Effects of statins and exercise on postprandial lipoproteins in metabolic syndrome vs metabolically healthy individuals

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Abstract

Aims: To determine if the combination of exercise and statin could normalize postprandial triglyceridemia (PPTG) in hypercholesteraemic individuals. Mehods: Eight hypercholesteraemic (blood cholesterol 182±38 mg·dL-1; LDL-c 102±32 mg·dL-1) overweight (BMI 30±4 kg·m-2) individuals with metabolic syndrome (i.e., Met Synd) were compared to a group of eight metabolically healthy controls (i.e., MetH, blood cholesterol 149±23 mg·dL-1; LDL-c 77±23 mg·dL-1, and BMI 23±2 kg·m-2). Each group underwent two PPTG tests, either 14-h after a bout of intense exercise (EXER) or without previous exercise (REST). Additionally, Met Synd individuals were tested 96 h after withdrawal of their habitual statin medication (PLAC trials) to study medication effects. Results: A bout of exercise before the test meal did not reduce PPTG in Met Synd (P=0.347), but reduced PPTG by 46% in MetH (224±142 to 413±267 mg·dL-1·for 5 h iAUC; P=0.02). In both trials (i.e., REST and EXER) statin withdrawal in Met Synd greatly increased PPTG (average 65%; P<0.01), mean LDL-c (average 25%; P<0.01), total cholesterol (average 16%; P<0.01) and Apo B48 (24%; P<0.01), without interference from exercise. However, Apo B100 was not affected by statin withdrawal. Conclusions: Hypercholesteraemic Met Synd individuals (compared to metabolically healthy controls) are resistant to the effects of exercise on reducing PPTG. However, chronic statin medication blunts the elevations in TG after a fat meal (i.e., iAUC of PPTG) reducing their cardiovascular risk associated to their atherogenic dyslipidemia. Statin decreases PPTG by reducing the secretion or accelerating the catabolism of intestinal Apo B48.

What is known about this subject?

- Statins are the main pharmacological treatment to lower blood fasting cholesterol and triglycerides level.
- Statins could blunt the elevations in lipid after a fat meal (a highly atherogenic situation) and a bout of exercise has similar effects.
- It is unclear in which atherogenic particles statins and exercise act on, and if exercise could enhance statin actions.

What this study adds

- A bout of exercise lowers postprandial triglycerides (PPTG) in healthy individuals, while hypercholesteremic Met Synd individuals are resistant to the exercise lowering PPTG.
- However, statins lower PPTG in hypercholesteremic Met Synd individual.
- Statins reduce intestinal chylomicron formation or increase its clearance although do not fully normalize postprandial lipoproteins in Met Synd.

INTRODUCTION

The blood lipid imbalance common in individuals with the Met Synd (i.e., high TG, LDL-c, VLDL-c and low HDL-c) is strongly correlated with the risk of atherogenesis and endothelial disfunction by stimulation of thrombogenic and inflammatory pathways [1]. LDL-$_C$ has been regarded as the main lipoprotein inducing the accumulation of sterols in macrophages while chylomicrons are not considered to be directly involved in atherogenesis, because of their larger size and inability to efficiently penetrate arterial tissue. However, once chylomicrons are hydrolyzed their remnant penetrates arterial tissue and becomes preferentially trapped within the subendothelial space [2]. Thus, the risk for atherogenic plaque formation and endothelial dysfunction increases after ingestion of meals with high fat content [3] due to the rise in lipoproteins remnant (i.e., chylomicrons and VLDL with high cholesterol content).

At rest, hypercholesteremic Met Synd individuals have an exaggerated postprandrial triglyceride (PPTG) response compared to lean counterparts for the same meal ingestion [4]. This seems to be due to increased blood TG influx from the ingested fat (chylomicrons) [4] although increases in hepatic secreted triglycerides (VLDL-TG) could also be involved. A bout of exercise could activate endothelial LPL and therefore lipolysis to reduce PPTG. However, it is unclear if exercise lowering PPTG, reflects only an increased clearance of TG (i.e., by muscles, adipocytes or liver) or also reduced intestinal lipoprotein formation [5]. Each lipoprotein is surrounded by a single copy of apolipoprotein, being the B type the most representative of LDL particle concentration. A subtype of this, Apo B48, is the major apolipoprotein involved in the formation of chylomicrons. Enzyme-linked immunosorbent assay (ELISA) permits to measure blood concentration of apolipoprotein B48 and B100 to investigate the intestinal vs the hepatic origin of postprandial lipoproteins. This could be used to unveil what is the mechanism behind the reductions in PPTG with exercise or statin treatment.

Statins (3-hydroxy-methyl-glutaryl coenzyme A reductase inhibitors) are the main pharmacological treatment for hypercholesterolemia. Statins effectively inhibit liver cholesterol synthesis inducing the expression of hepatic LDL-receptors in hepatocyte cell surface [6] which in turn catabolizes Apo B containing lipoproteins (i.e., chylomicrons, VLDL-c, LDL-c and IDL-c). Statin effects on reducing blood fasting TG extends to the PPTG [7, 8]. The effects of statin on reducing PPTG may not just involve enhancing liver TG clearance, but also clearance by other tissues. In normolipidemic subjects statins lowers VDLD-c pool which triggers a reduction of Apo C-III, a protein that inhibits LPL [8, 9]. The coordinated actions of exercise (non-pharmacological) and statin (pharmacological) therapies to reduce PPTG are starting to be explored [7].

This study investigates the effects of 3HMGCoA reductase inhibitor (statins) on postprandial intestinally and hepatically derived lipoproteins (Apo B48 and 100, respectively) in Met Synd hypercholesteraemic individuals. Since Met Synd individuals are more susceptible to developing cardiovascular disease, correcting PPTG with bouts of exercise prior to the ingestion of a high-fat meal could became a therapeutic measure of clinical importance in this population. The present study investigates the effect of a bout of exercise before a high-fat meal on lowering PPTG, blood lipoproteins and its possible interactions with statin medication. Finally, all data is compared to a sample of metabolically healthy individuals to assess treatment capacity to revert blood lipids to normal values. Our hypothesis was that the combination of exercise and statin could normalize PPTG in Met Synd hypercholesteremic individuals.

METHODS

Participants and preliminary testing.A group of eight subjects (one woman and 7 men) with an average age of 61±7 years, BMI of 30±4 kg·m^{-2} and hypercholesterolemia treatment with statins was recruited. These subjects were diagnosed with the metabolic syndrome based on the criteria previously defined [10], as showed in Table 1 (Met Synd group). Subjects were physically active and medicated with statins ("ator", "pita", "sim", "rosu"-vastatin) during at least 6 months before the onset of the study. The diary dosage for each drug was prescribed by participant's primary care physicians which followed the Spanish National Institute of Health guidelines for management of lipids as a cardiovascular risk factor. Eight subjects of 30±10 years-old subjects (1 woman and seven men) were recruited as the control metabolically healthy group (i.e., Met Healthy) with the characteristics shown in Table 1. All the individuals signed a witnessed,

informed consent of the protocol approved by the local Hospital's Ethics Committee following the declaration of Helsinki (revised October 2013). Subjects underwent a medical physical examination and completed a maximal cardiopulmonary graded exercise test (GXT) to exhaustion on an electronically braked cycle ergometer (Ergoselect 200, Ergoline, Germany) with ECG monitoring (Quark T12, Cosmed, Italy) to screen for myocardial diseases and determine their maximal oxygen consumption (VO_{2MAX}). After a cool down and 15 min of passive rest including rehydration, a short (2 - 3 min) confirmatory test was performed at 110% of the maximum load reached during the previous ramp test [11]. The VO_{2MAX}obtained was used to set exercise intensity during the exercise bout. This is a sub-study part of a larger clinical trial evaluating the effects of 4-month exercise training and habitual medication in individuals with metabolic syndrome (ClinicalTrials.gov Identifier: NCT03019796).

Experimental design. Using repeated-measures crossover trial design subjects completed two trials. Met Synd group performed these trials by duplicate, taking either a placebo or their habitual statin medication using a randomized control trial (RCT) design. Upon study enrollment, Met Synd participants turned in their statin prescription drugs to the team physician for masking into larger capsules. Identical tablets were used for placebo but filled with dextrose. On the morning of every fifth day for the duration of the experiment (4 weeks), participants turned in their empty research pill bottle to receive a new prescription bottle. In that way, we altered participants' drug intake between placebo and statins in a double-blinded fashion. Placebo was taken for 4 days (i.e., 96-hr) prior to the trials because this time exceeds by 5-fold the longer-lasting statin half-life prescribed to our subjects (i.e., Rosuvastatin, 19 h). During the first trial, subjects filled out an activity/diet diary and were instructed to replicate those for the 48-h before every trial. Met Synd subjects underwent 4 trails to measure postprandial lipoproteins, a) substituting their habitual statin medication by placebo medicine (REST+PLAC trial), b) taking their habitual statin medicine (REST+STA trial), c) placebo medicine combined with a bout of intense aerobic exercise (EXER+PLAC trial), d) combining exercise and statin medicine (EXER+STA trial). Met Healthy group did not take statins and thus underwent only the REST and EXER trials. Trials were separated by at least a week among them.

Experimental trials. Subjects arrived at the laboratory between 7 and 8 AM after an 10-12 hours overnight fast preceded by a standardized 322 kcals dinner (325 gr of pre-cooked pork tenderloin in mushroom sauce with 4 gr of fat, 9.5 gr of carbohydrate, 6 gr of protein per 100 g, 500 mL of water and a medium-sized apple). Upon arrival, subjects' body weight (Hawk, Mettler Toledo, USA), body composition (BIA using Tanita BC-418-MA, Japan) were assessed. Subjects lie in a gurney while a catheter (20G, BD Insyte, Becton and Dickinson, Spain) was inserted in an antecubital vein and a 3-way stopcock attached (Luer-lock, CPK IV, Farmaban, Spain). After 20 min of lying in a quiet, (22±1 ^{o}C and 25±6% humidity). Then, a blood sample was withdrawn (i.e., -60 min blood sample) and blood pressures (ECG gated electro-sphygmomanometer; Tango, Suntec Medical; NC; USA) measured in triplicate. This blood sample was used as a baseline for the calculations of the incremental area under the curve for blood triglycerides. Following, in trials with exercise (EXER+PLAC and EXER+STA trial) subjects pedaled continuously during 41 min alternating intensities (i.e., 40%-70%-85% VO_{2MAX}) interspersed with 5 min of low-intensity pedaling to end with 5 min warm-down (40% VO_{2MAX}). We chose this interval aerobic exercise scheme because a recent meta-analysis review deems that high-intensity interval training is more effective in reducing PPTG [12]. The exercise bout entailed 41 min of moderately-high average intensity cycling (i.e., 72% of HR_{MAX}) which represented a tolerable exercise bout that could be implemented on health promotion for the Met Synd population. After exercise subjects returned to the gurney and after 20 min of supine rest a blood sample was drawn (i.e., 0 min, blood sample).

High-Fat meal. Following, subjects sat and ingested within 10 min a high-fat meal, 244 g of Oreo® frozen cheesecake (Granderroble Deserts, Spain) containing every 100 grams, 24 gr of dairy-derived fat (0.71±0.03 g kg^{-1} BW), 34 gr of simple sugar carbohydrate (1.06±0.04 g·kg^{-1} BW) and 5 gr of milk-derived protein (0.20±0.01 g· kg^{-1} BW). The cheesecake was blended with 150 mL of skimmed milk (Asturiana®, Spain) for a total volume of 394±21 mL. The meal amounted to 11.6 kcal·kg^{-1} body weight for a group average of 862±109 kcals. This meal was chosen because it was commercially available, the source of fat (i.e., mostly dairy) is what is commonly used in fat meal experiments and we could deliver in a sizable volume (394 mL)

more than 0.7 g of fat·kg^{-1} BW which is the threshold for high-fat meal consideration [13]. During the 5 hours that followed the high-fat test meal ingestion, subjects remained seated in the lab and blood samples were collected hourly (i.e., samples 60, 120, 180, 240 and 300 min) while the catheter was maintained patent by flushing with 5 cc of 0.9% saline (Grifols, Spain) after each blood collection.

Data from blood triglyceride concentration was modeled by the trapezoidal rule to calculate the iAUC as follows [14]:

iAUC (mg·dL^{-1}* 5 h) = (2 * (S60 min + S120 min + S180 min + S240 min) + S300 min) - (9 * S0 min)

Blood analysis. 5-cc blood samples were collected in tubes with a clot activator (Vacutainer®; USA) to upon centrifugation, obtain serum. Another 3 cc were mixed with 3K EDTA and then centrifuged to obtain plasma. Serum was analyzed for triglyceride, total cholesterol, and HDL-c. Then, LDL-c was calculated using the Friedewald formula [15]. Blood triglycerides with glycerol-3-phosphate oxidize method (interassay CV; 0.8-1.7%). Total serum cholesterol by an enzymatic method with a single aqueous reagent (iCV; 1.1-1.4%). HDL-c using accelerator selective detergent method (iCV; 1.7-2.9%). Glucose was analyzed using glucose oxidase peroxidase method with the intra-inter assay coefficient of variation (iCV; 0.9-1.2%). These analyses were run in an automated analyzer (Mindray BS 400 Medical Instrumentation, China). Apolipoproteins B levels were quantified through enzyme-link immunosorbent assay (ELISA), according to the manufacturer instructions, Apo B100 (iCV; 2.6-10.4%; Mabtech AB, Nacka, Sweden) and Apo B48 (iCV; 2.8 – 8.6%; Shibayagi, Shibukawa, Japan).

Statistical analysis. Shapiro-Wilk test confirmed that the main dependent variable, basal TG, was normally distributed. Power analysis suggested that 8 participants would be required as determined by using the variance in postprandial TG iAUC at an effect size of $\beta = 0.80$ and an $\alpha = 0.05$. Data collected on arrival at the laboratory (anthropometrics, blood lipid, heart rate, blood pressure) were analyzed using 1-way (treatment) repeated-measures ANOVA. Data collected overtime was summarize as AUC and analyzed using 2-factor (exercise × statin) ANOVA in the MetSynd group. To analyze differences between Met Synd and Met Healthy groups we used a mixed-design analysis of variance (ANOVA) in all reported variables. After a significant F test, pairwise differences were identified using posthoc Tukey's HSD. Data are presented as means ± standard deviation unless otherwise noted. All analyses were performed with SPSS version 21 (Chicago, IL). Statistical significance level was set at P[?]0.05, if not indicated.

RESULTS

Exercise and statin effects on postprandial lipoproteins in Met Synd. In the Met Synd group statin withdrawal increased PPTG by 65% in average (P<0.01), with no effect of exercise. The iAUC of PP triglycerides levels in the REST trials increased with statin withdrawal (i.e., REST+STA, 425+-268 vs REST+PLAC, 874+-589 mg*dL^{-1}; P=0.026) and in the EXER trials (i.e., EXER+STA, 690+-340 vs EXER+PLAC 857+-400 mg*dL^{-1}; P=0.049; Figure 1A). Figure 1B shows the hour by hour PPTG response in both experimental groups in response to treatments. In Met Synd stain reduced average PPTG concentration in EXER trials (i.e., EXER+STA, 157+-93 vs EXER+PLAC, 183+-81 mg*dL^{-1}; P=0.014) and REST group (i.e., REST+STA, 141+-69 vs REST+PLAC, 180+-94 mg*dL^{-1}; P=0.045). In Met Synd group, a bout of exercise did not affect average (AUC) PPTG.

Statins in the Met Synd group lowered blood lipid concentration (Figure 2). A reduction on total cholesterol levels was observed in response to statin treatment (average 16%; P<0.01), in the EXER trials (i.e., EXER+STA, 167+-45 vs EXER+PLAC 191+-34 mg*dL-1; P<0.01) and in the REST trials (i.e., REST+STA, 161+-47 vs REST+PLAC, 205+-36 mg*dL-1; P<0.01). LDL-c concentration was reduced by STA similarly in the EXER and REST trials (i.e., 25%; P<0.01). In the EXER trials LDL-c was reduced from 108+-30 to 89+-41 mg*dL^{-1} (P=0.018) in the EXER+PLAC vs EXER+STA trials. Similarly, in the REST trials, LDL-c decreased from 123+-32 to 88+-33 mg*dL^{-1} (P<0.01) in the REST+PLAC vs REST+STA trials.

Statin withdrawn triggered an increase on VLDL-c (i.e., STA, 35+-20 vs PLAC 40+-18 mg*dL^{-1}; P=0.017)

and a decrease on HDL-c (i.e., STA, 46+-11 vs PLAC 44+-11 mg*dL-1; P<0.01) on the EXER trials. Apo B48 levels were also reduced by statin treatment (average 24%; P<0.01), in EXER (i.e., STA, 13+-6 vs PLAC 16+-7 mg*dL^{-1}; P=0.045) and in REST trial (i.e., STA 13+-3 vs PLAC 18+-7 mg*dL^{-1}; P=0.028; Figure 3). No effects of statin or exercise were found on postprandial total Apo B100 levels.

With statin withdrawn, a bout of exercise induced a decrease of total cholesterol (i.e., PLAC+EXER, 191+-34 vs PLAC+REST, 205+-36 mg*dL^{-1}; P<0.01) and LDL-c levels (i.e., PLAC+EXER, 108+-30 vs PLAC+REST, 123+-32 mg*dL^{-1}; P=0.011; Figure 2).

Comparison between Met Healthy and Met Synd groups. Met Synd and Met Healthy group characteristics at baseline are listed in Table 1. In the Met Healthy group, exercise (bout of 41 min 14 hours prior to the fat meal) significantly reduced the iAUC of PPTG when comparing EXER vs REST trials (i.e., 224+-142 vs 413+-267 mg*dL^{-1}; P=0.02). Total cholesterol and LDL-c concentrations approached the Met Healthy group levels when Met Synd subjects were taking statins (Table 2) but exercise had no effect on normalizing lipid levels. Despite taking statins, HDL-c, VLDL-c and triglycerides were lower in Met Healthy than in Met Synd group (Table 2). Apo B 48-100 levels were not significantly different between groups.

DISCUSSION

The main finding of this study is that whilst a bout of aerobic exercise reduced by 46% the area of postprandial TG vs time curve in normolipidaemic metabolically healthy (Met Health) individuals, the same session of exercise (same relative intensity and duration) had no effect on PPTG in metabolic syndrome (Met Synd) hypercholesteraemic individuals. Since these individuals were medicated to treat their hypercholesterolemia with statins, we presumed that statin strong effect on lowering PPTG (i.e., 35% in average, Figure 1) did not permit to appreciate the effects of exercise on lowering PPTG. However, when Met Synd individuals were withdrawn from statins for 4 days and their basal blood TG concentration increased, exercise neither reduce PPTG (i.e., EXER+PLAC vs REST+PLAC; Figure 1). Our data suggest that Met Synd had a limitation (i.e., resistance) to respond to exercise with reductions in PPTG in comparison to metabolically healthy counterparts.

Some reports show that individuals with obesity and Met Synd have a PPTG lowering response to exercise [16, 17]. However, those studies did not directly compare the responses of Met Synd to a Met Healthy group. When lean individuals are compared to age-matched obese counterparts exercise causes similar PPTG reductions in both groups [18, 19]. The obese individuals in these studies were young (15-48 years) with blood lipid levels (i.e., total cholesterol and LDL-c) in the same range than the lean group. In contrast, our sample is composed of obese (BMI=30+-4 kg*m^{-2}) older (61+-7 years old; Table 1) individuals that have been diagnosed and treated against hypercholesterolemia with statins for 5 years in average. In our Met Synd individuals with chronic disarrangements in their lipid metabolism we do not observe an effect of exercise alleviating PPTG. Our results are not isolated since others have reported that moderately intense and prolonged (i.e., 60 min) of exercise did not lower PPTG response in Met Synd individuals [20]. Likewise, in diabetic type 2 individuals, a bout of 40-90 min of moderately intense exercise (40-60% VO_2max) neither lowers PPTG [21, 22]. Our data suggest that older obese individuals with excess blood lipid levels to the point of needing pharmacological treatment, are more prone to be resistant to the effects of a bout of exercise on lowering PPTG.

Although exercise did not have an effect on postprandial lipoproteins in Met Synd individuals, their habitual statin medication was very effective at reducing PPTG and other lipids (Figure 2). Of note, statin in Met Synd normalize the concentrations of total cholesterol and LDL-c to levels that were not different that in the Met Healthy group (Table 2). However, statin did not reduce TG or VLDL-c to the levels of Met Healthy (Table 2). Statin had a reductive effect on Apo B48 concentration (Figure 3) a fair surrogate of chylomicron metabolism. Reductions in the postprandial initial rise of the Apo B48 concentration curve would suggests reduction in chylomicron secretion with statins. Other studies have not observed a reduction in the initial slope [8, 23] arguing that statins increase chylomicron clearance [24]. It is uncertain from our data (Figure 3) if statins blunt the initial rise in Apo B48 after the meal. More frequent sampling during the first 2 hours

after the meal is required to explore this possibility.

Several studies have examined the kinetics of Apo B48 by infusing a bolus of isotopically labeled leucine to measure the incorporation of this amino acid into Apo B48. One recent study on healthy normolipemic men reveals that atorvastatin (80 mg*day^{-1}) reduces both the number of Apo B48 particles secreted in response to the fat load (-29%; P<0.01) while at the same time increasing Apo B48 fractional catabolic rate (i.e., FCR; +32%, P<0.001; [25]). In another study, atorvastatin (20 mg*day^{-1}) in adults with combined hyperlipidemia, reduces postprandial Apo B48 production rate (-16%; P=0.104; NS) and increases FCR (11%; P=0.102; NS) while a higher dose (i.e., 80 mg*day^{-1}) has a larger effect on FCR than in production rate [26]. Thus, current literature does not discard an effect of statins on reducing postprandial production of chylomicrons although it favors increased clearance.

The putative mechanism by which statin reduce PPTG is that the statin-induced increased LDL receptor activity may enhance the removal not only of LDL-c but also of triglyceride-rich lipoprotein and chylomicron remnants. However, apolipoprotein B48 (marker of chylomicron concentration) does not bind to LDL receptor and requires the Apo E moiety for hepatic removal of chylomicrons. In turn, Apo E activity is inhibited by C apolipoproteins. It has been documented that statins reduce Apo C-III [9] liberating the inhibition of Apo C-III on lipoprotein lipase (LPL). Some studies support that atorvastatin increase LPL activity [27] which may explain the reduction observed in PPTG in the present data with statin use (Figure 1).

Parhofer et al., [8] found that in hypertriglyceridemic individuals, atorvastatin reduced large triglyceride rich lipoproteins (i.e., TRL composed of chylomicrons and VLDL) but not small TRL (i.e., their remnants). They argue that the increased conversion of chylomicrons to chylomicron remnants balances the increased turnover of chylomicron remnants observed in hypertriglyceridemic individuals. A similar mechanism may be explaining our reduction in Apo B48 with statins in hypercholesterolemic Met Synd individuals while unchanged Apo B100 (Figure 3). Statins may induce to complete chylomicron catabolism with unavoidable loss of Apo B48, but only partial hydrolysis of the triglyceride content of large VLDL converting them into VLDL remnants without the loss of Apo B100 in their lipoprotein core. In our study, plasma triglycerides decreased from a mean of 865+-495 to 557+-304 mg*dL^{-1} which meant a 35% reduction in iAUC of TG (Figure 1). Since Apo B100 did not change with statins, the ratio of triglyceride to Apo B100 was significantly reduced. This suggests that statins may have a beneficial effect by producing a triglyceride poor postprandial lipoprotein particle in individuals with Met Synd. A decrease in this ratio might also decrease the risk of coronary artery disease [28]. Finally, our data argue against the linear association between Apo B liver secretion and triglyceride concentration that others have proposed [29].

This study has several limitations. Our two groups of subjects were not matched by fitness, body composition or age. However, we sought to study if pharmacological (statin) or non-pharmacological (exercise) therapies could return postprandial lipoprotein response to normality and thus, we recruited a group of undoubtedly metabolically healthy individuals (although younger and leaner) from the same population. Secondly, Met Synd subjects were taking different types and dosages of statins with different pharmacokinetics. However, to ensure a full wash out effect, statins were withdrawn during 96 hours which is 5 times the half-life time of the more resilient statin (rosuvastatin). One of the strengths of this study, is that normally, lipoproteins are separated by ultracentrifugation based on density gradients. However, this method does not separate lipoprotein fractions containing chylomicrons and chylomicron remnants but rather heterogenous particle populations containing both Apo B100 and Apo B48. Thus, it is not rare that the chylomicron fraction (large TRL) contains more hepatically derived (Apo B100) than intestinally derived particles [8]. In this study we have directly analyzed in plasma Apo B48 and B100 using enzyme-linked immunosorbent assay (ELISA) which has high sensitivity and specificity for these proteins and thus we are confident on our surrogate indexes of intestinal and hepatic lipoprotein concentration.

In summary, our data suggest, that a bout of aerobic exercise is not effective on reducing PPTG in hypercholesterolemic Met Synd individuals. The actions of exercise were neither evident when statins were withdrawn to better study the possible effects of exercise. Finally, the same exercise bout lowered PPTG in metabolically healthy individuals. These three results combined, suggest that hypercholesterolemic Met

Synd individuals are "resistant" to the beneficial effects of exercise on lowering PPTG. However, statins were very effective lowering fasting and PPTG in hypercolesterolemic Met Synd individuals throughout an increased metabolism of the intestinally derived chylomicrons (i.e., Apo B48).

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

CONFLICT OF INTEREST

The authors report no potential conflicts of interest. The team physician had direct clinical responsibility for patients.

FINANCIAL DISCLOSURE

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Author contributions

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1. Formulated the research question; 2. Designed the study; 3. Collected data; 4. Analyzed the data; 5. Wrote the article; 6. Revised the article

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FIGURE LEGENDS

Figure 1. Postprandial blood triglyceride (PPTG) response to a high-fat meal in metabolic syndrome (Met Synd; n=8) and metabolically healthy (Met Healthy; n=8) individuals after exercise (EXER) or without exercise (REST). In Met Synd group trials were conducted with (STA) or without statins (PLAC). Data are mean +- SEM. * Lower than STA as AUC or iAUC of triglycerides ($P<0.05$). + In Met Healthy EXER lower than REST as AUC or iAUC of triglycerides ($P<0.05$).

Figure 2. Blood serum lipid concentrations in response to a high-fat meal in metabolic syndrome (Met Synd; n=8) and metabolically healthy (Met Healthy; n=8) individuals after exercise (EXER) or without exercise (REST). In Met Synd group trials were conducted with (STA) or without statins (PLAC). Data are mean +- SEM. * Lower than STA as AUC ($P<0.05$). + In Met Healthy EXER lower than REST as AUC ($P<0.05$).

Figure 3 . Blood plasma apolipoprotein concentration (B48 intestinal and B100 hepatic origin) in response to a high-fat meal in metabolic syndrome (Met Synd; n=8) and metabolically healthy (Met Healthy; n=8) individuals after exercise (EXER) or without exercise (REST). In Met Synd group trials were conducted with (STA) or without statins (PLAC). Data are mean +- SEM. * Lower than STA as AUC ($P<0.05$).

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Figure 1

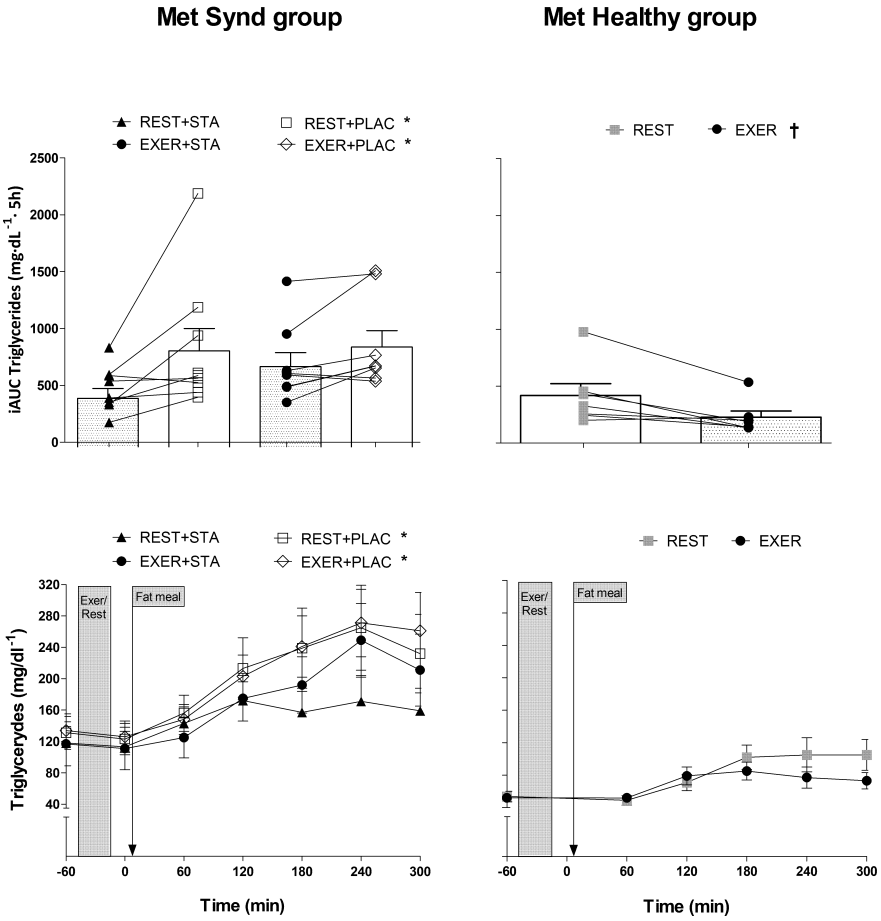

Figure 2

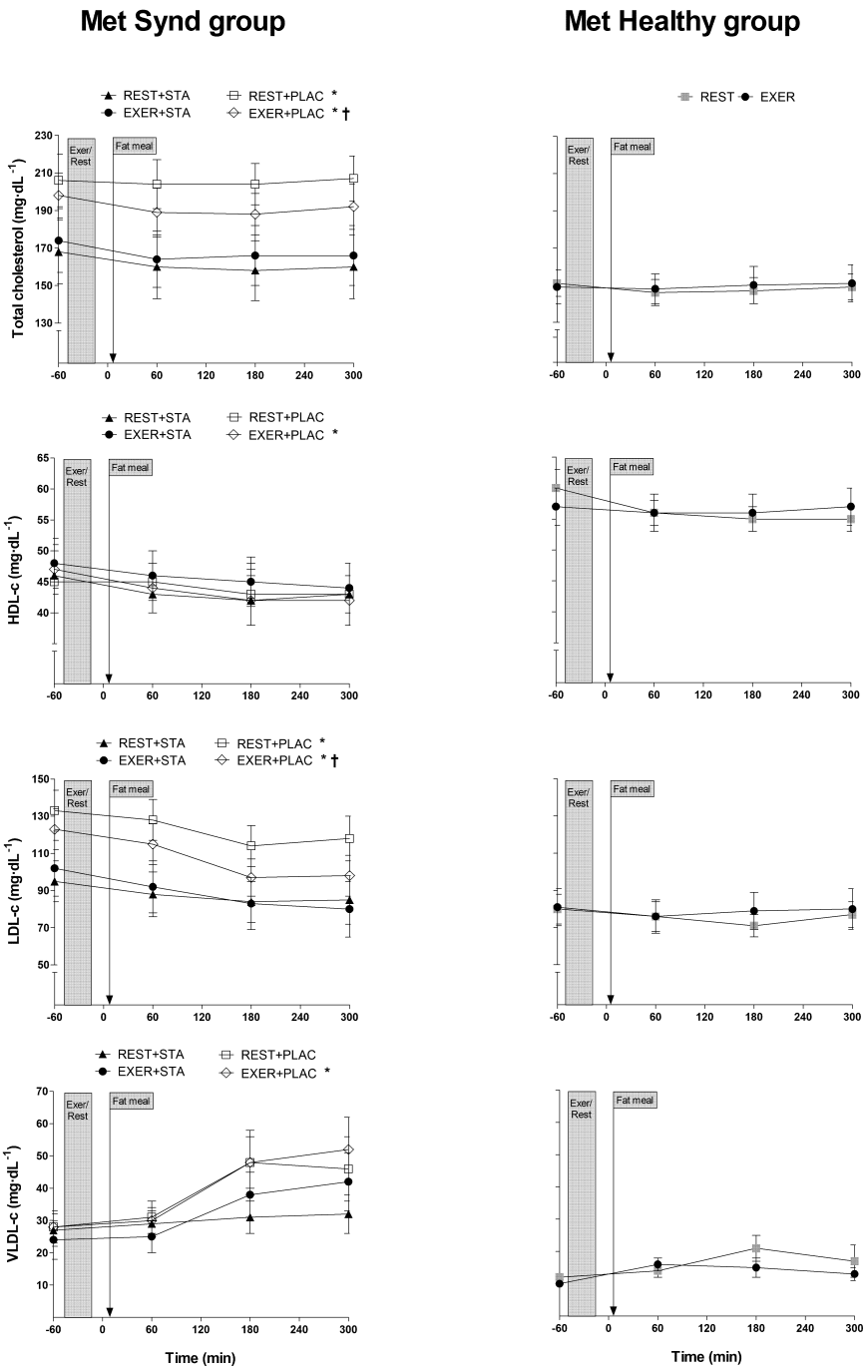

Figure 3