



Review

Impact of intermittent fasting on the lipid profile: Assessment associated with diet and weight loss

Heitor O. Santos ^{a,*}, Rodrigo C.O. Macedo ^b^a School of Medicine, Federal University of Uberlandia (UFU), Uberlandia, Minas Gerais, Brazil^b University of Santa Cruz do Sul (UNISC), Santa Cruz do Sul, Brazil

ARTICLE INFO

Article history:

Received 6 January 2018

Accepted 8 January 2018

Keywords:

Fasting

Lipids

Clinical analysis

Diet

ABSTRACT

Intermittent fasting, whose proposed benefits include the improvement of lipid profile and the body weight loss, has gained considerable scientific and popular repercussion. This review aimed to consolidate studies that analyzed the lipid profile in humans before and after intermittent fasting period through a detailed review; and to propose the physiological mechanism, considering the diet and the body weight loss. Normocaloric and hypocaloric intermittent fasting may be a dietary method to aid in the improvement of the lipid profile in healthy, obese and dyslipidemic men and women by reducing total cholesterol, LDL, triglycerides and increasing HDL levels. However, the majority of studies that analyze the intermittent fasting impacts on the lipid profile and body weight loss are observational based on Ramadan fasting, which lacks large sample and detailed information about diet. Randomized clinical trials with a larger sample size are needed to evaluate the IF effects mainly in patients with dyslipidemia.

© 2018 European Society for Clinical Nutrition and Metabolism. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Human fasting is considered as food abstinence and even beverages between 4 h to three weeks [1,2]. Practical application of human fasting encompasses the pre-analytical phase of several laboratory testing, preoperative and postoperative which the discontinuation of intake is necessary, as gastrointestinal trauma [2–6].

Intermittent fasting (IF) is a restricted feeding period originates in religious and spiritual traditions [7]. The most studied type of IF occurs in the holy month of Ramadan, which is a period that millions of Muslims abstain from caloric and water intake from sunrise to sunset. On average, the Ramadan day is divided in 12 h of fasting and 12 h of non-fasting [7]. Other types of IF are also studied, such as alternate day fasting – e.g., 1 day or more a week fasting – and IF with a longer fasting period during the day, for example, 16 h of fasting for 8 h of non-fasting [1]. These types of IF do not require restriction of water intake because they have no connection with religion [8–10].

IF has gained considerable scientific and popular repercussion, being introduced as a feeding method under certain conditions in the clinical practice. Studies that elaborate pathways created on the basis of the animal experiments may lead to overestimation of IF

regarding biochemical markers, such as the traditional lipid profile – including high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol and triglycerides [11,12].

IF can be considered an energy deficit protocol that leads to lipid profile improve by energy deficit and/or body weight reduction [13]. Hence, the caloric intake and weight loss evaluations are important to investigate the biological effects of IF on lipid profile. This review aimed to consolidate studies that analyzed the effects of IF on lipid profile in humans, emphasizing the physiological mechanisms.

2. Methods

A detailed literature research in English was carried with a view to identify relevant studies and to describe and consolidate observational and intervention data that provided parameters of the lipid profile through humans, such as HDL, VLDL, LDL, total cholesterol and triglycerides. In parallel, body weight and dietary information were also considered as data.

In order to improve the evidences regarding biological support, studies that used more detailed markers than the traditional lipid profile were also explored, thus suggesting physiological mechanisms to clarify the improvement of the lipid profile through IF. For this purpose, using the Pubmed, Cochrane and Web of Science databases, the following keywords were used: “Intermittent fasting”, “Ramadan”, “Alternate day fasting”, “lipid profile” and

* Corresponding author. Av. Pará, nº1720 Bloco 2U Campus, Umuarama, 38400-902, Uberlandia, MG, Brazil.

E-mail address: heitoroliveirasantos@gmail.com (H.O. Santos).

“intermittent fasting and human metabolic health”. The search for the data involved studies published until October 2, 2017.

3. To what extent can intermittent fasting affect the lipid profile in humans?

Intermittent fasting (IF) is a restricted feeding period emerged from religious and spiritual traditions [7]. The most studied type of IF occurs in the holy month of Ramadan. In the meantime, millions of Muslims cease foods and beverages consumption from sunrise to sunset. Overall, Ramadan day consist in 12 h fasting and 12 h feeding [7].

Besides Ramadan, other types of IF are also studied. Alternate day fasting is a broad term so have several definitions. One day or two intervals days a week fasting are most extended examples [1,14,15]. The presence of caloric intake in the fasting day is controversial. Some studies consider high calorie restriction as a fasting day, for example, 25% ingestion of total caloric expenditure in one day, and caloric overcompensation intake on another day – i.e. non-fasting day [8,10]. An interest daily type of IF is 16 h fasting for 8 h feeding [1], however, there can be daily types with more fasting duration, as 16–20 h fasting for 4–8 h feeding. These types of IF do not require restriction of water intake because they have no connection with religion [8–10].

Weight loss methods are important for lipid profile improvement. There is an important link between obesity and dyslipidemia over pro-inflammatory gradient from adipose tissue. The pathophysiology of the typical dyslipidemia observed in obesity is multifactorial, in which overconsumption of calories is crucial [13]. Low-calorie diets can enhance the lipid profile [16]; likewise, IF can leads to lipid profile improve by energy deficit and/or body weight reduction [13].

Lipid profile improvement through IF can occur with or without changes in weight loss (Table 1). Observational studies based on Ramadan are the majority, undoubtedly exhibiting many limitations, such as the lack of food recall from calories to macronutrients (Table 1).

Comparing the pre and post IF period, HDL levels can increase between 1 and 14 mg/dL, LDL levels decrease between 1 and 47 mg/dL, total cholesterol levels decrease between 5 and 88 mg/dL and triglycerides levels decrease between 3 and 64 mg/dL (Table 1).

Although observational studies are the majority of IF research, there are randomized clinical trials showing enhanced lipid profile association with weight loss by virtue of IF program [8,10]. Klempel et al. tested two types of alternate day fasting: 1) High-fat, Low-Carb diet; 2) Low-fat, High-Carb diet. They showed decreased cholesterol, LDL triglycerides and cholesterol, levels and body weight in both groups [8]. Recent study by Trepanowski et al. also tested High-fat, Low-Carb diet and Low-fat, High-Carb diet over alternate day fasting with greater follow-up, corresponding to six months. In contrast to Klempel et al., authors found just improves in HDL levels, while did not decrease LDL, triglycerides and cholesterol levels [10]. Moro et al. found lipid profile improvement in healthy resistance-trained males during two months of normocaloric IF. There was increased HDL and decreased LDL levels in the IF group, whereas normal diet group did not change [9].

4. Proposed mechanisms

The increase of tumor necrosis factor alpha (TNF- α) and several proinflammatory cytokines are associated with worsening of the lipid profile [17]. In the study by Unalacak et al. interleukin (IL)-2 and IL-8 and TNF- α levels were decreased after the period of Ramadan in eutrophic and obese, however, IL-1 and IL-6 levels weren't decreased. Although there was a decrease in the serum triglycerides

of both groups, the other markers of lipid profile did not change, therefore, being inaccurate to affirm that the decrease of TNF- α levels by IF impacts the improve of the lipid profile [18]. It is known that the antioxidant system is substantial in the lipid profile, thus modulating the lipoproteins [19–21]. However, glutathione, glutathione peroxidase and catalase analyzed in the red blood cells did not improve after Ramadan, according to a study by Ibrahim et al. [22]

IF may increase hepatic production of apolipoprotein A (apo A) and apolipoprotein B (apo B) [23,24]. By means of the apo A production, the serum HDL increases, since apo A is a precursor of HDL. The increase of the PPAR α expression is also responsible for the increase in the serum HDL. Through reducing apo B production the serum levels of VLDL, LDL and small and dense LDL (sdLDL) are decreased [25,26] (Fig. 1). In 1993, Maislos et al. analyzed the apo A – a percussive molecule of HDL, which increased after Ramadan and could be one of the mechanisms that supports the increase of HDL by IF [27]. Five years later, Maislos et al. analyzed the lipoprotein (a) – a harmful lipoprotein to the organism [28], which in turn did not change after Ramadan fasting [29]. In this way, Hammouda et al. also did not find alteration of lipoprotein (a) after Ramadan; in addition, they also did not find alterations of the C-reactive protein [24]. Adlouni et al. and Hammouda et al. found an increase of the Apo AI and a decrease of the apo B after Ramadan, reflecting the HDL increase and LDL reduction [23,24]. Akanji et al. also found an increase of the apo AI after Ramadan, however, it wasn't observed neither increase in HDL nor decrease in apo B in patients with dyslipidemia [30].

Klempel et al. measured LDL subtypes. At the end of two months of alternate day fasting, the diameter of the LDL subtypes increased, whereas there was decrease of the serum levels of sdLDL [8], which is beneficial in the cardiovascular scope, because the lower the LDL, the more susceptible to arterial penetration [21,31].

All things considered, the mechanisms that justify the improvement of the lipid profile through IF are not surprising. Probably the mechanism of IF for the improvement of lipoproteins, cholesterol and serum triglycerides are similar to the classics that occur through fat mass loss (Figs. 1 and 2). Above all, dietary quality should be considered. The type of normocaloric or hypocaloric IF improves lipoproteins by greater efficacy of fatty acid oxidation and modulation of apolipoproteins [8,23,24]. In the liver, the oxidation of fatty acids is increased through higher expression of peroxisome proliferator-activated receptor alpha (PPAR α) and peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1 α) in the fasting state [26]. Through increase of fatty acid oxidation in the liver, the accumulation of triglycerides in the hepatocytes decreases, thus decreasing the production of very low density lipoprotein (VLDL). By means of decreasing the VLDL production thus reducing levels of VLDL and TG in the bloodstream, Since apo B composes VLDL, serum apo B levels are also reduced [13,32]. Through reducing these factors that involve VLDL, consequently the LDL and sdLDL are also reduced. In parallel, serum apo B levels are also reduced, for apo B is part of LDL as well as sdLDL and VLDL [21] (Fig. 1).

IF may also decrease the expression of cholesteryl ester transfer protein (CETP) when associated with fat mass loss [33]. The CETP is a protein responsible for transferring cholesterol esters from HDL to VLDL, being responsible for lowering HDL levels and increasing VLDL levels. Therefore, the decrease in CETP through fasting can be another fact that can increase HDL [34,35] (Fig. 1).

Inherent in the improvement of serum cholesterol, the probable mechanism of fasting and cholesterol reduction occurs by means of enzymatic action. Fasting decreases the expression of sterol regulatory element-binding protein 2 (SREBP-2) [36], diminishing the action of several enzymes responsible for cholesterol synthesis [37,38] (Fig. 2).

Table 1
Impact on lipid profile and body weight in comparison to pre and post intermittent fasting.

Study	Participants (n)	Duration (month)	Type of intermittent fasting	Diet composition (CHO:FAT:PROT)	Outcomes	Type of study
Adlouni et al., 1997 [39]	32 health men	1	12 h fasting/12 h feeding	52:33:15	HDL: ↑ 14% (5 mg/dL) LDL: ↓ 12% (14 mg/dL) TC: ↓ 25% (38 mg/dL) TG: ↓ 30% (27 mg/dL) BW: ↓ 2.4% (1.7 kg)	Observational
Afrasiabi et al., 2003 [40]	22 men	1	12 h fasting/12 h feeding. Low fat and hypocaloric diet	62:24:14	HDL: ↑ 12% (5 mg/dL) LD: ↔ TC: ↔ TG: ↓ 13% (34 mg/dL) BW: ↓ 1.6% (1.4 kg)	Non-randomized controlled trial
Afrasiabi et al., 2003 [40]	16 men	1	12 h fasting/12 h feeding. Without any special diet interference	61:26:13	HDL: ↔ LDL: ↔ TC: ↔ TG: ↓ 27% (64 mg/dL) BW: ↔	Non-randomized controlled trial
Aksungar et al., 2005 [55]	12 health men	1	12 h fasting/12 h feeding	‡	HDL: ↑ 14% (7 mg/dL) LDL: ↔ TC: ↔ TG: ↔ BW: ↔	Observational
Aksungar et al., 2005 [55]	12 health women	1	12 h fasting/12 h feeding	‡	HDL: ↑ 16% (9 mg/dL) LDL: ↔ TC ↔ TG: ↔ BW: ↔	Observational
Akanji et al., 2000 [30]	31 dyslipidemic women	1	12 h fasting/12 h feeding	‡	HDL: ↔ LDL: ↔ TC: ↔ TG: ↔ BW: ↔	Observational
Akanji et al., 2000 [30]	33 dyslipidemic men	1	12 h fasting/12 h feeding	‡	HDL: ↔ LDL: ↔ TC: ↔ TG: ↔ BW: ↔	Observational
Akaberi et al., 2014 [56]	43 (22 men and 21 women)	1	12 h fasting/12 h feeding	‡	HDL: ↑ 27% (9 mg/dL) LDL: ↔ TC: ↔ TG: ↔	Observational
Ara et al., 2016 [41]	61 health men	1	12 h fasting/12 h feeding	‡	LDL: ↓ 7% (7 mg/dL) TC: ↓ 5% (8 mg/dL) BW: ↓ 4.1% (2.5 kg)	Observational
Bilto, 1998 [57]	43 (34 men and 9 women) health	1	12 h fasting/12 h feeding	‡	HDL: ↓ 18% (9 mg/dL) LDL: ↓ 16% (19 mg/dL) TC: ↓ 14% (27 mg/dL) TG: ↔ BW: ↔	Observational
Fakhrzadeh et al., 2003 [58]	41 health women	1	12 h fasting/12 h feeding	‡	HDL: ↑ 29% (14 mg/dL) LDL: ↓ 37% (47 mg/dL) TC: ↓ 29% (59 mg/dL) TG: ↓ 19% (25 mg/dL) BW: ↔	Observational
Fakhrzadeh et al., 2003 [58]	50 health men	1	12 h fasting/12 h feeding	‡	HDL: ↑ 23% (9 mg/dL) LDL: ↓ 36% (43 mg/dL) TC: ↓ 24% (43 mg/dL) TG: ↓ 37% (44 mg/dL) BW: ↔	Observational
Gur et al., 2015 [59]	78 health pregnant	1	12 h fasting/12 h feeding	57:25:18	HDL: ↑ 9% (6 mg/dL) LDL: ↔ TC: ↔ TG: ↔ BW: ↔	Observational
Hammouda et al., 2013 [24]	15 athletes men	1	12 h fasting/12 h feeding	55:32:13	HDL: ↑ 3% (1 mg/dL) LDL: ↓ 2% (1 mg/dL) TC: ↔ TG: ↓ 3% (3 mg/dL) BW: ↓ 4% (2.4 kg)	Observational
Attarzadeh Hosseini and Hejazi, 2013 [60]	13 physically active health men	1	12 h fasting/12 h feeding	‡	HDL: ↑ 5% (2 mg/dL) LDL: ↓ 4% (4 mg/dL) TC: ↓ 3% (5 mg/dL) TG: ↔	Observational

Table 1 (continued)

Study	Participants (n)	Duration (month)	Type of intermittent fasting	Diet composition (CHO:FAT:PROT)	Outcomes	Type of study
Attarzadeh Hosseini and Hejazi, 2013 [60]	13 sedentary men	1	12 h fasting/12 h feeding	‡	HDL: ↑ 3% (1 mg/dL) LDL: ↓ 9% (11 mg/dL) TC: ↓ 5% (10 mg/dL) TG: ↔	Observational
Ibrahim et al., 2008 [22]	14 (9 men and 4 women) health	1	12 h fasting/12 h feeding	56:30:14	TC: ↔ TG: ↓ 11% (13 mg/dL) BW: ↔	Observational
Kassab et al., 2003 [46]	6 eutrophic women	1	12 h fasting/12 h feeding	‡	TC: ↔ TG: ↔ BW: ↔	Observational
Kassab et al., 2003 [46]	18 obese women	1	12 h fasting/12 h feeding	‡	TC: ↔ TG: ↔ BW: ↔	Observational
Klempel et al., 2013 [8]	17 obese women	2	Alternate days of high fat intermittent fasting	40:45:15	HDL: ↔ LDL: ↔ TC: ↓ 13% (26 mg/dL) TG: ↓ 15% (15 mg/dL) BW: ↓ 5% (4.3 kg)	Randomized clinical trial
Klempel et al., 2013 [8]	18 obese women	2	Alternate days of low fat intermittent fasting	60:25:15	HDL: ↔ LDL: ↓ 25% (28 mg/dL) TC: ↓ 16% (31 mg/dL) TG: ↓ 14% (14 mg/dL) BW: ↓ 4% (3.7 kg)	Randomized clinical trial
Maislos et al., 1993 [27]	24 (16 men and 8 women) health	1	12 h fasting/12 h feeding	‡	HDL: ↑ 32 (9 mg/dL) LDL: ↔ TC: ↔ TG: ↔ BW: ↔	Observational
Maislos et al., 1998 [29]	22 (14 men and 8 women) health	1	12 h fasting/12 h feeding	65:14:21	HDL: ↑ 26% (9 mg/dL) LDL: ↔ TC: ↔ TG: ↔ BW: ↔	Observational
Mirzaei et al., 2012 [42]	14 athletes men	1	12 h fasting/12 h feeding	‡	HDL: ↑ 4% (2 mg/dL) LDL: ↓ 20% (20 mg/dL) TC: ↓ 9% (15 mg/dL) TG: ↔ BW: ↓ 2% (1.65 kg)	Observational
Moro et al., 2016 [9]	17 resistance-trained men	2	16 h fasting/8 h feeding	51:25:24	HDL: ↑ 7% (4 mg/dL) LDL: ↔ TC: ↔ TG: ↓ 7% (8 mg/dL) BW: ↔	Randomized clinical trial
Nematy et al., 2012 [61]	82 (34 men and 44 women) metabolic syndrome	1	12 h fasting/12 h feeding	52:34:14	HDL: ↑ 12% (5 mg/dL) LDL: ↓ 12% (13 mg/dL) TC: ↓ 5% (9 mg/dL) TG: ↓ 19% (42 mg/dL) BW: ↔	Observational
Ramadan et al., 1999 [62]	7 health men	1	12 h fasting/12 h feeding	‡	TC: ↔ TG: ↔ BW: ↔	Observational
Ramadan et al., 1999 [62]	6 physically active health men	1	12 h fasting/12 h feeding	‡	TC: ↔ TG: ↔ BW: ↔	Observational
Sadiya et al., 2011 [43]	19 (14 women and 5 men) metabolic syndrome	1	12 h fasting/12 h feeding	45:42:13	HDL: ↔ LDL: ↔ TC: ↔ TG: ↔ BW: ↓ 2% (1.8 kg)	Observational
Salehi and Neghab, 2007 [44]	28 overweight men	1	12 h fasting/12 h feeding	70:16:14	TC: ↓ 38% (88 mg/dL) TG: ↔ BW: ↓ 6% (5.1 kg)	Observational
Temizhan et al., 2000 [63]	25 health men	1	12 h fasting/12 h feeding	‡	HDL: ↔ LDL: ↔ TC: ↓ 8% (15 mg/dL) TG: ↔	Observational
Temizhan et al., 2000 [63]	27 health women	1	12 h fasting/12 h feeding	‡	HDL: ↔ LDL: ↓ 12% (15 mg/dL) TC: ↓ 10% (20 mg/dL) TG: ↓ 28% (26 mg/dL)	Observational
Trepanowski et al., 2017 [10]	25 [†] obese	6	Alternate days fasting	55:30:15	HDL: 11% (6 mg/dL) LDL: ↔ TC: ↔ TG: ↔ BW: ↓ 7% (6.5 kg)	Randomized clinical trial

(continued on next page)

Table 1 (continued)

Study	Participants (n)	Duration (month)	Type of intermittent fasting	Diet composition (CHO:FAT:PROT)	Outcomes	Type of study
Unalacak et al., 2011 [18]	10 obese men	1	12 h fasting/12 h feeding	‡	HDL: ↔ LDL: ↔ TC: ↔ TG: ↓ 15% (22 mg/dL) BW: ↓ 3% (2.9 kg)	Observational
Unalacak et al., 2011 [18]	10 eutrophics men	1	12 h fasting/12 h feeding	‡	HDL: ↔ LDL: ↔ TC: ↔ TG: ↔ BW: ↔	Observational
Ziaee et al., 2006 [45]	41 health men	1	12 h fasting/12 h feeding	‡	HDL: ↓ 11% (4 mg/dL) LDL: ↔ TC: ↔ TG: ↔ BW: ↓ 2% (1.2 kg)	Observational
Ziaee et al., 2006 [45]	39 health women	1	12 h fasting/12 h feeding	‡	HDL: ↔ LDL: ↔ TC: ↔ TG: ↔ BW: ↓ 2% (1.1 kg)	Observational

BW, body weight; CHO, carbohydrates; HDL, high density lipoprotein; LDL, low density lipoprotein; PROT, protein; TC, Total cholesterol; TG, triglycerides; †, gender not specified after final sample; ‡, not analyzed data by the study; †, statistical significance of increased levels; ↓, statistical significance of decreased levels; ↔, not statistical significance.

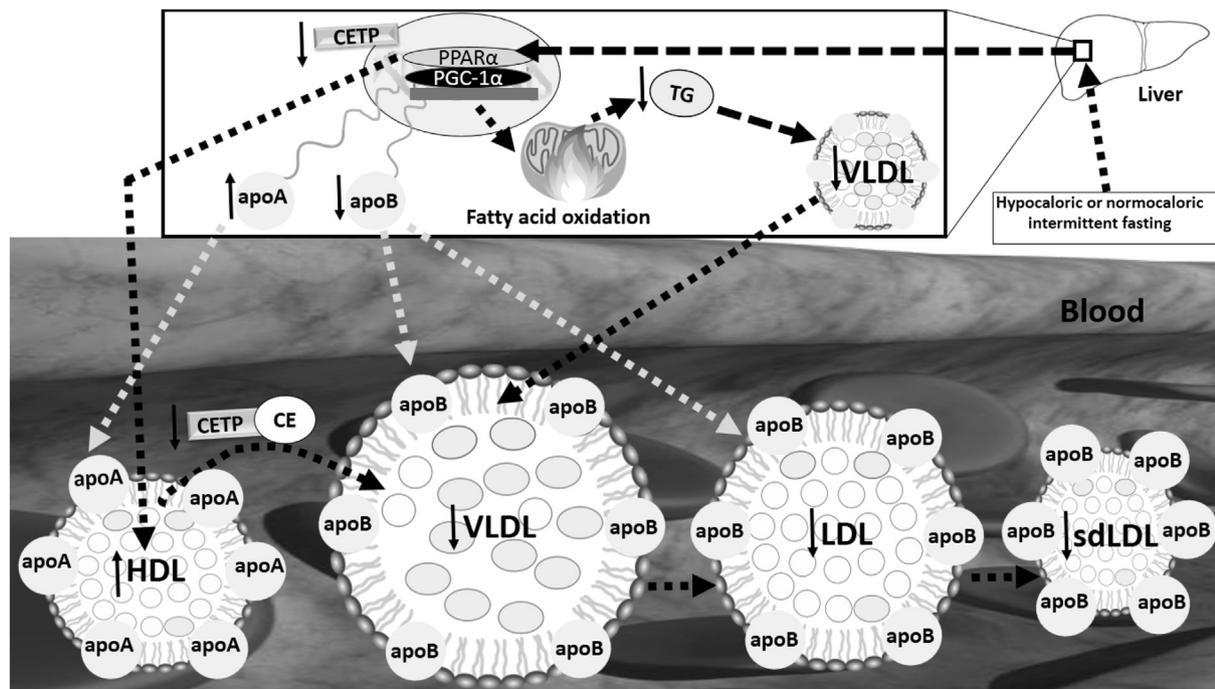


Fig. 1. Proposed mechanisms for the increase of HDL and decrease of the lipoproteins directly related to LDL through intermittent fasting. Lipid profile improvement over intermittent fasting is caused by molecules modulation in the liver. Nuclear expression of PPAR α and PGC-1 α primarily occurs, which leads to increased fatty acid oxidation and apoA production, whereas apoB decreases. Boosted fatty acid oxidation leads to the decreased hepatic triglycerides, hence decreasing VLDL production and serum levels of VLDL, LDL and sdLDL. Increased HDL levels are due to raised apoA production. As a result of decreased VLDL, LDL and sdLDL levels, there is loss of transported cholesterol and triglycerides within them, which reflects in reduction of serum cholesterol and triglycerides through intermittent fasting. ApoA, apolipoprotein A; apoB, apolipoprotein B; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; HDL, high density lipoprotein; LDL, low density lipoprotein; PGC-1 α , Peroxisome proliferator-activated receptor-gamma coactivator 1-alpha; PPAR α , Peroxisome proliferator-activated receptor alpha; TG, triglycerides; VLDL, very low density lipoprotein. Dotted express transport and metabolic actions; solid arrows indicate changes in the lipoprotein levels.

5. Weight loss analysis

Regarding the dietary intake and weight loss, when comparing the pre and post IF periods showed in Table 1, eleven studies had a significant decrease in the body weight, which changed between 1.1 and 6.5 kg [8,10,18,24,39–45]. Interventions resulted in a greater

decrease of body weight, as the Klempel et al. and Trepanowski et al. studies, both occurring during 2 and 6 months, respectively [8,10].

Within the groups that analyzed the changes of the fat mass after the IF (Table 2), six of them showed statistical significance in the decrease when compared to the baseline [8–10,42,46]. Two

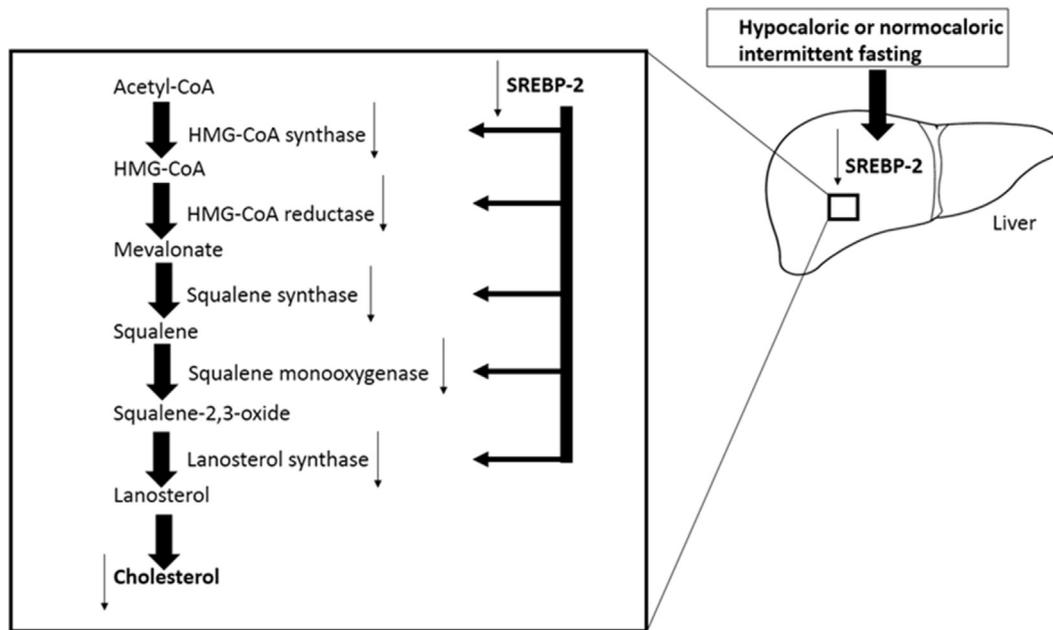


Fig. 2. Proposed mechanisms for the decrease of the cholesterol through intermittent fasting. Adapted from Shibata et al. [37]. SREBP-2, Sterol regulatory element-binding protein 2.

Table 2
Changes of body weight and body fat pre and post intermittent fasting.

Study	Participants (n)	Duration (month)	Body fat pre and post intermittent fasting (kg)	Body fat change between pre and post intermittent fasting	Used method for analyzing body fat
Trepanowski et al., 2017 [10]	25† obese	6	38 → 33.8*	↓4.8	DXA
Moro et al., 2016 [9]	17 resistance-trained men	2	10.9 → 9.3*	↓1.62	DXA
Klempel et al., 2013 [8]	17 obese women	2	44.4 → 39.0*	↓5.4	DXA
Klempel et al., 2013 [8]	18 obese women	2	44.7 → 39.5*	↓4.2	DXA
Kassab et al., 2003 [46]	6 eutrophic women	1	34.9 → 31.3*	↓3.6	Bioelectrical impedance
Kassab et al., 2003 [46]	18 obese women	1	17.7 → 17.5	↓0.2	Bioelectrical impedance
Ibrahim et al., 2008 [22]	14 (9 men e 4 women) health	1	21.7 → 22.1	↑0.4	Bioelectrical impedance
Mirzaei et al., 2012 [42]	14 athletes men	1	10.3 → 9.3*	↓1.0	Bioelectrical impedance
Sadiya et al., 2011 [43]	19 (14 women e 5 men) metabolic syndrome	1	50.0 → 49.5	↓0.5	Bioelectrical impedance
Hammouda et al., 2013 [24]	15 athletes men	1	10.8 → 10.1	↓0.7	Bioelectrical impedance

*, statistical significance considered for $p < 0.05$ before and after intermittent fasting as used in the original study; †, gender not specified after final sample; DXA, Dual-energy X-ray absorptiometry; †, increased levels; ↓, decreased levels.

studies that showed a decrease in the fat mass after Ramadan found a reduction of 1 kg and 3.6 kg [42,46], whereas the largest decrease of fat mass was evidenced in the group of the Klempel et al. [8].

6. Cardiovascular outcome

Analysis of cardiovascular disease outcomes is paramount for a better assessment of the lipid profile through IF. To this end, from a total 448 patients in a study that evaluated the cardiovascular risk potential, 122 patients periodically practiced religious fasting, and there was a 54% reduction in the risk of coronary artery disease in subjects who followed the periodic fasting, a value obtained after multivariate adjustment for age, sex, body mass index, dyslipidemia, diabetes, smoking, and family history [47].

On the other hand, in a recent cross-sectional study with a large sample ($n = 4052$), the non-breakfast individuals had a higher risk of atherosclerosis compared to those who ingested high-calorie for breakfast (>20% of daily calorie intake). However, non-breakfast patients, when compared to the high caloric intake group of

this meal, exhibited unfavorable parameters, such as: higher percentage of central obesity, body weight, body mass index, waist circumference, dyslipidemia and glycemia; they were older, with a higher percentage of women and smokers; ingested more daily calories, animal protein, total fat, cholesterol, processed foods and alcoholic beverage; and, they ate less dietary fiber, vegetables and whole grains [48]. In the sight of this, it is hasty to say that food deprivation at breakfast leads to cardiovascular events.

7. Clinical practice: strong points and limitations

Reviews that highlight IF as an effective method for lipid profile control have not made explicit the value of lipid profile markers and dietary data [7,49]. To avoid incomprehension and improve the interpretation of this review: we standardized all units of the lipid profile in mg/dL through classical equations [50], analyzed the loss of body weight and feeding before and soon after the IF period; since it is a consensus that weight loss, calorie deficit and dietary quality interfere in the variation of the lipid profile [17,51,52].

Furthermore, it is a consensus that women exhibit a more favorable profile than men – mainly the HDL – [53,54], and this review provide the assessment of the lipid profile of both genders through Table 1.

IF can improve the lipid profile in humans but is necessary to consider the duration, gender and weight loss. Taken together, this review included these considerations (Tables 1 and 2) in order to provide better consciousness of physiological variations.

Importantly, one fact to be considered is the use of medicines, especially lipid-lowering drugs. The majority of studies selected in this review did not use drugs and most subjects were healthy. Only the study by Akanji et al. analyzed IF in patients who were using the lipid-lowering drug, such as statins and fibrates, since the patients were dyslipidemic [30]. Akanji et al. did not find improvement in the lipid profile in both men and women [30] (Table 1), therefore it is hasty to consider IF as the main method for the dyslipidemia control – this should not be considered a treatment to substitute the use of lipid-lowering drugs.

Analyzing the lipid profile after IF follow-up is essential to understand the repercussion of this dietary method in the lipid profile. Of the few studies that verified the lipid profile after 1 month of the IF period (Table 1), increased HDL levels remained the same after 1 month of the Ramadan fasting by Aksungar et al. and Adlouni et al. studies [39,55].

A limitation of this review is not to have amplified a specific systematization for the inclusion of scientific articles.

8. Conclusion

IF may be a dietary method to aid in the improvement of the lipid profile in healthy, obese and dyslipidemic men and women, reducing total cholesterol, LDL, triglycerides and increasing HDL levels. However, the majority of studies that analyze the IF impacts on the lipid profile and body weight loss are observational and lack detailed information about diet. Randomized clinical trials with a larger sample size are needed to evaluate the IF effects mainly in patients with dyslipidemia.

Statement of authorship

HOS wrote the manuscript and carried out the conception and design of the study. RCOM participated in the interpretation of the data, wrote, and contributed to the revision of the manuscript.

Conflict of interest

None.

Statement and funding sources

None.

Acknowledgements

None.

References

- [1] Longo VD, Mattson MP. Fasting: molecular mechanisms and clinical applications. *Cell Metabol* 2014 Feb 4;19(2):181–92.
- [2] Lima-Oliveira G, Volanski W, Lippi G, Picheth G, Guidi GC. Pre-analytical phase management: a review of the procedures from patient preparation to laboratory analysis. *Scand J Clin Lab Invest* 2017 May;77(3):153–63.
- [3] Kackov S, Simundic A-M, Gatti-Drnic A. Are patients well informed about the fasting requirements for laboratory blood testing? *Biochem Med* 2013 Oct 15;23(3):326–31.
- [4] Stanga Z, Brunner A, Leuenberger M, Grimble RF, Shenkin A, Allison SP, et al. Nutrition in clinical practice—the refeeding syndrome: illustrative cases and guidelines for prevention and treatment. *Eur J Clin Nutr* 2008 Jun;62(6):687–94.
- [5] Ellis LM, Copeland EM, Souba WW. Perioperative nutritional support. *Surg Clin North Am* 1991 Jun;71(3):493–507.
- [6] Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F, et al. ESPEN guidelines on parenteral nutrition: surgery. *Clin Nutr Edinb Scotl* 2009 Aug;28(4):378–86.
- [7] Trepanowski JF, Bloomer RJ. The impact of religious fasting on human health. *Nutr J* 2010 Nov 22;9:57.
- [8] Klempel MC, Kroeger CM, Varady KA. Alternate day fasting increases LDL particle size independently of dietary fat content in obese humans. *Eur J Clin Nutr* 2013 Jul;67(7):783–5.
- [9] Moro T, Tinsley G, Bianco A, Marcolin G, Pacelli QF, Battaglia G, et al. Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males. *J Transl Med* 2016 Oct 13;14:290.
- [10] Trepanowski JF, Kroeger CM, Barnosky A, Klempel MC, Bhutani S, Hoddy KK, et al. Effect of alternate-day fasting on weight loss, weight maintenance, and cardioprotection among metabolically healthy obese adults: a randomized clinical trial. *JAMA Intern Med* 2017 Jul 1;177(7):930–8.
- [11] Martin B, Mattson MP, Maudsley S. Caloric restriction and intermittent fasting: two potential diets for successful brain aging. *Ageing Res Rev* 2006 Aug;5(3):332–53.
- [12] Patterson RE, Laughlin GA, LaCroix AZ, Hartman SJ, Natarajan L, Senger CM, et al. Intermittent fasting and human metabolic health. *J Acad Nutr Diet* 2015 Aug;115(8):1203–12.
- [13] Klop B, Elte JWF, Castro Cabezas M. Dyslipidemia in obesity: mechanisms and potential targets. *Nutrients* 2013 Apr 12;5(4):1218–40.
- [14] Longo VD, Panda S. Fasting, circadian rhythms, and time-restricted feeding in healthy lifespan. *Cell Metabol* 2016 Jun 14;23(6):1048–59.
- [15] Mattson MP. Challenging oneself intermittently to improve health. *Dose Response* 2014 Oct 20;12(4):600–18.
- [16] Fothergill E, Guo J, Howard L, Kerns JC, Knuth ND, Brychta R, et al. Persistent metabolic adaptation 6 years after “The Biggest Loser” competition. *Obesity* 2016 Aug 1;24(8):1612–9.
- [17] Alexander RW. President’s address: common mechanisms of multiple diseases: why vegetables and exercise are good for you. *Trans Am Clin Climatol Assoc* 2010;121:1–20.
- [18] Unalacak M, Kara IH, Baltaci D, Erdem O, Bucaktepe PGE. Effects of Ramadan fasting on biochemical and hematological parameters and cytokines in healthy and obese individuals. *Metab Syndrome Relat Disord* 2011 Apr;9(2):157–61.
- [19] Rosenson RS, Brewer HB, Ansell BJ, Barter P, Chapman MJ, Heinecke JW, et al. Dysfunctional HDL and atherosclerotic cardiovascular disease. *Nat Rev Cardiol* 2016 Jan;13(1):48–60.
- [20] Lüscher TF, Landmesser U, von Eckardstein A, Fogelman AM. High-density lipoprotein: vascular protective effects, dysfunction, and potential as therapeutic target. *Circ Res* 2014 Jan 3;114(1):171–82.
- [21] Krauss RM. Dietary and genetic probes of atherogenic dyslipidemia. *Arterioscler Thromb Vasc Biol* 2005 Nov 1;25(11):2265–72.
- [22] Ibrahim WH, Habib HM, Jarrar AH, Al Baz SA. Effect of Ramadan fasting on markers of oxidative stress and serum biochemical markers of cellular damage in healthy subjects. *Ann Nutr Metab* 2008;53(3–4):175–81.
- [23] Adlouni A, Ghalim N, Saïle R, Hda N, Parra HJ, Benslimane A. Beneficial effect on serum apo A1, apo B and Lp AI levels of Ramadan fasting. *Clin Chim Acta Int J Clin Chem* 1998 Mar 23;271(2):179–89.
- [24] Hammouda O, Chtourou H, Aloui A, Chahed H, Kallel C, Miled A, et al. Concomitant effects of Ramadan fasting and time-of-day on apolipoprotein AI, B, Lp-a and homocysteine responses during aerobic exercise in tunisian soccer players. *PLoS One* 2013 Nov 11;8(11) [Internet]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3823586/>.
- [25] Kingwell BA, Chapman MJ. Future of high-density lipoprotein infusion therapies: potential for clinical management of vascular disease. *Circulation* 2013 Sep 3;128(10):1112–21.
- [26] Wang Y-X. PPARs: diverse regulators in energy metabolism and metabolic diseases. *Cell Res* 2010 Feb;20(2):124–37.
- [27] Maislos M, Khamaysi N, Assali A, Abou-Rabiah Y, Zvili I, Shany S. Marked increase in plasma high-density-lipoprotein cholesterol after prolonged fasting during Ramadan. *Am J Clin Nutr* 1993 May;57(5):640–2.
- [28] Jacobson TA. Lipoprotein(a), cardiovascular disease, and contemporary management. *Mayo Clin Proc* 2013 Nov;88(11):1294–311.
- [29] Maislos M, Abou-Rabiah Y, Zvili I, Iordash S, Shany S. Gorging and plasma HDL-cholesterol—the Ramadan model. *Eur J Clin Nutr* 1998 Feb;52(2):127–30.
- [30] Akanji AO, Mojiminiyi OA, Abdella N. Beneficial changes in serum apo A-1 and its ratio to apo B and HDL in stable hyperlipidaemic subjects after Ramadan fasting in Kuwait. *Eur J Clin Nutr* 2000 Jun;54(6):508–13.
- [31] Siri-Tarino PW, Chiu S, Bergeron N, Krauss RM. Saturated fats versus polyunsaturated fats versus carbohydrates for cardiovascular disease prevention and treatment. *Annu Rev Nutr* 2015;35:517–43.
- [32] Jiang ZG, Robson SC, Yao Z. Lipoprotein metabolism in nonalcoholic fatty liver disease. *J Biomed Res* 2013 Jan;27(1):1–13.
- [33] Ebenbichler CF, Laimer M, Kaser S, Ritsch A, Sandhofer A, Weiss H, et al. Relationship between cholesteryl ester transfer protein and atherogenic

- lipoprotein profile in morbidly obese women. *Arterioscler Thromb Vasc Biol* 2002 Sep 1;22(9):1465–9.
- [34] Shinkai H. Cholesteryl ester transfer-protein modulator and inhibitors and their potential for the treatment of cardiovascular diseases. *Vasc Health Risk Manag* 2012;8:323–31.
- [35] Haas JT, Staels B. Cholesteryl-ester transfer protein (CETP): a Kupffer cell marker linking hepatic inflammation with atherogenic dyslipidemia? *Hepatology* 2015 Dec 1;62(6):1659–61.
- [36] Horton JD, Bashmakov Y, Shimomura I, Shimano H. Regulation of sterol regulatory element binding proteins in livers of fasted and refeed mice. *Proc Natl Acad Sci U S A* 1998 May 26;95(11):5987–92.
- [37] Shibata N, Jishage K, Arita M, Watanabe M, Kawase Y, Nishikawa K, et al. Regulation of hepatic cholesterol synthesis by a novel protein (SPF) that accelerates cholesterol biosynthesis. *FASEB J Off Publ Fed Am Soc Exp Biol* 2006 Dec;20(14):2642–4.
- [38] Tao R, Xiong X, DePinho RA, Deng C-X, Dong XC. Hepatic SREBP-2 and cholesterol biosynthesis are regulated by FoxO3 and Sirt6. *J Lipid Res* 2013 Oct;54(10):2745–53.
- [39] Adlouni A, Ghalim N, Benslimane A, Lecerf JM, Saïle R. Fasting during Ramadan induces a marked increase in high-density lipoprotein cholesterol and decrease in low-density lipoprotein cholesterol. *Ann Nutr Metab* 1997;41(4):242–9.
- [40] Afrasiabi A, Hassanzadeh S, Sattarivand R, Mahboob S. Effects of Ramadan fasting on serum lipid profiles on 2 hyperlipidemic groups with or without diet pattern. *Saudi Med J* 2003 Jan;24(1):23–6.
- [41] Ara T, Jahan N, Sultana N, Choudhury R, Yeasmin T. Effect of Ramadan fasting on total cholesterol (TC) low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) in healthy adult male. *J Bangladesh Soc Physiol* 2016 Mar 31;10(2):46–50.
- [42] Mirzaei B, Rahmani-Nia F, Moghadam MG, Ziyaolhagh SJ, Rezaei A. The effect of Ramadan fasting on biochemical and performance parameters in collegiate wrestlers. *Iran J Basic Med Sci* 2012 Nov;15(6):1215–20.
- [43] Sadiya A, Ahmed S, Siddieg HH, Babas IJ, Carlsson M. Effect of Ramadan fasting on metabolic markers, body composition, and dietary intake in Emiratis of Ajman (UAE) with metabolic syndrome. *Diabetes Metab Syndrome Obes Targets Ther* 2011 Dec 15;4:409–16.
- [44] Salehi M, Neghab M. Effects of fasting and a medium calorie balanced diet during the holy month Ramadan on weight, BMI and some blood parameters of overweight males. *Pak J Biol Sci PjBS* 2007 Mar 15;10(6):968–71.
- [45] Ziaee V, Razaeei M, Ahmadinejad Z, Shaikh H, Yousefi R, Yarmohammadi L, et al. The changes of metabolic profile and weight during Ramadan fasting. *Singap Med J* 2006 May;47(5):409–14.
- [46] Kassab SE, Abdul-Ghaffar T, Nagalla DS, Sachdeva U, Nayar U. Serum leptin and insulin levels during chronic diurnal fasting. *Asia Pac J Clin Nutr* 2003;12(4):483–7.
- [47] Horne BD, Muhlestein JB, Anderson JL. Health effects of intermittent fasting: hormesis or harm? A systematic review. *Am J Clin Nutr* 2015 Aug;102(2):464–70.
- [48] Uzhova I, Fuster V, Fernández-Ortiz A, Ordovás JM, Sanz J, Fernández-Friera L, et al. The importance of breakfast in atherosclerosis disease: insights from the PESA study. *J Am Coll Cardiol* 2017 Oct 2;70(15):1833–42.
- [49] Mazidi M, Rezaie P, Chaudhri O, Karimi E, Nematy M. The effect of Ramadan fasting on cardiometabolic risk factors and anthropometrics parameters: a systematic review. *Pak J Med Sci* 2015;31(5):1250–5.
- [50] Rugge B, Balshem H, Sehgal R, Relevo R, Gorman P, Helfand M. Lipid conversion factors [Internet]. US: Agency for Healthcare Research and Quality; 2011 [cited 2017 Oct 10]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK83505/>.
- [51] Medina-Remón A, Casas R, Tresserra-Rimbau A, Ros E, Martínez-González MA, Fitó M, et al. Polyphenol intake from a Mediterranean diet decreases inflammatory biomarkers related to atherosclerosis: a substudy of the PREDIMED trial. *Br J Clin Pharmacol* 2017 Jan;83(1):114–28.
- [52] Ros E, Hu FB. Consumption of plant seeds and cardiovascular health: epidemiological and clinical trial evidence. *Circulation* 2013 Jul 30;128(5):553–65.
- [53] Kolovou GD, Anagnostopoulou KK, Damaskos DS, Bilianou HI, Mihas C, Milionis HJ, et al. Gender differences in the lipid profile of dyslipidemic subjects. *Eur J Intern Med* 2009 Mar;20(2):145–51.
- [54] Wang X, Magkos F, Mittendorfer B. Sex differences in lipid and lipoprotein metabolism: it's not just about sex hormones. *J Clin Endocrinol Metab* 2011 Apr;96(4):885–93.
- [55] Aksungar FB, Eren A, Ure S, Teskin O, Ates G. Effects of intermittent fasting on serum lipid levels, coagulation status and plasma homocysteine levels. *Ann Nutr Metab* 2005 Apr;49(2):77–82.
- [56] Akaberi A, Golshan A, Moojidekanloo M, Hashemian M. Does fasting in Ramadan ameliorate lipid profile? A prospective observational study. *Pak J Med Sci* 2014;30(4):708–11.
- [57] Bilito YY. Effects of Ramadan fasting on body weight and the biochemical and haematological parameters of the blood. *Arab Gulf J Sci Res* 1998;16(1):1–14.
- [58] Fakhrazadeh H, Larijani B, Sanjari M, Baradar-Jalili R, Amini MR. Effect of Ramadan fasting on clinical and biochemical parameters in healthy adults. *Ann Saudi Med* 2003 Jul;23(3–4):223–6.
- [59] Gur E, Turan G, Ince O, Karadeniz M, Tatar S, Kasap E, et al. Effect of Ramadan fasting on metabolic markers, dietary intake and abdominal fat distribution in pregnancy. *Hippokratia* 2015;19(4):298–303.
- [60] Attarzadeh Hosseini SR, Hejazi K. The effects of Ramadan fasting and physical activity on blood hematological-biochemical parameters. *Iran J Basic Med Sci* 2013 Jul;16(7):845–9.
- [61] Nematy M, Alinezhad-Namaghi M, Rashed MM, Mozhdehifard M, Sajjadi SS, Akhlaghi S, et al. Effects of Ramadan fasting on cardiovascular risk factors: a prospective observational study. *Nutr J* 2012 Sep 10;11:69.
- [62] Ramadan J, Telahoun G, Al-Zaid NS, Barac-Nieto M. Responses to exercise, fluid, and energy balances during Ramadan in sedentary and active males. *Nutrition* 1999 Oct 1;15(10):735–9.
- [63] Temizhan A, Tandogan I, Dönderici Ö, Demirbas B. The effects of Ramadan fasting on blood lipid levels. *Am J Med* 2000 Sep 1;109(4):341.