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Hellenic Postprandial Lipemia Study (HPLS): Rationale and design of a prospective, open-label trial to determinate the prevalence of abnormal postprandial lipemia as well as its interaction with statins in patients at high- and very high-risk for cardiovascular disease

Genovefa Kolovou[a,*], Vasiliki Giannakopoulou[b], Petros Kalogeropoulos[c], Katherine Anagnostopoulou[d], Georgios Goumas[e], Georgios Kazianis[f], Sotiria Limberi[g], Despina Perrea[h], Constantinos Mihas[i], Vana Kolovou[a,j], Helen Bilianou[b]

[a] Cardiology Department and Lipoprotein Apheresis Unit, Onassis Cardiac Surgery Center, 356 Sygrou Ave, 176 74 Athens, Greece
[b] Department of Cardiology, Tzaneio Hospital, Afentouli blv and Zanni str, 18536 Piraeus, Greece
[c] Department of Cardiology, General Ongology Hospital Agioi Anargyroi, Timiou Stavrou str and Noufaron str, 14564 Nea Kifisia, Greece
[d] Department of Molecular Genetics, Genomedica S.A., Kanari 5-7, 18537 Piraeus, Greece
[e] Cardiology Clinic, Athens Euroclinic, Athanasiadou 7-9, 11521 Athens, Greece
[f] Hellenic College of Treatment of Atherosclerosis, Aigiidon 16, 11853 Kato Petralona, Greece
[g] Department of Cardiology, Sotiria Hospital, Mesogeion 152, 11527 Athens, Greece
[h] Laboratory of Experimental Surgery and Surgical Research 'N.S. Christeas', National and Kapodistrian University of Athens Medical School, 11527 Athens, Greece
[i] 1st Department of Internal Medicine and Diabetes Center, Tzaneio Hospital, Afentouli blv and Zanni str, 18536 Piraeus, Greece
[j] Molecular Immunology Laboratory, Onassis Cardiac Surgery Center, 356 Sygrou Ave, Athens 17674, Greece

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ABSTRACT

Fasting and postprandial hypertriglyceridemia have been related to cardiovascular (CV) disease. We describe the design and methods of the Hellenic Postprandial Lipemia Study (HPLS, NCT02163044), a prospective, open-label, randomized, multicentre trial. The study will recruit 900 participants from 8 centers, and aims to determinate the prevalence of abnormal postprandial lipemia in patients at high- and very high-risk for CV disease, the efficacy of statin treatment and other medications on postprandial lipemia, and the interaction between postprandial lipemia and CV risk during a treatment period of 3 years. Participants will be screened in an outpatient lipid clinic setting.

Methods: High- and very high-risk individuals with fasting triglycerides (TGs) < 220 mg/dL (2.5 mmol/L) will be included. At baseline visit demographic and clinical characteristics will be recorded. At the first follow-up visit (within 2–4 weeks from baseline), plasma TG concentrations will be measured, following an overnight 12 h fasting period, before and 4 h after ingestion of a commercially available oral fat tolerance test (OFTT) meal. Then a statin will be prescribed. At the second follow-up visit (within 3–5 month from baseline), plasma TG concentrations will be measured again following an overnight 12 h fasting period, before and 4 h after ingestion of OFTT and then patients will be followed annually for 3 years.

Conclusion: HPLS is the largest trial assessing the effects of statin therapy on postprandial lipemia. Its results will provide useful insight on the prevalence of postprandial lipemia, the efficacy of statins regarding postprandial lipemia and the clinical significance of this effect.

Clinical trial registration information

The HPLS trial is registered with clinicaltrials.gov (NCT Identifier: NCT02163044).

1. Introduction

Nowadays the assessment of plasma triglyceride (TG) levels can be performed in 3 different settings: fasting, non-fasting and postprandial [1–3]. Most of the guidelines suggest the assessment of fasting [4,5] or non-fasting TGs [1,6–8]. Nevertheless, we believe that postprandial

* Corresponding author at: Cardiology Department, Lipid Disorders Clinic, Onassis Cardiac Surgery Center, 356, Sygrou Avenue, 176 74 Athens, Greece.
E-mail addresses: genovefa@kolovou.com (G. Kolovou), nikipe@otenet.gr (P. Kalogeropoulos), dperrea@lessr.eu (D. Perrea).

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hypertriglyceridemia defined as an increase in plasma TG containing lipoproteins [postprandial TG (pTG) concentrations > 2.5 mmol/L (> 220 mg/dL) at any time after the fat meal] following the ingestion of a standardised high-fat meal [oral fat tolerance test (OFTT)], should also be considered [2]. Postprandial hypertriglyceridemia may in fact be a predictor for the development of atherosclerotic cardiovascular (CV) disease (ASCVD) as well as other chronic diseases [9,10]. However, the recent European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines do not specifically recommend treatment goals for elevated pTG [11]. For decades, TG measurements were performed in the fasting state. Currently, there is an expert panel statement [2] as well as guidelines [3–8,11,12] reporting that non-fasting TG levels are clinically valid and that pTG measurements may be useful for the precise evaluation of CV risk, especially in a time that everyone recognizes the importance of residual risk, remaining despite aggressive low density lipoprotein cholesterol (LDL-C) lowering with statins alone or in combination with other medications [13–17]. In fact, elevated fasting, non-fasting or postprandial levels of TG-rich lipoproteins may very well be one of multiple factors contributing to residual risk [2,18–20]. Overproduction and decreased catabolism of TG-rich remnant lipoproteins are the 2 main mechanisms leading to postprandial lipid and lipoprotein abnormalities. TG-rich remnant lipoproteins form a spectrum of larger to smaller particles, and although most of them are larger and have a lower potential to traverse endothelial cells than smaller LDL particles, some are almost as small as LDL. Furthermore, each TG-rich remnant lipoprotein is 5–20 times richer in cholesterol content compared with each LDL particle [1–3,10], and as they are also larger in size, once they have penetrated into the intima they are held there much longer [1–3,10]. Therefore, the retention of TG-rich remnant lipoproteins in the arterial intima in the postprandial state may lead to atherosclerosis development. Non-lipid risk factors for atherosclerosis, including smoking, diabetes mellitus (DM), hypertension, autoimmune diseases, chronic kidney or rheumatic disease, genetic predisposition and epigenetics, may also contribute to residual ASCVD risk. Statins lower substantially ASCVD risk, and present as the first and usually the only choice as they are lowering both LDL-C and moderately elevated TG levels [11]. However, and for the time being, several but rather small studies assessing the effect of statins on pTG are available [3,21–29]. To our knowledge, Hellenic Postprandial Lipemia Study (HPLS) is the largest trial assessing the effects of statins treatment on postprandial lipemia. HPLS will evaluate postprandial lipemia in patients at high- and very high-risk for ASCVD, as defined by the ESC/EAS guidelines [11]; pTG will be assessed using a standardised OFTT [30,31]. HPLS will assess the influence of statins on postprandial lipemia as well as other biochemical markers and will provide useful insight on the clinical significance of this effect. The present paper reports on the design and methods of HPLS.

2. Material and methods

The trial was organized by the board of the Hellenic College for the Treatment of Atherosclerosis (HCTA). The accuracy and completeness of the data collected by participating from 8 centers is being examined by a Contract Research Organization (CRO, Remed Projects, Athens, Greece). The HPLS trial is a multicentre, observational, open-label, randomized study performed in patients at high- and very high-risk for ASCVD events and fasting TG < 220 mg/dL.

2.1. Study objectives

The study primary objectives are to assess: 1. The prevalence of abnormal postprandial lipemia in patients at high- and very high-risk for ASCVD and fasting TG < 220 mg/dL, after the ingestion of a commercially available OFTT meal. 2. The effects of hypolipidemic, hypoglycaemic and antihypertensive medications on postprandial lipemia. 3. The association of postprandial lipemia and its treatment with CV risk: Major adverse CV events (MACE) which are death from CV causes, non-fatal myocardial infarction and non-fatal stroke will be recorded and a risk prediction model (defining an abnormal pTG response and examining the predictors of an abnormal response with logistic regression analysis with multivariate analysis to assess significant predictors of abnormal response). Furthermore, several risk variables such as high sensitivity C-reactive protein (hsCRP), gene variants, lipidomics and others, will be collected, correlated to the above-mentioned data and reported in future publications.

2.2. Study population

2.2.1. Source of participants and recruitment

Participants are recruited from OutPatient Clinics (Lipid, Diabetic and Hypertension) of 8 Athenian hospitals.

2.2.2. Enrollment

Approximately 10,000 participants were questioned for possible enrollment. The difficulty was to find patients who were lipid lowering treatment native. All patients had to sign a detailed informed consent.

The study aims to recruit 900 participants ≥18 years old with fasting TG concentration < 220 mg/dL (2.5 mmol/L) who are at high- or very high-risk for CV death. Power analysis showed that this sample size is adequate in order to detect proportion differences of 5% at a two-sided significance level of < 0.05, achieving statistical power of 85%. This sample size is also adequate to detect real differences in Hazard Ratio higher than 0.2, attaining statistical power of 77.6% when testing for survival analysis and based on relevant literature results [32]. Very high-risk patients for ASCVD are defined according to the ESC/EAS guidelines [11], as follows: documented ASCVD clinical or unequivocal on imaging, DM with target organ damage or with a major risk factor such as smoking, hypertension, dyslipidemia, severe chronic kidney disease (CKD), or a calculated SCORE ≥ 10% for 10-year risk of fatal ASCVD. High-risk patients for ASCVD are defined according to the ESC/EAS guidelines [11], as follows: markedly elevated single risk factors, in particular total cholesterol (TC) > 310 mg/dL (8 mmol/L) or BP ≥180/110 mmHg, most other people with DM, moderate CKD or a calculated SCORE ≥ 5% and < 10% for 10-year risk of fatal ASCVD. SCORE risk will be calculated using the Greek version of the low-risk regions charts [33] defined by the ESC/EAS guidelines [11]. SCORE risk calculation is recommended for asymptomatic adults > 40 years without evidence of ASCVD, DM, CKD or familial hypercholesterolemia [33]. Exclusion criteria are the history of liver, kidney (creatinine clearance < 60 mL/min), pancreatic, or gall bladder disease, history of acute coronary syndrome within one month prior to entering the study, pregnancy, presence of any inflammatory disease or treatment with any hypolipidemic medication. The institution ethics committee of all participating centers approved the study and informed consent will be obtained from all participants. The information protection rules in the National Institute for Health and Welfare *(http://nih.gov/)* (former National Public Health Institute until 2009) will be followed throughout the study.

2.3. Study design

All investigators have to fil the CRO fields, which include all parameters stated bellow.

The following data will be collected at the baseline visit: demographic details (name, surname, age, sex, address, telephone number), family and personal medical history (including smoking, hypertension, hyperlipidemia, glycemic status and ASCVD), past measurements of blood pressure (BP), glucose and lipid profile, as well as past vascular interventions (coronary or other angioplasty, coronary artery bypass surgery). Measurements of weight and height will be performed for all patients at the time of baseline visit as well as waist circumference which will be measured at the midpoint between the bottom of the rib cage and the top of the lateral border of the iliac crest during minimal

respiration. Body mass index (BMI) will be calculated as weight (kg)/height $(m)^2$. Smoking status will be self-reported as a simple question (yes or no). Hypertension will be defined as systolic BP (SBP) ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg or receiving antihypertensive treatment. BP measurements will be performed after 5 min of sitting and the mean of the 2 measurements at an interval of 5 min will be recorded. Dyslipidemia will be defined as LDL-C > 70 mg/dL (1.8 mmol/L) and > 100 mg/dL (2.6 mmol/L) for patients at very high risk and high-risk for ASCVD, respectively, according to the ESC/EAS guidelines [3]. DM will be defined by fasting glucose levels ≥126 mg/dL (on two occasions) according to the American Diabetes Association criteria [34]. No participant will be on lipid-lowering drug before entering the study. Patients with DM could be either already on antidiabetic treatment [i.e. metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylurea, insulin, sodium-glucose co-transporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists or combinations of these drugs] or treatment will be initiated after the first follow up visit. Hypertensive patients could be either on antihypertensive drugs [angiotensin-converting enzyme inhibitors, diuretics, beta-blockers, calcium-blockers, and others or combination of these drugs] or treatment will be initiated after the first follow up visit.

Serum TC, high-density lipoprotein cholesterol (HDL−C), TG, glucose, creatine kinase (CK) and liver tests will be measured mainly by using enzymatic colorimetric methods on a Roche Integra Biochemical analyzer (manufactured in Rotkreuz, Switzerland) with commercially available kits (Roche). hsCRP will be determined using a latex-enhanced immunonephelometric assay on aBNII analyzer (Dade Behring, Marburg, Germany). LDL-C will be calculated according to the Friedewald formula [LDL-C = TC - (TG/5 + HDL-C) mg/dl] only in patients with TG levels < 400 mg/dL (4.5 mmol/lL). Also, non-HDL-C will be calculated as TC minus HDL−C. pTG levels will be calculated as area under the curve (AUC) using the trapezoidal method [fasting TG, 4 h TG, 4 h TG Δ (from baseline/fasting)], total AUC (tAUC), and incremental AUC (iAUC), which represents the pTG response above fasting levels.

Plasma, serum and DNA samples from the white cells will be frozen at -80 °C for further analysis. All baseline biochemical measurements will be performed in the fasting state (12 h overnight fast). Only TG levels will be measured postprandially.

Each individual will have to complete 2 OFTT meals; the first at the beginning of the study (first follow-up visit) and the second after 3–6 months on hypolipidemic treatment (second follow-up visit). Blood samples will be collected before and 4 h after the OFTT meal based on the results from a meta-analysis of 113 studies revealing that the optimal time for a single point test of pTG is 4 h after consuming OFTT [35]. That was also documented by other studies [30,31,36].

2.3.1. Abnormal postprandial lipemia

The abnormal postprandial lipemia will be defined as pTG concentration > 220 mg/dL (2.5 mmol/L) according to an Expert Panel Statement [2].

2.3.2. LIPOTEST meal

The LIPOTEST meal (D. GENOMERES Advanced Medical Research, Athens, Greece) is a standardised OFTT meal recognized by the Hellenic Drug Organization (EOF, National Drug Organization). A single serving is provided in a sachet (115 g powder that is rehydrated by adding 150 ml water). The powder and water are mixed to homogeneity (2–3 min with a hand-held mixer) and then refrigerated to form a mousse. All ingredients are food grade and are stable for a period of 24 h after the preparation as proved by antioxidant tests.

The composition of the LIPOTEST is hydrogenated vegetable fat, glucose syrup solids, milk proteins, sugar, emulsifiers (lactic and acetic acid esters of monoglycerides and diglycerides), cocoa powder (20–22% fat content), defatted cocoa powder (10–12% fat content) and flavouring. On a per serving basis, the LIPOTEST meal provides 832 kcal [42% FDA Daily reference value (DRV) for adults, and 42% of the European Guideline Daily Amount, GDA], 10 g protein (20% DRV, 20% GDA), 25 g of carbohydrates (8.3% DRV, 10% GDA) of which simple sugars comprise 14.3 g (no DRV, 16% GDA), 2.1 g fiber (8.4% DRV), 0.15 g salt (2.5% DRV for sodium), and 75 g fat (115% DRV, 109% GDA), all of which is fully saturated (375% DRV and GDA) through hydrogenation of vegetable fat. The fat used is coconut oil named Cegepal VF HC 77 and Lamequick 6068, both from Cognis (Ludwigshafen, Germany), which are fully approved for use in food applications and are in powder form. The LIPOTEST meal will be administrated in the morning after 12 h overnight fast. Participants will consume meal within 20 min and will be instructed to keep physical activity to a minimum, refrain from smoking and fast during the 4 h of the test. The LIPOTEST meal will be provided by the study committee.

During the first follow-up examination patients will be randomized to one of the following hypolipidemic treatments: simvastatin (up to 40 mg/day), atorvastatin (up to 80 mg/day) or rosuvastatin (up to 40 mg/day). Patients at very high risk and high-risk for ASCVD will be treated to LDL-C target (< 70 or < 100 mg/dL, respectively) as recommended by ESC guidelines. If LDL-C is not on target after statin monotherapy, they will receive ezetimibe and, if they are still not on target, PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitor will be added if eligible by national regulations. Statin intolerant individuals will be treated with colesevelam (up to 3.75 g/day), nanocrystallized fenofibrate (145 mg/day) or ezetimibe 10 mg/day, as monotherapy or in combination. All participants at study inclusion will be evaluated for gene polymorphisms as part of their dyslipidemic profile assessment.

After that, participants will be followed annually for 3 years. All participants will receive concomitant medication in accordance to the everyday practice of their treating physician. All adverse events will be recorded in accordance to all applicable laws and regulations concerning medications prescribed according to their approved summary of product characteristics.

2.3.3. Genetic testing

New generation sequencing will be performed for the identification of genetic variants at the Greek Genome Center in the Biomedical Research Foundation of the Academy of Athens (BRFAA). The Greek Genome Center provides a number of Illumina sequencers (MiSeq, NextSeq, NovaSeq). The type of the sequencer will be selected in a way to minimize the cost. After sequencing, all samples will be analysed by standard bioinformatic tools specific for new generation sequencing method (bwa, samtools, GATK) for the variant calling of the targeted genetic regions. In the case of common variants (MAF > 1%), variant classification will be based on the American College of Medical Genetics standards and guidelines (2015) as well as on the scientific literature. The aim of the analysis is the identification of known genetic variants of genes responsible for dyslipideamias. In patients negative for the presence of pathogenic variants, an association analysis will be performed between the variants of unknown significance and the patient lipid profile. According to the progress of the study, new associations and gene sets may arise from the genetic analysis.

2.3.4. Lipidomics

Lipidomics, offer a means to identifying markers that may be indicative of pathways modulating response to OFTT and lipid lowering treatment. In this study, they will be analysed by mass spectrometry (details will be provided on time of analysis) in 4 plasma samples (at baseline and 4 h after consuming the first OFFT as well as at baseline and 4 h after consuming the second OFFT) from the first 30 individuals. The analysis will provide possible metabolite differences postprandially and after lipid lowering treatment.

2.4. Statistical analysis

The statistical analysis will include classical bivariate tests of hypotheses (Pearson's χ^2, Student's *t*-test) or their non-parametric analogues, depending on the data's distribution as well as univariate and multivariate modeling (logistic regression, survival analysis (Cox proportional hazard modeling)). Aims 1 and 2 will require multiple linear or/and multiple logistic regression (depending on the definition of lipemia, either as a quantitative or a qualitative variable) while Cox proportional hazard modeling and survival analysis in general evaluating the effect of lipemia and other already described independent variables of interest on MACE will be the main statistical method used for the 3rd aim of our study. Data will be analysed using STATA® statistical software (Version 14.0, Stata Corporation, College Station, TX 77845, USA).

3. Discussion

Numerous published studies support the benefits derived from multiple risk factors interventions aiming to improve CV outcomes and decrease CVD risk [13–17]. Despite aggressive LDL-C lowering and improved therapeutic strategies for smoking cessation, arterial hypertension and DM, residual CVD risk is still high [13–17]. This fact implies the need for new additional therapeutic targets. [3,6,8]. Our previous research on this field [30,31,35–39] suggests that interventions for ACVD prevention may be more effective if they also target postprandial lipemia. Despite the undisputable benefits of lifestyle interventions and aggressive lipid lowering treatment to reduce CVD risk, there is almost no evidence regarding the subject of postprandial lipemia and potential interventions to improve it.

HPLS trial has been carefully designed to address certain critical unanswered questions regarding postprandial lipemia: which is the pattern of the postprandial increase of TG in patients at high and very high-risk for ASCVD as defined by the ESC/EAS guidelines? How often these groups of patients present with abnormal TG increase in the postprandial state? What is the influence of treatment with statins on this increased postprandial lipemia as well as other markers (e.g. inflammatory) which existing evidence suggest that closely interact; We believe that clinical follow-up for three years of patients participating in this study will provide useful insight on the clinical significance of this effect. We are expecting to collect data on the added risk for those with increased pTG as well as data for risk reduction in those that treatment with statins will lead to marked decreases in pTG. Of course, one may point out that statins probably are not the best medication for treating TGs, either fasting or postprandial. This is partially true but, on the other hand, no one can ignore the fact that statins, compared to other hypolipidemic medications, have been extremely and consistently efficient in lowering CVD risk [40], while fibrates for example presented rather controversial results [23]. If our study provides evidence that lowering the increase of pTG may lower CVD risk, maybe in the future other more potent and focused interventions will be evolved and tested. Data from the few patients that will be treated with other than statins hypolipidemic medications will also be collected and taken into consideration.

Initial site recruitment for the HPLS study began in 2015. The HPLS study is registered with clinicaltrials.gov (NCT Identifier: NCT02163044) and is being monitored by a Clinical Research Organization (CRO, Remed Projects, Athens, Greece).

Conflict of interests

These recommendations were written independently; no company or institution supported the authors financially or by providing a professional writer. The Hellenic College of Treatment of Atherosclerosis (HCTA) endorsed the committee.

Genovefa Kolovou, Vasiliki Giannakopoulou, Georgios Goumas, Helen Bilianou have given talks, attended conferences and participated in trials sponsored by Amgen, Angelini, MSD, Lilly, Vianex, Sanofi-Aventis, Innovis, Bayer, Elpen, Menarini and have also accepted travel support to conferences from Amgen, Sanofi, MSD, Bayer, Elpen, Menarini.

Petros Kalogeropoulos, Sotiria Limberi, Katherine Anagnostopoulou, Georgios Kazianis, Despina Perrea, Constantinos Mihas, Vana Kolovou have no conflicts of interest.

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