During Ramadan	After Ramadan
Caloric intake (Kcal/j) mean [95% CI]			
Overall population	1693 [1643–1743]	1322 [1285–1359]*	1753 [1704–1802] ^{§£}
Nondiabetics	1652 [1574–1729]	1278 [1218–1338]*	1703 [1625–1782] [§]
Diabetics	1716 [1651–1781]	1348 [1300–1396]*	1781 [1718–1844] [§]
Carbohydrates % [95% CI]			
Overall population	55.2 [54.3–56.1]	55.3 [54.4–56.3]	54.9 [53.9–55.8]
Nondiabetics	56.9 [55.4–58.3]	56.2 [54.3–58.1]	55.9 [54.3–57.4]
Diabetics	54.4 [53.2–55.5]	54.9 [53.7–56.0]	54.3 [53.1–55.5]
Lipids % [95% CI]			
Overall population	28.2 [27.4–29.0]	27.0 [26.2–27.9]	31.1 [25.6–36.7]
Nondiabetics	26.8 [25.4–28.2]	26.7 [25.2–28.2]	27.5 [18.1–36.9]
Diabetics	28.9 [27.9–29.9]	26.7 [25.2–28.2]	33.1 [26.2–40.1]
Protids % [95% CI]			
Overall population	16.6 [16.1–17.1]	17.6 [17.2–18.0]	16.5 [16.0–17.0]
Nondiabetics	16.3 [12.6–18.7]	16.8 [13.9–20.2]	16.1 [13.3–19.3]
Diabetics	16.7 [13.6–19.5]	17.5 [14.7–20.6]	16.2 [13.3–19.3]

Notes: * $P < 0.05$ vs before and during Ramadan, § $p < 0.05$ vs during and after Ramadan, £ $p < 0.05$ vs before and after Ramadan.

Table 3 Changes of biological parameters during the three study periods (before, during, and after Ramadan) in the overall population (n=517)

	Moyenne [95% CI]		
	Before Ramadan	During Ramadan	After Ramadan
Blood glucose level (mmol/L)	8.25 [7.91–8.59]	9.09 [8.73–9.44]*	8.04 [7.72–8.35] [§]
Insulin level (μUI/mL)	12.7 [2.3–23.1]	16.9 [6.5–27.3]*	15.1 [4.6–25.6] ^{§£}
Triglyceride (mmol/L)	1.58 [1.50–1.66]	1.81 [1.70–1.92]*	1.60 [1.51–1.69] [§]
Total Cholesterol (mmol/L)	4.55 [4.45–4.65]	4.67 [4.56–4.77]*	4.60 [4.50–4.71] [£]
HDL-C (mmol/L)	1.20 [1.18–1.23]	1.15 [1.12–1.17]*	1.30 [1.15–1.46] ^{§£}
LDL-C (mmol/L)	2.62 [2.54–2.71]	2.69 [2.60–2.78]*	2.57 [2.39–2.75]
Serum creatinine (μmol/L)	96 [94.2–98.8]	99 [96.9–101.8]*	95 [93.0–97.7]
Creatinine Clearance (ml/min/1.73m²)	69 [67–70]	67 [65–68]*	70 [68–71]
Uric acid (μmol/L)	344 [335–353]	343 [333–352]	343 [334–352]
Sodium level (mmol/L)	148.8 [148.0–149.5]	148.3 [147.5–149.0]	149.1 [148.4–149.9]
Serum Potassium (mmol/L)	4.55 [4.50–4.61]	4.52 [4.47–4.56]	4.60 [4.56–4.64]
Serum Chloride (mmol/L)	110.2 [105.3–115.1]	106.1 [105.4–106.8]	106.8 [106.1–107.6]
Bilirubin (μmol/L)	7.9 [7.55–8.30]	6.0 [5.75–6.39]*	7.5 [7.18–7.93]
Albumin (g/L)	45 [42–47]	43 [43–44]	43 [43–44]
White blood cells (10³/mm³)	6.9 [6.8–7.1]	7.1 [6.8–7.4]	6.7 [6.6–6.9]
Red blood cells (10⁶/mm³)	4.68 [4.43–4.93]	4.46 [4.42–4.51]	4.47 [4.43–4.51]
Hemoglobin (g/dl)	12.9 [12.8–13.1]	12.8 [12.7–13.0]	12.9 [12.9–13.1]
Hematocrit (%)	40.6 [39.9–41.2]	39.20 [38.6–39.7]*	38.66 [38.2–39.2]
Platelets (10³/mm³)	238 [194–276]	239 [191–277]	238 [187–276]

Notes: * $P < 0.05$ vs before and during Ramadan, § $p < 0.05$ vs during and after Ramadan, £ $p < 0.05$ vs.

fasting,¹⁵ proving a post Ramadan beneficial effect. Some authors attributed this improvement in blood glucose level profile to a better compliance with treatment and dietary rules as well as to a decrease in the number of daily meals and hyperglycemic peaks.^{23,24}

This hypothesis did not seem entirely satisfactory. It has been contradicted by a very recent study where a continuous measurement of blood glucose level was performed on 63 patients before and after Ramadan. 6 This study carried out in the United Arab Emirates clearly showed that the different

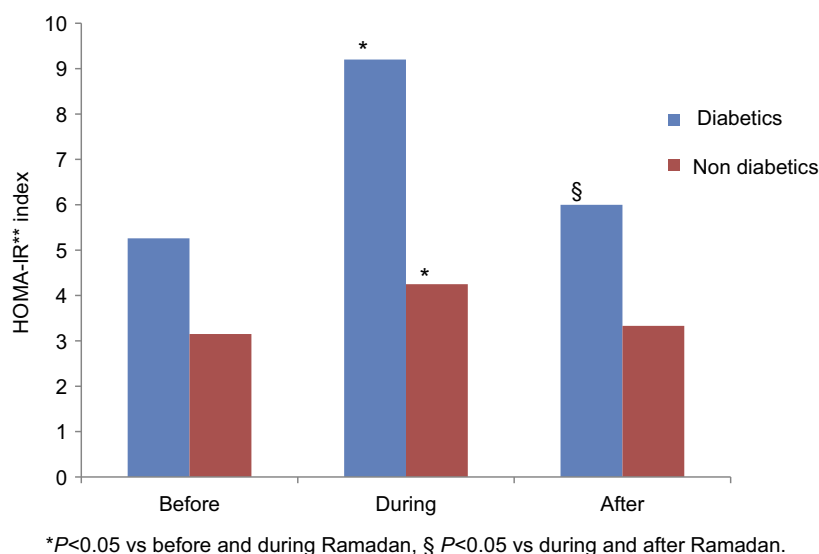


Figure 1 Evolution of the HOMA-IR** index during the three study periods (before, during, and after Ramadan) in the diabetic and nondiabetic populations. * $p < 0.05$ vs before and during Ramadan, § $p < 0.05$ vs during and after Ramadan.

blood glucose level variation indices [Mean Amplitude of Glycaemic Excursions (MAGE), High and Low Blood Glucose Indices (HBGI/LBGI)] were not different in fasting and non fasting periods. Our findings support these data while

showing that blood glucose level disturbances do not have any correlation with food intake in quantitative as well as qualitative terms. A recent study has shown that Ramadan fasting improves the parameters of oxidative stress in diabetic

Table 4 Changes of biological parameters during the three study periods (before, during, and after Ramadan) in the diabetic population (n=323)

	Before Ramadan	During Ramadan	After Ramadan
	Mean [95% CI]		
Blood glucose level (mmol/L)	9.70 [9.22–10.18]	10.65 [10.15–11.15]*	9.34 [8.89–9.79]§
HbA1c (%)	9.0 [8.6–9.4]	-	7.6 [7.4–7.8]£
Insulin level (µUI/mL)	14.3 [3.9–24.7]	17.9 [7.5–28.3]*	15.2 [4.7–25.7]§
Hypoglycaemia (<3.9mmol/L) n (%)	5 (1.6)	6 (1.9)	9 (2.8)
Triglyceride (mmol/L)	1.65 [1.55–1.75]	1.92 [1.78–2.07]*	1.63 [1.52–1.73]§
Total Cholesterol (mmol/L)	4.43 [4.31–4.55]	4.52 [4.39–4.65]*	4.47 [4.34–4.60]
HDL-C (mmol/L)	1.18 [1.14–1.21]	1.11 [1.08–1.15]*	1.32 [1.07–1.57]§£
LDL-C (mmol/L)	2.50 [2.40–2.60]	2.53 [2.42–2.64]	2.41 [2.14–2.68]
Serum creatinine(µmol/L)	96.0 [93–99]	98.7 [96–102]*	94.5 [92–97]§£
Creatinine Clearance (ml/min/1.73m ²)	70 [68–72]	68 [66–70]*	71 [69–73]§£
Uric acid (µmol/L)	333 [322–344]	334 [322–346]	332 [322–344]
Sodium level (mmol/L)	148.3 [147–149]	147.8 [147–149]	148.6 [148–150]
Serum Potassium (mmol/L)	4.60 [4.53–4.66]	4.57 [4.50–4.64]	4.63 [4.57–4.68]
Serum Chloride (mmol/L)	111.6 [104–119]	105.5 [105–106]*	106.4 [106–107]
Bilirubin (µmol/L)	7.8 [7.3–8.3]	6.0 [5.7–6.5]*	7.5 [7.1–8.1]
Albumin (g/L)	45.8 [42.3–49.2]	43.8 [43.2–44.3]	43.6 [42.9–44.3]
White blood cells (10 ³ /mm ³)	7.14 [6.75–7.53]	7.26 [6.67–7.86]	6.99 [6.58–7.40]
Red blood cells (10 ⁶ /mm ³)	4.79 [4.39–5.18]	4.43 [4.38–4.49]	4.46 [4.41–4.52]
Hemoglobin (g/dl)	12.8 [12.7–13.0]	12.7 [12.6–12.9]	12.8 [12.7–13.1]
Hematocrit (%)	40.37 [39.7–41.1]	38.81 [38.2–39.5]*	38.49 [37.9–39.1]£
Platelets (10 ³ /mm ³)	243 [228–258]	241 [226–257]	240 [224–256]

Notes: * $P < 0.05$ vs before and during Ramadan, § $p < 0.05$ vs during and after Ramadan, £ $p < 0.05$ vs before and after Ramadan.

Table 5 Correlation between caloric intake and metabolic parameters during the three study periods (before, during, and after Ramadan)

	Nutrient intake	Correlation coefficient (r)		
		Before	During	After
Glycemia (mmol/L)	Carbohydrate	0.020	0.006	-0.064
	Lipids	0.057	-0.003	0.034
	Protids	-0.019	-0.003	0.008
Triglyceride (mmol/L)	Carbohydrate	-0.064	-0.037	-0.050
	Lipid	0.076	0.059	0.208
	Protid	0.001	0.157	0.022
Cholesterol (mmol/L)	Carbohydrate	-0.055	-0.112	-0.103
	Lipid	0.038	-0.007	0.096
	Protid	0.038	0.050	-0.069
HDL-C (mmol/L)	Carbohydrate	-0.035	-0.091	-0.017
	Lipid	0.027	-0.065	-0.56
	Protid	0.027	-0.092	-0.017
LDL-C (mmol/L)	Carbohydrate	-0.043	-0.109	-0.126
	Lipid	0.013	-0.031	0.060
	Protid	0.013	-0.031	0.060

patients,²⁵ which may explain the post Ramadan beneficial effect on blood glucose level profile. However, patients whose diabetes is poorly controlled should still need a close monitoring. In fact, the EPIDAR study (Epidemiology of Diabetes and Ramadan) conducted in 13 countries showed a significant increase in the incidence of severe hyperglycaemia during the holy month, which seems to correlate with the increase in food and carbohydrate intake.⁷

As for the effect of fasting on lipid profile, some contradictory findings were also noted during Ramadan.^{2,16,19,24,26} The most important finding in our work was related to the significant increase in HDL-C after Ramadan and the fact that there was no increase or even a decrease in LDL-C and triglyceride especially in diabetic patients.

Like blood glucose level, lipid profile underwent a transient disturbance during fasting then improved markedly and in a comparable fashion with blood glucose level, which suggests a possible intricacy.²⁷ It is clear, however, that this effect is not directly linked to the nutritional intake as shown by the lack of correlation between lipid markers and the caloric intake.

At kidney level, we noted a discrete transient increase of creatinine during Ramadan compared with the basic state. At the same time, there was a transient and significant decrease of clearance in both the overall population and diabetic patients. The same findings were noted in a Tunisian study performed in 2013 on athletes whose decrease in kidney function during Ramadan was attributed to a hydration defect that is frequent in the summer period.²⁸

Limitations of our research

The current study has got a few limitations that should be pointed out. The estimation method of food intake is certainly open to criticism, but it is currently the most widely used among self-reporting methods.¹² Besides, the question of the study period is raised. In fact, our study may not be representative because it was conducted in summer, a period that is characterized by a longer fasting day and higher temperatures. It should therefore be checked whether our findings would have been different if the study had been conducted in different periods of the year. Furthermore, our data are lacking details concerning patients' physical activity and sleep, two important factors that could interfere with our findings. Finally, a control group of non fasting subjects could have been considered, which would have strengthened that causal relationship between our results and Ramadan fasting. However, this methodology is difficult as it requires the inclusion of subjects similar to those in our study but who do not fast. Few Tunisians meet this condition.

Conclusion

So far, the effects of Ramadan fasting on health are little known. The available data show that fasting does have some effects, but these should be investigated more thoroughly among a larger sample of patients. Our findings demonstrated that after Ramadan, blood glucose level and lipid profiles, particularly among diabetic patients, improved.

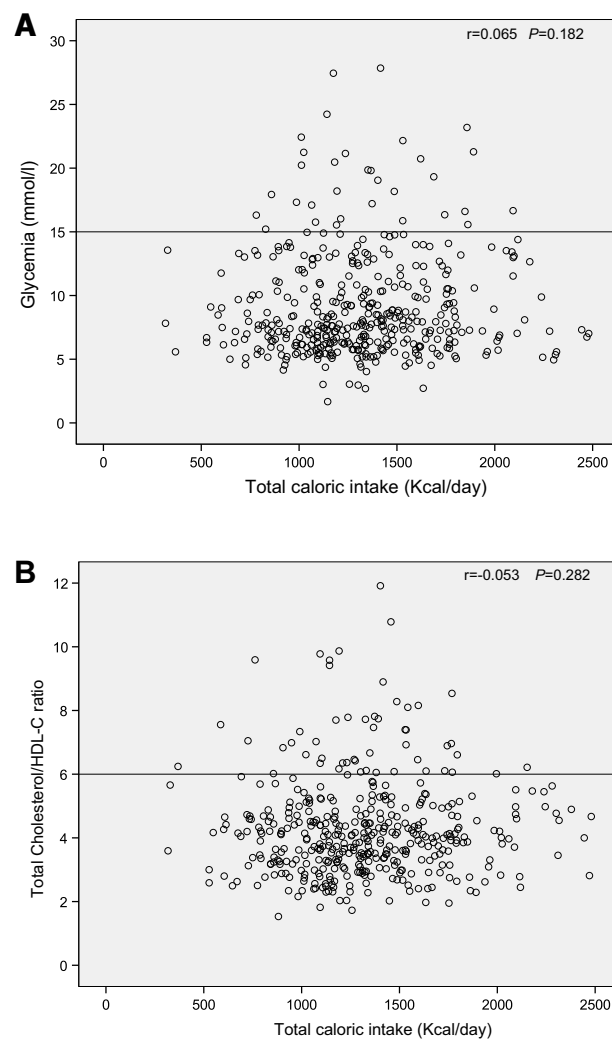


Figure 2 (A) Correlation between total caloric intake and glycemia. **(B)** Correlation between total caloric intake and total Cholesterol/HDL-C ratio.

However, the fasting period itself is marked by a transient disturbance of metabolic parameters, which urges caution when deciding whether high risk individuals should fast or not. A specific monitoring should be implemented. It should be started before the beginning of the Ramadan and continued after the holy month.

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Disclosure

The authors declare no conflicts of interest in regard to this work.

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