Postprandial metabolic heterogeneity in men with primary dyslipidaemia

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Abstract

Introduction: Familial combined hyperlipidaemia (FCH) and familial hypercholesterolaemia (FH) have been strongly linked to premature coronary artery disease. Postprandial hypertriglyceridaemia is also associated with atherosclerotic disease. We evaluated the postprandial lipaemia in men with FCH and FH and compared them to a group of healthy men.

Material and methods: The study population consisted of 83 men: 34 FCH, 29 FH and 20 healthy. The FCH and FH groups were further divided into five subgroups, according to their lipid phenotype: FCH-IIA (n = 13), FCH-IIB (n = 10), FCH-IV (n = 11), FH-IIA (n = 21) and FH-IIB (n = 8). Postprandial lipaemia was evaluated by the areas under the curve for triglyceride (TG) concentrations (TG-AUC).

Results: The TG levels after oral fat tolerance test were significantly higher in FCH, compared to FH and healthy groups (TG-AUC in mg/dl/h; 2678 ±1415 vs. 1503 ±1147 and 1011 ±652 respectively, p < 0.001). The postprandial response was higher in FCH-IV and FCH-IIB, compared to FCH-IIA (TG-AUC in mg/dl/h; 3220 ±824 or 3409 ±770 vs. 1863 ±577 respectively, p < 0.001, for both comparisons). The FCH-IIA group showed higher postprandial TG levels when compared to FH-IIA (TG-AUC in mg/dl/h; 1863 ±577 vs. 1374 ±428 respectively, p = 0.008). There were no significant differences between FH-IIB and FCH-IIB subgroups. There was a significant correlation (r = 0.907, p < 0.001) between the postprandial TG-AUC and fasting TG levels in all FCH subjects.

Conclusions: All phenotypes of FCH and the FH IIB phenotype demonstrate an exaggerated postprandial response that could partially contribute to the high cardiovascular risk. These patients should be identified and treated early with the appropriate hypolipidaemic agents.

Key words: postprandial lipaemia, familial combined hyperlipidaemia, familial hypercholesterolaemia

Introduction

The majority of epidemiological studies (Framingham, Prospective Cardiovascular Münster [PROCAM], Multiple Risk Factor Intervention Trial [MRFIT]) come to conclusions regarding triglycerides (TG) as a cardiovascular (CV) risk factor, based on fasting TG levels [1-3]. Lately, studies have suggested that non-fasting TG may predict CV events similarly or even better, compared to fasting TG, and have the practical advantage that patients do not need to fast [4]. Also, it is accepted that atherosclerosis is a postprandial phenomenon; thus investigating the fate of lipoproteins...
after the administration of a fat meal may be very useful in certain subjects [5, 6].

Familial combined hyperlipidaemia (FCH) accounts for approximately 100,000 myocardial infarctions per year in the United States and the European Union [7]. FCH is characterised by intra-individual and intrafamilial variability of the lipid profile, expressed as periodic increase of TG and/or total cholesterol (TC) levels [8].

Familial hypercholesterolaemia (FH) is an autosomal, co-dominant, monogenic disorder of lipoprotein metabolism, characterised by very high levels of low density lipoprotein (LDL), tendon xanthomas and increased risk of premature atherosclerosis.

Postprandial lipaemia is a physiological polygenic metabolic process, following ingestion of dietary fat, mainly characterised by a marked increase in TG rich lipoprotein levels, such as chylomicrons (CM), very low density lipoproteins (VLDL) and their remnants [5].

We evaluated the postprandial TG response after a fat tolerance meal in men with FCH and FH and a group of healthy subjects.

Material and methods

Participants

The independent ethics committee of the Onassis Cardiac Surgery Center in Athens approved the study protocol and all participants gave informed written consent. The study population consisted of 83 Greek men who where referred to our Lipid Clinic. Only patients without hypolipidaemic treatment were eligible to enter the study. Heavy drinking (more than 3 units/day), thyroid, liver or renal disorders and professional sport activity were exclusion criteria. This study complies with the Declaration of Helsinki.

Study groups

The study population was divided into three main groups:

1. The FH group (n = 29), median age 34 (16). The diagnosis of FH was based on the widely accepted Simon Broome diagnostic criteria [9]: a) TC > 290 mg/dl, LDL cholesterol > 190 mg/dl, b) tendinous xanthomata in the patient or a first degree relative, c) family history of myocardial infarction in a first degree relative age < 60 years or in a second degree relative age < 50 years and d) family history of raised TC > 290 mg/dl in a first or second degree relative.

2. The FCH group (n = 34), median age 47 (14). The FCH status was diagnosed according to widely used diagnostic criteria [10, 11]: a) TC and/or TG levels > 90th percentile, adjusted for age and gender, on the basis of the PROCAM study [2], b) primary variability of the lipid phenotype in the patient and/or one member of the family, c) plasma apoB concentrations > 120 mg/dl, d) family history of myocardial infarction in a first degree relative age < 60 years, or in a second degree relative age < 50 years and e) absence of xanthomas.

3. The control group (n = 20), median age 46 (11). There was no previous medical history or family history of premature atherosclerosis, diabetes mellitus (DM), hypertension or dyslipidaemia. None of them was receiving any treatment. Three of the subjects were smokers.

Study subgroups

FH and FCH groups were further divided into subgroups, according to the Fredrickson lipid phenotype, by using the Lipid Research Clinic reference values [12]. Type IIA (hypercholesterolaemic phenotype) defined as TC ≥ 95th percentile, type IIB (mixed, hypercholesterolaemic and hypertriglyceridaemic phenotype) as both TG and TC ≥ 90th percentile and type IV (hypertriglyceridaemic phenotype) as TG ≥ 95th percentile.

FH subjects were divided into two subgroups, FH-IIA (n = 21) and FH-IIB (n = 8), and FCH subjects into three subgroups, FCH-IIA (n = 13), FCH-IIB (n = 10) and FCH-IV (n = 11). Postprandial TG response was compared among the three different FCH subgroups, as well as between FH and FCH subgroups with the same lipid phenotype (FH-IIA vs. FCH-IIA and FH-IIB vs. FCH-IIB).

Fat tolerance test

All subjects underwent a standardized oral fat tolerance test (FTT) following a 12 h overnight fast. Participants were forbidden to eat for 8 h after consumption of the meal, but were allowed free access to water. Each participant was given a meal containing 75 g fat/m² of body surface area, as previously described [13]. The meal provided 83.5% of energy from fat, 14.0% from carbohydrates and 2.5% from protein and was given in a dose based on the patient’s body surface area (350 g for 2 m²). It was consumed within 20 minutes and TG levels were measured at 0, 2, 4, 6 and 8 hours (h). TC and high density lipoprotein (HDL) levels were only measured in the fasting state, since it is has been shown that their levels do not present significant alterations postprandially [14, 15].

Plasma lipid, lipoprotein and apolipoprotein analysis

Plasma TC, TG and HDL cholesterol levels were measured using enzymatic colorimetric methods,
on a Roche Integra Biochemical analyser, with commercially available kits (Roche Diagnostics GmbH, Mannheim, Germany). The serum LDL cholesterol levels were calculated using the Friedewald formula [16], only in subjects with TG levels < 400 mg/dl. Three FCH patients had TG > 400 mg/dl, so LDL was not calculated. ApoA, apoB and Lp(a) were measured by nephelometry (Nephelometer: BN-100, Behring, Germany). All samples were analysed within 24 h.

Glucose, insulin and insulin resistance analysis

Blood glucose was measured by the hexokinase method with a Dade Behring reagent on a Dimension (Dade Behring, Liederbach, Germany) instrument and blood insulin with the IMX ABBOTT Diagnostics instrument. Whole-body insulin resistance was assessed with the HOMA-IR formula (fast glucose × fast insulin/22.5) [17]. All samples were analysed within 24 h.

Statistical methods

All data were collected in an MS-Excel 2007 spreadsheet and analysed using SPSS 14.0 (SPSS Inc, Chicago, Illinois, USA) for Windows. Categorical variables are presented as percentages. Values of numerical characteristics were tested for normality and are presented as mean value (± SD) if normally distributed, and median (± IQR) if not distributed normally. Area under the curve (AUC) for serial measurements of TG levels at baseline and after the fatty meal was calculated using the trapezoid rule. An ANOVA or Kruskal-Wallis H test with a Bonferroni correction (whichever appropriate) was performed for three group comparisons. The t-test for independent samples or the Mann-Whitney U test was used for the comparison of numerical values between different groups, where appropriate. Chi square test was performed for comparison of categorical values between groups. Spearman’s rank correlation coefficient was used as a measure of association between variables in order to reveal any correlation between values not normally distributed. The level of significance was set at $p \leq 0.05$.

Results

The fat loading test was ingested and tolerated well by all subjects. The amount of fatty meal ingested was 341 (19) g, 341 (35) g and 357 (41) g for controls, FH and FCH groups respectively.

Baseline characteristics of the three main groups

Clinical characteristics of the three main groups (controls, FH and FCH) are shown in Table I. FCH subjects had higher body mass index (BMI) and waist values, compared to controls and FH. As expected, DM, insulin resistance and hypertension were also more prevalent in the FCH group, compared to others. Fasting TG (TG$_0$) levels were significantly higher in the FCH group, compared to controls and FH, and were also higher in FH compared to controls.

Baseline characteristics of different subgroups

Clinical characteristics of the five subgroups (FH-IIA, FH-IIB, FCH-IIA, FCH-IIB, and FCH-IV) are summarised in Table II.

The FCH-IIA group had higher BMI and waist values, compared to FH-IIA. DM and hypertension were more prevalent in FCH-IIA, compared to FH-IIA. FCH-IIB and FCH-IV had higher TG$_0$ levels compared to FCH-IIA ($p < 0.001$). Metabolic syndrome was more prevalent in FCH-IV, compared to FCH-IIB ($p = 0.04$), as well as in FCH-IIA, compared to FH-IIA ($p = 0.001$). No differences were observed in TG$_0$ levels between FH and FCH subgroups with the same Fredrickson phenotype.

Postprandial characteristics of the three main groups

FCH showed significantly increased postprandial TG levels, at all hours, compared to controls and FH. FH showed significantly increased postprandial TG levels, at all hours, compared to controls.

Postprandial characteristics of different subgroups

Comparison of postprandial TG levels between the three different FCH subgroups is shown in Figure 1.

FCH-IV and FCH-IIB showed higher area under the curve for TG concentrations (TG-AUC), compared to FCH-IIA ($p < 0.001$). TG-AUC in FCH-IIA was significantly higher, compared to FH-IIB ($p = 0.008$). No significant postprandial differences were observed between FCH-IV and FCH-IIB or between FH-IIB and FCH-IIB subgroups.

Correlations

There was a significant correlation ($r = 0.907$, $p < 0.001$) between the postprandial TG-AUC values and TG$_0$ in all FCH subjects. There were no significant correlations in the control group. A correlation between fasting TG levels and postprandial lipaemia in men with FH has already been shown [18].

Discussion

We evaluated the response to FTT in the two most common hereditary dyslipidaemias and
We previously showed that FH patients with an abnormal TG response had higher baseline TG levels, compared to FH with a normal response [18]. Therefore, in the current study we did not assess the differences in the postprandial response between FH patients with hypercholesterolaemic and mixed phenotypes. Conflicting opinions exist regarding the role of LDL receptors (LDLr) in chylomicron clearance in FH patients [23-25]. Nevertheless, delayed chylomicron clearance, secondary to LDLr deficiency, is considered as one of the possible mechanisms responsible for the abnormal postprandial response in some FH subjects [26]. Moreover, coexistence of mutations in the LDLr related protein (LRP) has been linked to LDLr mRNA downregulation, in the postprandial state [27].

An abnormal response to fat loading in FCH patients has already been demonstrated by other studies.
investigators; however, the number of patients in these studies was relatively small [28-29]. In our study, TG-AUC was 264% higher compared to the control group, which is lower than that found by others [28]. In addition, peak TG levels (401 ±241 mg/dl) were seen at 4 h following the fat loading test and were lower than peak TG levels found by others [28, 29]. The above findings could be partially attributed to the different amount of fat load that was used by other investigators. Based on our previous studies, we defined an increased TG response to the fatty meal as any postprandial TG concentration higher than the highest TG concentration (220 mg/dl) observed in healthy subjects [30].

To our knowledge, this is the first study to compare postprandial lipaemia between FH and FCH. The FCH group demonstrated higher TG levels, abnormal postprandial lipaemia and delayed TG clearance, compared to FH. Hypercholesterolaemic FCH patients (IIA) showed significantly higher postprandial TG, in comparison to FH patients with the same Fredrickson phenotype, despite the fact that TG0 concentrations were normal in both groups and did not differ significantly. There are two possible explanations for this. Firstly, FCH-IIA patients were older than FH-IIA (mean age 49[15] vs. 37[12]; \( p = 0.01 \)).

### Table II. Clinical characteristics of different subgroups according to lipoprotein phenotype

| Characteristics | FH IIA (n = 21) | FH IIB (n = 8) | FCH IIA (n = 13) | FCH IIB (n = 10) | FCH IV (n = 11) |
|----------------|---------------|---------------|-----------------|-----------------|----------------|
| Age [years]    | 37 (12)*      | 37 (12)       | 49 (15)*        | 45 (8)          | 48 (9)         |
| BMI [kg/m²]    | 25 (2)*       | 26 (3)        | 28 (3)*         | 30 (5)          | 30 (4)         |
| Waist (cm)     | 92 (7)*       | 98 (9)        | 99 (9)*         | 107 (11)        | 103 (10)       |
| Coronary heart disease −/+ | 18/3 | 7/1 | 8/5| 10/0| 9/2 |
| Hypertension −/+ | 20/1* | 5/3 | 7/6* | 7/3 | 7/4 |
| Smokers −/+ | 14/7 | 2/6 | 6/7 | 3/7 | 2/9 |
| Diabetes mellitus − | 21/0* | 8/0 | 10/3* | 8/2 | 6/5 |
| Metabolic syndrome −/+ | 19/2* | 4/4 | 5/8* | 5/5 | 1/10 |
| Total cholesterol [mmol/l] | 338 (47)* | 360 (59)* | 273 (14)* | 277 (25)* | 239 (42)* |
| HDL cholesterol [mmol/l] | 47 (15) | 40 (9) | 43 (11) | 37 (8) | 38 (6) |
| LDL cholesterol [mmol/l] | 258 (48)* | 253 (47)* | 204 (18)* | 185 (23)* | 138 (57)* |
| Apolipoprotein A [mg/dl] | 144 (34) | 138 (26) | 142 (26) | 133 (20) | 140 (19) |
| Glucose [mg/dl] | 90 (8) | 92 (7) | 105 (38) | 120 (42) | 122 (68) |
| HOMA-IR | 1.7 (0.9) | 2.6 (1.8) | 1.9 (1.1)* | 4.4 (2.6)* | 4.4 (4.5)* |
| TG0 [mmol/l] | 110 (32) | 238 (44) | 124 (33)* | 276 (51)* | 333 (125)* |
| TG2 [mmol/l] | 168 (61)* | 310 (79) | 225 (86)* | 413 (111)* | 377 (108)* |
| TG4 [mmol/l] | 203 (73) | 391 (107) | 270 (103)* | 520 (145)* | 434 (121)* |
| TG6 [mmol/l] | 198 (77)* | 457 (142) | 276 (104)* | 478 (117)* | 442 (129)* |
| TG8 [mmol/l] | 146 (60)* | 346 (144) | 204 (67)* | 373 (61)* | 383 (97)* |
| TG AUC [mmol/l/h] | 1374 (428) | 2992 (660) | 1863 (577)* | 3409 (770)* | 3220 (824)* |

All values are presented as mean ±SD or percentages for categorical variables. TG0 – fasting plasma triglyceride concentration, TG2, TG4, TG6, TG8 – plasma triglyceride concentration 2, 4, 6, 8 hours after the fat load, respectively, TG AUC – area under the curve for triglycerides, HOMA-IR – index of homeostasis model of insulin resistance, NS – not statistically significant

* Significantly different between groups FCH IIA and FH IIA (\( p \leq 0.05 \)), † Significantly different between groups FCH IIB and FH IIB (\( p \leq 0.05 \)), § Significantly different between groups FCH IIA and FCH IIB (\( p \leq 0.05 \)), * Significantly different between groups FCH IIA and FCH IV (\( p \leq 0.05 \)), Ą Significantly different between groups FCH IIB and FCH IV (\( p \leq 0.05 \))
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metabolic syndrome among FCH-IIA and FH-IIA patients was 62% and 10% respectively. Our previous study clearly showed that male patients with metabolic syndrome demonstrate abnormal TG clearance following a fat loading test, even when TG0 levels are within normal limits [20]. Hypertension and DM have also been linked to abnormal postprandial lipaemia [15, 32].

On the other hand, although the FCH-IIB subgroup demonstrated higher fasting and postprandial TG levels, compared to FCH-IV, these differences never reached statistical significance. Parameters that can affect postprandial clearance, such as DM, hypertension, metabolic syndrome and obesity, did not differ among the two subgroups, while TG0 levels were comparable. An important finding of the present study is the fact that phenotypes FCH-IIB and FCH-IV, which showed a greater postprandial response, had lower LDL levels, but higher levels of glucose and insulin (although the differences were not statistically significant), with high prevalence of diabetes.

Diabetic FCH patients were compared to non-diabetic FCH patients and no additional exacerbation of postprandial lipaemia was revealed (data not shown). Insulin resistance has been linked to abnormal postprandial response [20-23, 33]. It is associated with fasting hypertriglyceridaemia [34], downregulation of LDLr [35] and overproduction of VLDL particles [36, 37]. These effects increase competition between chylomicron and VLDL remnants for hepatic receptors, thereby impairing the uptake of CM remnants by this pathway [38]. It is also known that in dyslipidaemias with IIB and IV phenotypes, where insulin resistance is usually common, cholesteryl ester transfer protein (CETP) acts as a mediator for the production of atherogenic small dense LDL particles [39].

Assessing the postprandial response in different phenotypic expressions of FCH can be of great clinical importance, in view of the intra-individual variability of the lipid profile. Phenotypic alterations, in the same subject, can cause a variable postprandial TG clearance in different periods of time, and therefore periodic adjustment of hypolipidaemic treatment may be required.

Limitations of our study include the small number of patients in the different subgroups and the non-age-matched comparisons between the main groups.

In summary, FH and FCH subgroups with hypertriglyceridaemic and mixed phenotypes demonstrate a significantly abnormal postprandial TG response. These subgroups of patients should be identified early and receive appropriate hypolipidaemic treatment, as they may be at higher risk of developing early atherosclerosis. This is especially a challenge in FCH patients who show intra-individual variability of their lipid profile and possibly alter their postprandial metabolic status,
within a certain period of time. Fibrates or statins with a potent effect on TG or combination therapy with statins plus fibrates or statins plus niacin could be considered as the appropriate treatment, according to the fasting phenotype.

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