Effect of Prolonged Fasting on Plasma Lipids, Lipoproteins and Apolipoprotein B in 12 Physicians Participating in a Hunger Strike: an Observational Study

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Key words: prolonged fasting. plasma lipoproteins, plasma lipids, obesity, hyperlipidemia, oral contraceptives

Abstract

Background: Dyslipidemia and obesity serve as risk factors for the development of atherosclerotic cardiovascular disease. Fasting is sometimes recommended for treating these conditions. This study was undertaken to try to resolve conflicting results reported in the literature.

Objectives: To study the effect of fasting (0 calories, with free intake of fluids) for 3–5 days on plasma concentration of triglyceride, cholesterol and apolipoprotein B.

Methods: Physicians, about to begin a hunger strike, were divided into four groups: normolipidemic non-obese men (group 1), two moderately obese men and two men with type IV hyperlipidemia (group 2), healthy non-obese women (group 3), and healthy non-obese women on oral contraceptives (group 4). Adherence to fasting was monitored daily by detailed interviews, loss of weight, drop in plasma glucose, presence of ketonuria, progressive rise in serum creatinine and uric acid, and decrease in plasma pH. We monitored their serum glucose, electrolytes, liver function, lipids, lipoproteins and apolipoprotein B on days 0, 3, and 5.

Results: Physicians who adhered to complete fasting lost more than 1.5% of their body weight after 3 days of fasting (n=12), and more than 3.2% at 5 days (n=5). All non-obese normolipidemic males and females (groups 1 and 3) showed an increase in plasma triglyceride (by 28–162%) and very low density lipoprotein cholesterol (by 22–316%) after 3 days of fasting. The obese and hyperlipidemic men (group 2) showed a decrease of 17–63% in their VLDL cholesterol, and the women on oral contraceptives (group 4) showed a 20% decrease in their plasma triglyceride on day 3. Low density lipoprotein cholesterol increased by 13% in group 2, decreased by 7.3% in group 4, and remained unchanged in group 1 and 3. Apolipoprotein B level correlated well with LDL cholesterol in all groups. High density lipoprotein cholesterol changes were inconsistent.

Conclusions: These results help to explain and reconcile previous published reports. The metabolic background of the individual together with the amount of energy consumed affect the behavior of plasma lipids and lipoproteins levels during fasting.

IMAJ 2000;2:215-219

VLDL = very low density lipoprotein
LDL = low density lipoprotein

Starvation affects the plasma concentration of lipids and lipoproteins. Previous studies have provided conflicting results: increase [1,2] and decrease [3–5] in plasma triglyceride, and increase [2,6–8] and decrease [3,5,9–11] in plasma cholesterol. Similar inconsistent results were obtained for high density lipoprotein cholesterol [2–4,8,12–14]. These contradictory reports may be explained in part by heterogeneity of the studied subjects, who differed in gender, body mass index [5,12–14], presence of hyperlipidemia [6,15,16], health status, and medications [3]. Moreover, these studies differed also in the amount of calories consumed: 0–1,000 kcal/day [1,2,5,7,8,10,11,13,14] and the physical activity of the participants: from bed rest [7] to a 50 km daily walk [4]. All these variables are known to affect plasma lipids and lipoprotein levels, and thus may also influence the response to fasting.

We had the opportunity to observe the effect of complete fasting (0 kcal/day) for 3–5 days on plasma lipids, lipoproteins and apolipoprotein B levels in 12 physicians participating in a national hunger strike. We divided the fasting individuals into subgroups according to gender, presence of obesity, hyperlipidemia, and consumption of oral contraceptives. Consequently, we were able to demonstrate different but specific changes in plasma lipids and lipoprotein levels during fasting in these subgroups. Furthermore, these results enabled us to reconcile most of the previously published reports.

Methods

Subjects

Hospital physicians, males and females aged 25–59, about to start a hunger strike volunteered for this study. All

underwent a detailed medical interview, physical examination and initial laboratory work-up, and were grouped into four subgroups. Twelve of them, who adhered to complete fasting for at least 3 days, are the subject of this study. The grouping was devised as follows. Groups 1 and 3 respectively comprised four men and two women who were non-obese (body mass index 21.6–25.5 and 23.6–24.5 kg/m^2, respectively), normotriglyceridemic (<200 mg/dl), healthy, and taking no medications. Group 2 consisted of two overweight men (BMI 28.7 and 37.7 kg/m^2), one of whom had hyperlipidemia (type II b) and was taking propranolol for hypertension, and two non-obese men (BMI 24.8, 25.8 kg/m^2) with type IV hyperlipidemia (one normotriglyceridemic following 3 months of a low carbohydrate diet). Group 4 comprised two healthy, non-obese normolipidemic women (BMI 17.4, 22.7 kg/m^2) who were taking oral contraceptives. Four of the subjects were smokers, two in group 1, one in group 2 and one in group 3. All were otherwise healthy and none of the subjects suffered from diabetes mellitus, thyroid, kidney or liver diseases.

Table 1. Compliance with fasting

		Males		Females	
			Obese	Oral contraceptives	
	Day	Normal (Group 1)	hyperlipidemic (Group 2)	No (Group 3)	Yes (Group 4)
N	3	4	4	2	2
	5	1	2	1	1
Initial weight (kg)	0	77.5±12.6	93.0±13.3	(63;65)	(44;64)
Body mass index (kg/m^2)	0	24.5±2.0	29.3±5.9	(23.6;24.5)	(17.4;22.7)
Weight change* (%)	3	97.1±0.4 (96.5–97.5)	97.0±0.6 (96.3–97.7)	(97.3;96.6)	(98.4;98.4)
	5	95.7	95.1	(94.4; -)	(- ; 96.8)
Glucose* (%)	3	85.9±9.2 (74.2–94.7)	79.5±9.1 (72.0–92.0)	(63.9;46.4)	78.9;87.0)
	5	88.2	85.4	(85.0; -)	(- ; 84.3)
Creatinine* (%)	3	124.2±11.8 (116.7–141.7)	125.1±4.3 (120.0–130.4)	(142.9;150.0)	111.1;112.5)
	5	127.3	134.6	(157.1; -)	(- ;125.0)
Uric acid* (%)	3	123.1±18.0 (104.9–141.0)	124.1±17.2 (107.5–145.2)	(188.6;175.9)	(107.3;110.7)
	5	172.1	146.7	(251.4; -)	(- ;185.1)
Venous pH	3	7.27±0.06 (7.21–7.35)	7.25±0.04 (7.19–7.29)	(7.22;7.19)	(7.29;7.32)
	5	7.25	7.27	(7.25; -)	(- ;7.29)
Ketonuria	3 & 5	+4	+4	+4	+4

* % of initial values; mean±SD (range)

All subjects ingested water and unsweetened tea or coffee, but consumed no calories throughout the study period of 3 to 5 days. They continued their daily activities in the hospital and maintained their medications and smoking habits. Their adherence to complete fasting was ascertained by daily interviews, weight loss, presence of ketonuria, and monitoring of blood glucose, creatinine, uric acid and pH.

Methods

Blood samples for lipid, lipoprotein and apolipoprotein analyses were obtained on day 0 after 12 hours fasting, and on days 3 and 5. At 8.00 a.m. 7 ml of blood was withdrawn from the antecubital vein into chilled tubes containing disodium EDTA (1 mg/ml final concentration). The plasma was separated promptly by centrifugation at 2,000 rpm for 20 min at 4°C. Aliquots of plasma were stored at –20°C for apo-B analysis and the remainder at 4°C for lipid and lipoprotein quantification. Lipoproteins were separated and quantified as published previously [17]. In brief, plasma samples were centrifuged at plasma density for 18 h at 39,000 rpm at 4°C in a Beckman 50.3 rotor, in a L-8 Beckman ultracentrifuge (Mountainview, CA, USA). The VLDL was removed by tube slicing. HDL cholesterol was quantified on the supernatant obtained after heparin-manganese precipitation and treatment with $NaHCO_3$ of the 1.006 g/ml infranatant. LDL-cholesterol was calculated from the cholesterol content of the 1.006 g/ml infranatant and the HDL-cholesterol (LDL = 1.006 g/ml infranatant cholesterol – HDL cholesterol).

Analytical methods

Plasma triglyceride was quantified by an enzymatic method (Biopack®, Biotrol laboratories, Paris, France). Plasma and lipoprotein cholesterol was quantified by a cholesterol oxidase method (Boehringer-Mannheim, Germany). All assays were carried out in triplicate with an intra-assay and interassay coefficient of variation of 3 and 8% for triglyceride and 2 and 4% for cholesterol, respectively. To minimize variability, all samples from each individual were ultracentrifuged, processed and analyzed on the same day (<6 days from blood drawing). Apo-B was quantified by radial immunodiffusion [17]. All samples were analyzed in triplicate on the same day with a coefficient of variation of 7%.

Data analysis

We used paired *t*-test, one way analysis of variance, and correlation coefficient by standard techniques [18].

Results

All subjects lost weight during the study period, 2.1±.8 and 3.8±1.2 kg (mean±SD) at days 3 and 5 respectively. When

BMI = body mass index

apo-B = apolipoprotein B

HDH = high density lipoprotein

expressed as percent of initial body weight, the mean weight reduction after 3 days of fasting was 2.9±0.5 and 2.3±0.9% in men and women respectively [Table 1]. Adherence to fasting was confirmed by persistent ketonuria, drop in plasma glucose and pH, and progressive rise in serum creatinine and uric acid [Table 1]. These parameters were similar among the subgroups, $P>0.5$ [Table 1].

Plasma triglyceride increased in all healthy men (Group 1) and women not taking oral contraceptives (group 3) [Tables 2 and 3]. After 3 days of fasting they rose by 38–162% and 28–52% in men and women respectively. In contrast, plasma triglyceride dropped by 2–56% in most of the obese and hypertriglyceridemic men (group 2), and by 16.5 and 24.5% in the women on oral contraceptives (group 4) [Table 3]. It is noteworthy that one patient, a treated type IV hyperlipidermic, behaved similarly to the normal individuals [Table 2]. The effect of fasting on plasma triglyceride in the whole study group showed no correlation with either the initial plasma triglyceride level, extent of weight loss or fasting serum glucose levels ($r<0.1$), and was most evident during the first 3 days. Five subjects fasting for an additional 2 days showed little or no change on day 5 compared to day 3 of fasting ($P>0.5$) [Table 2].

Fasting affected plasma cholesterol levels to a much lesser extent when compared with plasma triglyceride. VLDL-cholesterol correlated well with plasma triglyceride in all subgroups ($r=0.9$), and LDL-cholesterol levels correlated well with plasma cholesterol ($r=0.965$ and 0.987 for men and women respectively) [Tables 2 and 3]. Aside from a slight tendency for a decrease in HDL-cholesterol observed in group 1 ($P>0.5$), we observed no consistent changes in the other groups. No correlation could be demonstrated among the changes observed in lipoprotein cholesterol levels induced by fasting with either initial levels of lipids, lipoproteins and glucose or weight loss.

Changes in plasma apo-B level during fasting followed and maintained a good correlation with plasma LDL ($r=0.901$ for men and $r=0.944$ for women).

Table 2. Effect of fasting on plasma lipids lipoprotein cholesterol and apo-B (mg/dl)

	Triglyceride			Cholesterol												Apolipoprotein B		
				Total			VLDL			LDL			HDL					
Day	0	3	5	0	3	5	0	3	5	0	3	5	0	3	5	0	3	5
Males																		
Group 1																		
Patient 1	43	112	118	170	173	190	4	18	21	116	111	126	50	44	42	96	99	130
Patient 2	43	75	–	152	148	–	4	12	–	104	96	–	44	40	–	99	99	–
Patient 3	45	62	–	186	191	–	4	7	–	141	147	–	37	37	–	130	121	–
Patient 4	71	119	–	244	254	–	10	16	–	194	199	–	40	38	32	147	147	–
Group 2																		
Patient 1	142	140	136	206	216	221	32	27	26	139	158	167	34	31	27	147	137	165
Patient 2	251	194	147	314	330	320	63	41	27	219	250	261	32	39	32	182	245	200
Patient 3	247	108	–	233	246	–	44	17	–	151	185	–	37	44	–	156	169	–
Patient 4	73	84	–	218	220	–	14	11	–	178	182	–	27	28	–	134	160	–
Females																		
Group 3																		
Patient 1	59	76	76	184	219	224	9	10	10	126	143	172	49	55	45	107	130	125
Patient 2	68	104	–	198	189	–	7	13	–	135	136	–	56	40	–	121	130	–
Group 4																		
Patient 1	56	47	–	230	219	–	5	5	–	172	164	–	54	50	–	137	137	–
Patient 2	51	39	38	143	132	115	8	4	2	93	84	75	42	44	38	92	81	74

Table 3. Change in plasma lipids, lipoprotein cholesterol and apo-B after fasting for 72 hours*

	Triglyceride	Cholesterol Total	VLDL	LDL	HDL	Apolipoprotein B	
Males							
Group 1	185.3±53.1 (138.3–261.6)	101.4±3.0 (97.2–104.0)	263.1±116.0 (157.0–415.9)	9 7.9±4.9 (91.9–102.7)	94.4±6.5 (87.3–102.7)	99.1±4.2 (93.1–103.1)	(n=4)
Group 2	83.5±30.8 (46.6–115.0)	104.1±2.1 (101.1–105.5)	67.0±21.5 (37.4–83.3)	113.0±8.4 (102.0–122.4)	108.6±13.9 (90.9–121.4)	113.9±17.5 (93.2–134.6)	(n=4)
Females							
Group 3	140.3 (128.3;152.3)	107.1 (95.0;119.3)	153.9 (121.8;185.9)	107.2 (100.7;113.8)	91.3 (70.6;111.9)	114.4 (107.4;121.5)	(n=2)
Group 4	79.5 (75.5;83.5)	93.7 (92.0;95.3)	77.9 (53.7;102.1)	92.7 (89.6;95.8)	98.9 (93.3;104.5)	94.0 (88.0;100.0)	(n=2)

* % of initial values, mean±SD (range)

Discussion

Fasting for 3 to 5 days induced remarkable changes in plasma lipids, lipoproteins and apo-B in 12 physicians participating in a hunger strike. These changes were determined by body mass index, presence of hypertriglyceridemia and medication intake. Variability in these parameters may explain most discrepancies that were observed in previous studies [Table 4]. These studies differed also in the amount of energy ingested and the level of physical activity in the fasting subjects.

We observed that healthy non-obese normotriglyceridemic men and women showed a marked increase in plasma triglycerides (28–162%) and VLDL-cholesterol (22–316%) after fasting for 3 days. These findings are consistent with previous studies performed under similar conditions by Stout et al. [1], Rubin and Aladjem [19] and Markel et al. [2] who demonstrated a 54% increase in plasma triglycerides after 3 days of fasting and 23% increase in plasma VLDL after 4–5 days of fasting [Table 4]. In contrast, other studies by Ende [6], Carlson and Froberg [4], Wallentin and Skoldstam [3] and Vaisman et al. [10] demonstrated a decrease (26–59%) in plasma triglycerides and VLDL-cholesterol (14–28%). In the latter studies however, the subjects ingested 163–200 kcal/day mainly as carbohydrates. In addition, the group studied by Carlson and Froberg [4] walked 50 km/day during the study period, and 9 of their 12 subjects were vegetarians. The group studied by Wallentin and Skoldstam [3] included patients with rheumatoid arthritis who were taking anti-inflammatory medications. All these factors may have modulated the effects of fasting.

The observed increase in plasma triglycerides associated with complete fasting has been shown to result from increased synthesis, caused by enhanced influx of fatty acids to the liver induced by a decrease in plasma insulin, a rise in plasma glucagon growth hormone and catecholamines, and peripheral insulin resistance during fasting [1,20–23] On the other hand, obese subjects with elevated triglyceride levels in the non-fasting state caused by increased VLDL synthesis and secretion [24] show a drop in plasma triglycerides upon fasting or calorie restriction. Our findings are therefore consistent with the results obtained in most previous studies, some of which are listed in Table 4. Furthermore, it has been reported by Hendrikx et al. [25] that the direction of the observed change in plasma triglycerides during fasting is dependent on the pre-fast triglyceride levels. Normotriglyceridemic subjects showed an increase, whereas hypertriglyceridemic subjects showed a decrease in plasma triglycerides during a 7 day fast. The increased VLDL synthesis observed in obese subjects in the unfasted state depends upon elevated levels of insulin and provision of precursors from both tissue stores and food consumption [24]. During fasting or calorie restriction, both the lowered insulin levels and food deprivation result in lowered VLDL synthesis, leading to reduction of plasma triglyceride [24,26].

Consistent with previous observations, fasting healthy non-obese and normolipidemic subjects showed little change in plasma LDL-cholesterol [Table 4]. Both biosynthesis and secretion of cholesterol have been shown to decrease upon fasting [27,28], and small plasma increments have been

Table 4. Representative studies on the effect of fasting on concentration of plasma lipids and lipoproteins

	(Ref)	Subjects	Duration (days)	Intake (kcal/day)	Physical activity	Weight reduction*	TG*†	Cholesterol*			
								Total	VLDL	LDL	HDL
Non-obese, normolipidemic											
Rubin and Aladjem	[19]	3M & 3F	4–5	0	Normal	–			+23	+13	
Consolazio et al.	[7]	6M	6	0	Ward	6.5		+13			
Stout et al.	[1]	4M & 5F	3	0		5.2	+54	+4			
Ende	[6]	10M	3	163	Normal	3.5		+12			
		5F				5.4		+14			
Carlson and Froberg	[4]	12M†††	3	200	Heavy††	5.1	–59	–14	–78	–33	+18
			6			7.4	–38	–28	–78	–35	+15
Wallentin and Skoldstam	[3]	7(M & F)††††	10	200	Ward	5.0	–26	–21	–25	–27	–10
Present study		4M	3	0	Normal	2.9	+85	+1	+163	–2	–6
		2F	3	0		3.1	+40	+7	+54	+7	–9
Obese, normolipidemic											
Jackson et al.	[5]	5F	14	0	Minimal	8.7	–39	–8			
Sorbis et al.	[12]	14M & F	35	240		10.0	–42	–15		–21	+25
Zimmerman et al.	[14]	7M	7	1000	Normal	–	–37	–7		+1	–12
		7F					–40	–5		–3	–2
Obese, hyperlipidemic											
Ende	[6]	4M & 2F	3	163	Normal			+10			
			6					+25			
Olefsky et al.	[15]	44(M & F)	8–40	600–1600		12	–43	–21			
Kudchodkar et al.	[16]	5M	9–12	330–2027			–41	–11			
Present study et al.		4M	3	0	Normal	3.0	–16	+4	–33	+13	+9

* % Change from initial value

† Triglycerides

†† 50 km walk/day

††† including nine vegetarians

†††† Patients suffering from rheumatoid arthritis

attributed to cholesterol released from cell breakdown and increased turnover of VLDL to intermediate density lipoprotein and to LDL [11,28]. Such an increase in LDL was more prominent in our obese and hyperlipidemic subjects when compared to non-obese and normolipidemic subjects and may have resulted from increased VLDL catabolism by lipoprotein lipase. In previous studies of obese or hyperlipidemic subjects with LDL-cholesterol, the subjects consumed 240–1,000 kcal/day and thus are not comparable to our study [Table 4]. Apo-B concentration followed the changes observed in LDL-cholesterol in close correlation during the 3 to 5 days fasting.

Changes in HDL-cholesterol levels induced by fasting are heterogenous. HDL concentration tended to decrease in the non-obese normolipidemic group, which is consistent with some previous studies [2,3] but not with the report by Carlson and Froberg [4], who studied subjects engaging in heavy physical activity [4] which is known to affect HDL-cholesterol levels [29].

The two women on oral contraceptives showed unique changes in their lipoproteins upon fasting: a decrease in plasma triglycerides, VLDL and LDL-cholesterol, in contrast to men and women not consuming oral contraceptives. Oral contraceptives are known to affect plasma lipoprotein levels [30]. It is conceivable that oral contraceptives also affect the response of plasma lipoproteins to fasting, as observed in the present study.

Our observations in this limited number of subjects support the following conclusions. Fasting up to 5 days induces considerable changes in plasma lipoprotein levels. Both VLDL-cholesterol and triglyceride plasma concentrations increase in healthy non-obese or normoglyceridemic subjects but decrease in obese and hyperlipidemics. Intake of even small amounts of energy (200 kcal/day of carbohydrates) reverses the expected increase in plasma VLDL observed in normal individuals. The latter, together with the presence of obesity, hyperlipidemia, strenuous physical exercise or oral contraceptives, have introduced a remarkable heterogeneity in previously published reports studying the effect of fasting on plasma lipoproteins in humans.

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