CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Extended-Release Niacin Acutely Suppresses Postprandial Triglyceridemia

M. Haris U. Usman, MD, MSTR,[a,b,c] Arman Qamar, MD,[a] Ramprasad Gadi, MD,[f] Scott Lilly, MD, PhD,[b,e] Harsh Goel, MD,[g] Jaison Hampson, MD,[a] Megan L. Mucksavage, MSTR,[a] Grace A. Nathanson, BA,[a] Daniel J. Rader, MD,[a,b,c,d,e] Richard L. Dunbar, MD, MSTR[a,b,c,d,e]

[a]Department of Medicine, Division of Translational Medicine and Human Genetics, [b]Department of Medicine, Division of Cardiovascular Medicine, [c]Institute for Translational Medicine and Therapeutics, [d]Institute for Diabetes, Obesity, and Metabolism, and [e]The Cardiovascular Institute, Perelman School of Medicine at the University of Pennsylvania, and the University of Pennsylvania Health System, Philadelphia; [f]Division of Cardiovascular Medicine, Einstein Medical Center, Philadelphia, Pa; [g]Department of Medicine, York Hospital, York, Pa.

ABSTRACT

OBJECTIVE: Postprandial triglyceridemia predicts cardiovascular events. Niacin might lower postprandial triglycerides by restricting free fatty acids. Immediate-release niacin reduced postprandial triglycerides, but extended-release niacin failed to do so when dosed the night before a fat challenge. The study aims were to determine whether extended-release niacin dosed before a fat challenge suppresses postprandial triglycerides and whether postprandial triglycerides are related to free fatty acid restriction.

METHODS: A double-blinded, placebo-controlled, random-order crossover experiment was performed, in which healthy volunteers took 2 g extended-release niacin or placebo 1 hour before heavy cream. We sampled blood over 12 hours and report triglycerides and free fatty acid as means ± standard deviation for incremental area under the curve (AUC) and nadir.

RESULTS: By combining 43 fat challenges from 22 subjects, postprandial triglycerides incremental AUC was +312 ± 200 mg/dL*h on placebo versus +199 ± 200 mg/dL*h on extended-release niacin (33% decrease, $P = .02$). The incremental nadir for free fatty acid was −0.07 ± 0.15 mmol/L on placebo versus −0.27 ± 0.13 mmol/L on extended-release niacin ($P < .0001$), and free fatty acid incremental AUC decreased from +2.9 ± 1.5 mmol/L*h to +1.5 ± 1.5 mmol/L*h on extended-release niacin (20% decrease, $P = .0015$). The incremental AUC for triglycerides was strongly related to the post-dose decrease in free fatty acid ($r = +0.58$, $P = .0007$).

CONCLUSIONS: Given right before a fat meal, even a single dose of extended-release niacin suppresses postprandial triglyceridemia. This establishes that postprandial triglycerides suppression is an acute pharmacodynamic effect of extended-release niacin, probably the result of marked free fatty acid restriction. Further study is warranted to determine whether mealtime dosing would augment the clinical efficacy of extended-release niacin therapy.

KEYWORDS: Adult; African Americans; Clinical trial; Dietary fats; Drug; Evaluation; Free fatty acids; Humans; Hydroxybutyrate; Ketones; Lipids; Lipoprotein; Niacin; Niacin/pharmacology; Niacin/therapeutic use; Postprandial; Randomized controlled trial; Triglycerides

Funding: Support provided by NIH grants K23HL091130 and 5-K12-RR-017625-05 (RLD), SCCOR P50-HL-083799 (DJR), and RFA-HL-05-002 (MHUU) from the NHLBI; AHA grants 09SDG2180013 and 0725480U (RLD), and UL1RR024134 from the NCRR, including a Junior Investigator Pilot Grant (RLD) by the UPenn Institute for Diabetes, Obesity, and Metabolism and the UPenn Institute for Translational Medicine and Therapeutics. The content is solely the responsibility of the authors and not sponsoring institutions.

Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.

Requests for reprints should be addressed to Richard L. Dunbar, MD, MSTR, Perelman School of Medicine at the University of Pennsylvania, Translational Medicine & Human Genetics, 3600 Spruce St, 8046 Maloney Building, Philadelphia, PA 19104.

E-mail address: richard.dunbar@uphs.upenn.edu

0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2012.03.017

Hypertriglyceridemia is associated with premature coronary heart disease.[1,2] Although triglycerides peak after meals, they are measured in a fasting state for convenience. Nonfasting triglycerides predict coronary heart disease events better than fasting triglycerides, consistent with the atherogenic potential of alimentary triglyceride-rich lipoproteins and cholesterol-rich remnants.[3-6] Moreover, postprandial triglyceridemia predicts endothelial dysfunction and early atherosclerosis.[7,8] Statins and fibrates suppress postprandial triglycerides, perhaps enhancing cardiovascular benefits.[9,10]

Immediate-release niacin suppresses postprandial triglycerides.[11-14] Although it takes several days to lower cholesterol,[15] immediate-release niacin suppresses postprandial triglycerides within hours of the first dose, indicating that this is an acute pharmacodynamic response.[16] Extended-release niacin had no such benefit.[17] This disparity is relevant because extended-release niacin dominates clinical use, even though only immediate-release niacin prevented hard cardiovascular outcomes.[18,19] If suppression of postprandial triglyceride-rich lipoproteins retards atherosclerosis, extended-release niacin may prove less atheroprotective than immediate-release niacin. Recent cardiovascular outcome studies of niacin + statin exclusively used extended-release niacin.[20,21] Clinical dosing differs by formulation: immediate-release niacin 3× daily with meals versus extended-release niacin once daily at bedtime, that is, before the major/only daily fast. Because triglycerides peak after a meal, one would expect dosing before fasting to undermine efficacy if an acute dosing effect suppresses postprandial triglycerides.[16] We suspect extended-release niacin misses an opportunity for efficacy because its short-lived triglyceride-suppressive effects occur after bedtime, dissipating before breakfast. Conversely, we hypothesized that dosing extended-release niacin before a meal would suppress postprandial triglycerides.

CLINICAL SIGNIFICANCE

- Unlike immediate-release niacin, extended-release niacin previously failed to suppress postprandial triglycerides when dosed the night before a fat meal, implying it lacks an important atheroprotective benefit.
- Extended-release niacin suppressed postprandial triglycerides when given just before a fat meal.
- Suppressed postprandial triglycerides depended on acute restriction of free fatty acids immediately after niacin dosing.
- African Americans did not respond to niacin.

MATERIALS AND METHODS

Objectives

The study objectives were to determine whether extended-release niacin before a fat challenge suppresses postprandial triglyceridemia and whether restricted supply of free fatty acid or its metabolite hydroxybutyrate predicts postprandial triglyceride suppression.

Design

We performed a double-blind, random-order, crossover experiment of a single 2 g dose of extended-release niacin or placebo in niacin-naïve subjects lacking all elements of metabolic syndrome (Supplemental Figure 1).

Protocol

Subjects presented after a 12-hour overnight fast and took 2 g extended-release niacin (Kos Pharmaceuticals, Miami, Fla) or matching placebo (hour 0). After 1 hour, they drank heavy cream 50 g/m^2 surface area within 20 minutes, per the oral fat tolerance test of Cabezas et al.[22] We sampled blood from an antecubital intravenous catheter hourly for 12 hours. Subjects crossed to alternative treatment after ≥ 1 week. Some also provided 12 hours of fasting samples as a physiologic reference.

Laboratory Analysis

Within 30 minutes of collection into chilled ethylenediaminetetraacetic acid tubes, plasma was separated from whole blood in a 4°C centrifuge. This was stored at −70°C until assaying runs by subject for triglycerides, free fatty acid, and hydroxybutyrate enzymatically on a Hitachi 912 autoanalyzer (Roche Diagnostic Systems Inc, Indianapolis, Ind) using Sigma reagents (Sigma-Aldrich, St Louis, Mo). The respective intra-assay and interassay coefficients of variation were 1.5% and 1.8% for triglycerides, 0.75% and 0.75% for free fatty acid, and 10% and 5% for hydroxybutyrate.

Statistics

We calculated the area under the curve (AUC) over 12 hours using the trapezoidal rule, baseline by averaging −20-, −10-, and 0-minute samples, and incremental AUC as AUC − (baseline × 12 hours). Although the recommended sample size for postprandial triglycerides studies is at least 10 subjects,[23] our power calculations suggested a need for 22 subjects according to related literature.[22,24-26] By assuming a baseline triglyceride AUC of 2482 mg/dL*h, we needed 21 subjects for 80% power to detect a 615 mg/dL*h (25%) decrease with a standard deviation of 691 mg/dL*h for the study's significance threshold: a 2-tailed alpha at < 0.05. We performed all analyses in Stata v10.0 (StataCorp LP, College Station, Tex), comparing incremental AUC by mixed-effects regression, adjusting for sex, African American race, and body mass index. African Americans typically have lower fasting[27] and postprandial triglycerides,[28] so we tested for race interaction. We report mean, standard deviation, and 95% confidence intervals.

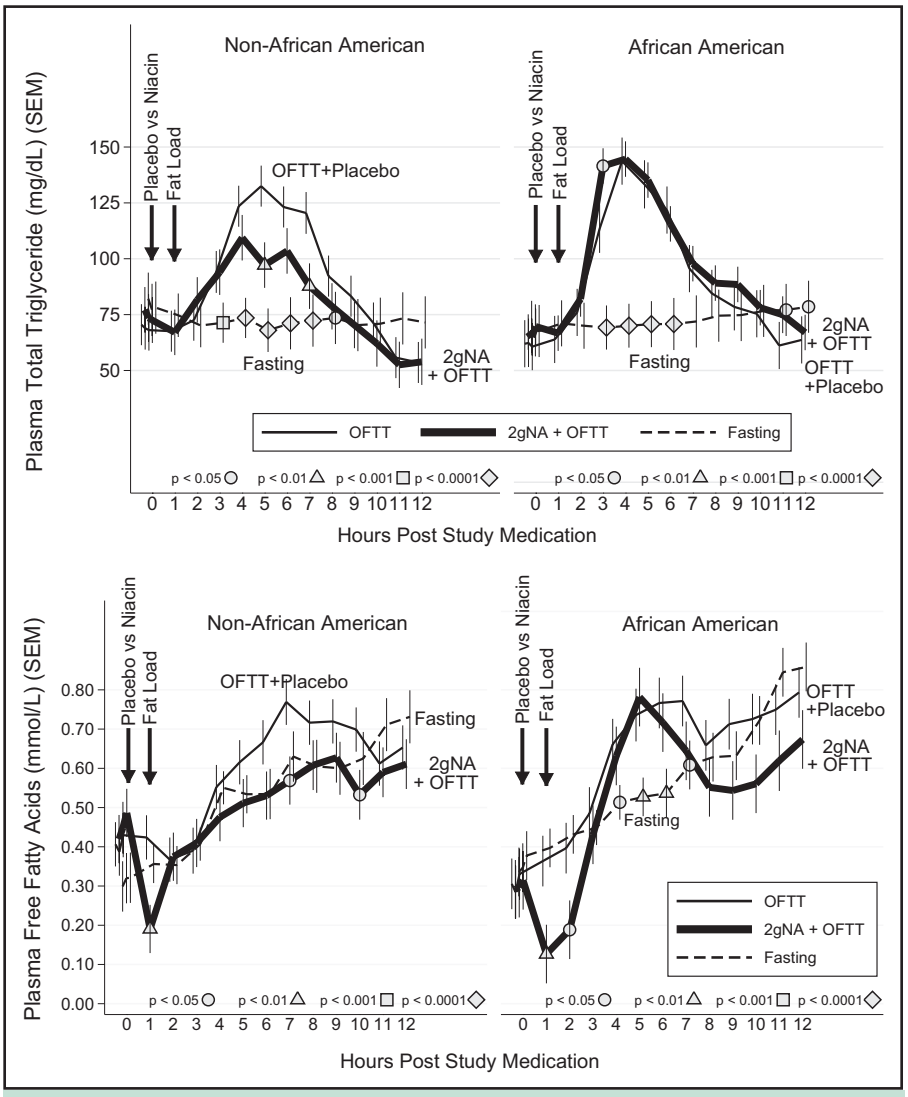


Figure 1 Effect of niacin on postprandial triglycerides. **A,** Time course of postprandial triglycerides. **B,** Time course of postprandial free fatty acids. *Filled shapes* denote a significant comparison with OFTT + placebo at the same hour. NA = niacin; OFTT = oral fat tolerance test; SEM = standard error of the mean.

RESULTS

Participants

Because 22 subjects received both oral fat tolerance tests, we analyzed 44 oral fat tolerance test studies (Supplemental Figure 1, Supplemental Table 1).

Extended-Release Niacin Suppresses Postprandial Triglycerides

On placebo, postprandial triglycerides increased $+82 \pm 35$ mg/dL, peaking at 150 ± 49 mg/dL after 5.6 ± 2.5 hours, and normalizing by 9 hours (**Figure 1**A). This bell-shaped curve is typical of postprandial triglycerides, for which the ascending phase indicates triglyceride-rich lipoprotein accumulation, and the descending phase indicates triglyceride-rich lipoprotein clearance.[23] On extended-release niacin, postprandial triglycerides increased $+72 \pm 41$ mg/dL, peaking at 143 ± 49 mg/dL after 4.8 ± 2.4 hours and normalizing by 9 hours. During the accumulation phase, the increase in triglycerides was superimposable. In contrast, extended-release niacin significantly decreased postprandial triglycerides levels during the post-peak clearance phase at 5 and 7 hours (both $P < .01$ vs placebo). On placebo, triglyceride incremental AUC was $+312 \pm 200$ mg/dL*h versus $+199 \pm 200$ mg/dL*h on extended-release niacin ($P = .02$), a median decrease of 82 mg/dL (−33%) from the oral fat tolerance test alone (**Figure 2**, **Table 1**).

With extended-release niacin, significant interactions were found by race. During triglyceride-rich lipoprotein accumulation, African Americans reach peak triglyceride faster. Post-peak, during the triglyceride-rich lipoprotein

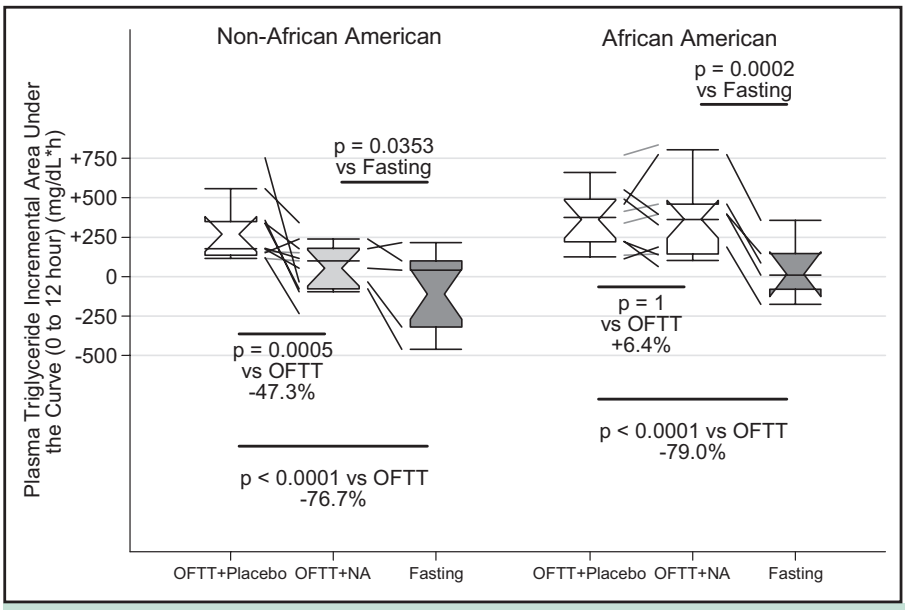


Figure 2 Effect of niacin on triglyceride incremental AUC. *Whiskers* delimit 10th and 90th percentiles, *enclosed region* depicts the IQR, *horizontal line* depicts the median, and *notches* depict the 95% confidence interval and mean. *Diagonal lines* depict change in each individual. Percent change is the median of individuals' change. NA = niacin; OFTT = oral fat tolerance test.

clearance phase, extended-release niacin failed to suppress triglyceride among African Americans (interaction $P = .01$, **Figure 1** A). The median percent change in triglyceride incremental AUC was −47% on extended-release niacin (interquartile range [IQR], −123 to −14) among non–African Americans versus +4% (IQR, −14 to +15) among African Americans. Thus, the 33% decrease in triglyceride incremental AUC pooling races obscures a marked disparity, falsely implying a benefit in African Americans and underestimating benefit in others. Accordingly, we recommend that outcomes be considered separately because interaction is present. The triglyceride incremental AUC among non–African Americans was +270 ± 196 mg/dL*h on placebo vs +54 ± 194 mg/dL*h on niacin ($P = .0005$, median decrease 160 mg/dL*h), driven by a decrease during the triglyceride-rich lipoprotein clearance phase from 5 to 7 hours. In contrast, triglyceride incremental AUC among African Americans was +363 ± 193 mg/dL*h on placebo and 364 ± 193 mg/dL*h on niacin (+26 mg/dL*h, $P = 1$). Moreover, niacin failed to reduce postprandial triglycerides from placebo at any time and even exceeded placebo at 3 hours ($P < .05$).

Effect of Niacin on Postprandial Free Fatty Acids and Hydroxybutyrate

On placebo, postprandial free fatty acid increased 0.561 ± 0.480 mmol/L, peaking at 7.3 ± 2.7 hours. The free fatty acid did not normalize because even fasting increases free fatty acid (**Figure 1**B). In non–African Americans, postprandial free fatty acid did not differ from the fasting reference. In African Americans, postprandial free fatty acid exceeded fasting levels at hours 4 to 7 (all $P < .05$). On niacin, the classic antilipolytic effect was seen, because free fatty acid decreased 0.274 ± 0.134 mmol/L to an absolute nadir of 0.108 ± 0.109 mmol/L at 3.9 ± 4.0 hours post-niacin. At hour 1, the nadir decreased below baseline irrespective of race ($P < .01$), and at hour 2, the nadir remained lower in African Americans ($P < .05$, **Figure 1**B). Among non–African Americans, post-nadir free fatty acid tracked with postprandial and fasting free fatty acid except for a few decreases after hour 7. Among African Americans, postprandial free fatty acid exceeded fasting free fatty acid at 4 to 6 hours (all $P < .03$), as well for non–African Americans (all $P < .05$). This suggests that free fatty acid rebound in African Americans prevented niacin from suppressing postprandial triglycerides. Irrespective of race, on placebo free fatty acid incremental AUC was +2.93 ± 1.48 mmol/L*h versus +1.49 ± 1.48 mmol/L*h on extended-release niacin over 12 hours ($P = .0015$), a decrease of 0.59 mmol/L*h (−20%, **Table 1**).

Because only hepatocytes convert free fatty acid to hydroxybutyrate, plasma hydroxybutyrate reflects hepatic free fatty acid exposure and corroborates free fatty acid substrate availability for hepatic triglyceride assembly. Postprandial hydroxybutyrate resembled free fatty acid, with a nadir of 63.4. ± 50.1 μmol/L on placebo and abruptly decreasing to 32.5 ± 50.1 μmol/L on niacin ($P = .006$). Among African Americans, hydroxybutyrate rebounded between 4 to 8 hours, but gradually peaked at 12 hours in others (Supplemental Figure 2). Irrespective of race, on placebo hydroxybutyrate incremental AUC was +3931 ± 2472 μmol/L*h

Table 1 Postprandial Lipid Changes

Effect of Niacin on Selected Outcomes

	Oral Fat Tolerance Test	2 g Extended-Release Niacin + OFTT	Fasting Alone	Fasting vs Niacin + OFTT
Plasma TG Total AUC (0-12 h) (mg/dL*h) in Non–African Americans				
Mean (95% CI)	1102.0 (921.0-1283.0)	917.6 (732.6-1102.5)	914.7 (688.1-1141.4)	$P = .6638$
P vs OFTT	Ref	$P = .0099$	$P = .02$	
Median delta (IQR)		−94.5 mg/dL*h (−469.5 to +11.0)	−286.9 mg/dL*h (−369.4 to −187.3)	
Median % change (IQR)		−11.6% (−30.3 to +1.8%)	−28.4% (−31.5 to −16.5%)	
Plasma TG Total AUC (0-12 h) (mg/dL*h) in African Americans (Interaction $P = .0488$)				
Mean (95% CI)	1125.1 (935.0-1315.3)	1145.4 (955.2-1335.5)	856.8 (640.5-1073.0)	$P = .045$
P vs OFTT	Ref	$P = .8$	$P = .031$	
Median delta (IQR)		+50.3 mg/dL*h (−153.5 to +117.5)	−149.9 mg/dL*h (−254.9 to −66.0)	
Median % change (IQR)		+4.0% (−13.7 to +14.8%)	−11.0% (−19.9 to −9.7%)	
Plasma TG Incremental AUC (0-12 h) (mg/dL*h) in Non–African Americans				
Mean (95% CI)	+270.0 (+159.3 to +380.7)	+53.7 (−61.1 to +168.5)	−111.1 (−269.8 to +47.5)	$P = .0353$
P vs OFTT	Ref	$P = .0005$	$P < .0001$	
Median delta (IQR)		−160.0 mg/dL*h (−414.5 to −16.0)	−133.4 mg/dL*h (−798.9 to −123.2)	
Median % change (IQR)		−47.3% (−123.0 to −13.9%)	−76.7% (−142.3 to −36.5%)	
Plasma TG Incremental AUC (0-12 h) (mg/dL*h) in African Americans (Interaction $P = .0174$)				
Mean (95% CI)	+362.8 (+243.2 to +482.5)	+363.5 (+243.8 to +483.1)	+14.2 (−127.6 to +156.0)	$P = .0002$
P vs OFTT	Ref	$P = 1$	$P < .0001$	
Median delta (IQR)		+26.0 mg/dL*h (−152.5 to +62.5)	−326.9 mg/dL*h (−329.4 to −286.0)	
Median % change (IQR)		+6.4% (−33.1 to +16.9%)	−79.0% (−97.4 to −73.2%)	
Plasma FFA AUC (0-12 h) (mmol/L*h) Pooled Across Race (Interaction $P = .9037$)				
Mean (95% CI)	7.326 (6.749-7.904)	6.014 (5.428-6.600)	6.638 (6.038-7.238)	$P = .0296$
P vs OFTT	Ref	$P < .0001$	$P = .059$	
Median delta (IQR)		−1.615 mmol/L*h (−2.075 to −0.515)	−0.815 mmol/L*h (−1.466 to −0.005)	
Median % change (IQR)		−23.7% (−30.3 to −5.6%)	−14.0% (−22.7 to −0.1%)	
Plasma FFA Incremental AUC (0-12 h) (mmol/L*h) Pooled Across Race (Interaction $P = .5578$)				
Mean (95% CI)	+2.930 (+2.311 to +3.550)	+1.492 (+0.857 to +2.126)	+2.474 (+1.807 to +3.141)	$P = .1762$
P vs OFTT	Ref	$P = .0015$	$P = .09$	
Median delta (IQR)		−0.585 mmol/L*h (−3.235 to +0.040)	−0.340 mmol/L*h (−2.355 to +1.079)	
Median % change (IQR)		−20.0% (−80.3 to +3.1%)	−9.3% (−40.8 to +32.5%)	

Table 1 Continued

Effect of Niacin on Selected Outcomes

	Oral Fat Tolerance Test	2 g Extended-Release Niacin + OFTT	Fasting Alone	Fasting vs Niacin + OFTT
Plasma Hydroxybutyrate AUC (0-12 h) (μmol/L*h) Pooled Across Race (Interaction $P = .4994$)				
Mean (95% CI)	3930.7 (2898.0-4963.5)	3328.9 (2291.0-4366.8)	2643.3 (1606.1-3680.4)	$P = .2305$
P vs OFTT	Ref	$P = .032$	$P = .0027$	
Median delta (IQR)		−547.5 μmol/L*h (−982.0 to +92.5)	−1438.5 μmol/L*h (−1938.5 to −1069.8)	
Median % change (IQR)		−19.9% (−36.1 to +5.0%)	−62.8% (−72.1 to −29.6%)	
Plasma Hydroxybutyrate Incremental AUC (0-12 h) (μmol/L*h) Pooled Across Race (Interaction $P = .5785$)				
Mean (95% CI)	+3094.4 (+1999.3 to +4189.4)	+2530.9 (+1492.0 to +3569.9)	+1829.7 (+875.5 to +2784.0)	$P = .0921$
P vs OFTT	Ref	$P = .07$	$P < .0001$	
Median delta (IQR)		−790.0 μmol/L*h (−1370.0 to −105.5)	−1154.6 μmol/L*h (−1573.4 to −817.8)	
Median % change (IQR)		−37.6% (−65.0 to −11.2%)	−67.5% (−79.5 to −24.4%)	

AUC = area under the curve; CI = confidence interval; FFA = free fatty acids; IQR = interquartile range; OFTT = oral fat tolerance test; TG = triglyceride.
Note that a negative incremental AUC is the same as –(incremental area over the curve) and represents a decrease from baseline.

versus +3329 ± 2427 μmol/L*h on niacin ($P = .032$), a decrease of 548 μmol/L*h (−20%, **Table 1**).

Restricted Fatty Acids Predict Suppressed Postprandial Triglyceride

Because the liver depends on adipose tissue for free fatty acid to make triglyceride, niacin-induced free fatty acid restriction could limit hepatic triglyceride assembly by substrate limitation. Accordingly, changes in free fatty acid or hydroxybutyrate predicted subsequent changes in triglyceride incremental AUC (**Figure 3**, Supplemental Table 2). As expected, regression often revealed a stronger relationship than Spearman's correlation coefficient, because the former adjusted for race (Supplemental Table 2). Triglyceride incremental AUC was strongly predicted by the incremental nadirs of free fatty acid ($r = +0.58$, $P = .0007$) and hydroxybutyrate ($r = +0.52$, $P = .0011$), suggesting that abruptly restricting free fatty acid or hydroxybutyrate drives subsequent triglyceride suppression. Time to hydroxybutyrate nadir inversely correlated with triglyceride incremental AUC ($r = -0.55$, $P = .05$), implying that prolonged restriction of hepatic free fatty acid supply predicts greater postprandial triglycerides suppression. The free fatty acid incremental AUC strongly correlated with triglyceride incremental AUC ($r = +0.49$). Thus, restricted free fatty acid supply predicts suppressed postprandial triglycerides.

DISCUSSION

The current study is the first to demonstrate that extended-release niacin suppresses postprandial triglyceridemia. Frequent sampling revealed that acutely dosed extended-release niacin suppresses triglycerides during the post-peak triglyceride-rich lipoprotein clearance phase only, as does immediate-release niacin.[11,12] Our pooled 33% reduction in triglyceride incremental AUC by 2 g extended-release niacin resembles reductions on chronic immediate-release niacin (Supplemental Table 3, online).[12-14] Others found immediate-release niacin 3× daily with meals suppressed diurnal/postprandial triglycerides (9 AM to 9 PM), as well as nocturnal/post-absorptive triglycerides (10 PM to 9 AM), and 24 hours AUC.[12] We show that extended-release niacin also suppresses diurnal/postprandial triglycerides for 12 hours, provided niacin is given before a meal; however, the full 24-hour effect remains unknown. Irrespective of formulation, niacin reduces triglyceride AUC 21% to 41%.[12-14] Statins suppress postprandial triglycerides 2% to 33%[29] and fibrates 33% to 55%,[30] suggesting 2 to 3 g niacin has intermediate potency. Additive effects are reported with statin + gemfibrozil[31] and statin + immediate-release niacin.[14] Because postprandial triglyceride-rich lipoproteins are considered atherogenic, we believe further study of combination therapy is warranted.

Our results vary from those of Plaisance et al,[17] whose bedtime dosing of ≤ 1500 mg extended-release niacin for 6 weeks failed to suppress postprandial triglycerides the next day, adversely distinguishing extended-release niacin from

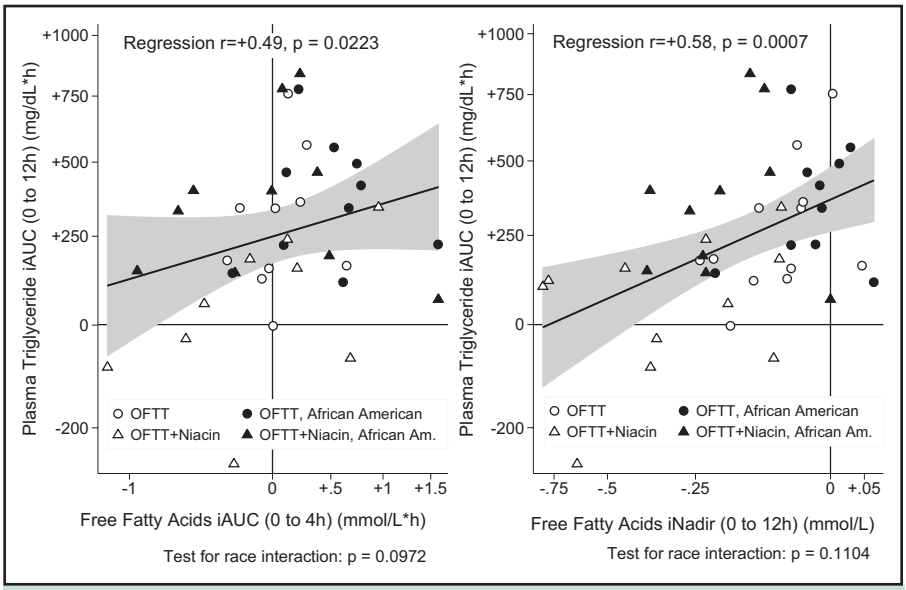


Figure 3 Relationship between postprandial fatty acids and postprandial triglycerides. We transformed the triglyceride incremental AUC to reduce heteroskedasticity and skew. iAUC = incremental area under curve; iNadir = incremental nadir; OFTT = oral fat tolerance test.

immediate-release niacin. Our results may differ for several reasons. Perhaps their subjects with metabolic syndrome took medications interfering with postprandial triglyceride suppression not used by our healthier cohort. They used chronic niacin therapy; conceivably, the first-exposure postprandial triglycerides response is greater than long-term response (ie, tachyphylaxis). If so, our suppression might not translate to chronic therapy. On the contrary, immediate-release niacin chronically suppresses postprandial triglycerides. Moreover, triglyceride suppression grows more potent at the end of the first week versus first exposure to immediate-release niacin.[15] Perhaps they enrolled more African Americans or other nonresponders. Differences in oral fat tolerance test might explain the disparate results; however, their carbohydrate-enriched oral fat tolerance test should amplify/prolong free fatty acid and hydroxybutyrate restriction by insulin's antilipolytic effect, thus deepening triglyceride suppression and not accounting for the discrepancy.

The simplest explanation may be that niacin's ability to suppress postprandial triglycerides depends on acute postdose pharmacodynamics. Accordingly, we speculate that bedtime dosing squanders an opportunity and suggest comparing bedtime with pre-prandial extended-release niacin to test this. Further study is justified because counterphysiologic dosing could diminish extended-release niacin's efficacy as an atheroprotective therapy, because nocturnally dosed extended-release niacin fails to suppress atherogenic postprandial remnant lipoproteins. A recent study found that cardiovascular benefits of ≤ 3 g mealtime immediate-release niacin did not materialize when ≤ 2 g bedtime extended-release niacin was compared with placebo, with aggressive statin titration or addition of ezetimibe therapy in both groups.[20] Disappointing cardiovascular effects of bedtime extended-release niacin may involve failure to suppress atherogenic triglyceride-rich lipoproteins/remnants during the postprandial phase that dominates the 24-hour period. By completely dissociating acute from chronic effects, we challenge the notion that niacin suppresses postprandial triglyceridemia by merely lowering baseline/fasting triglyceride.[17]

Froberg et al[12] proposed 3 candidate mechanisms for niacin-induced postprandial triglycerides suppression: (1) accelerating chylomicron or very low density lipoprotein catabolism (eg, by enhancing lipoprotein lipase activity); (2) retarding intestinal chylomicron production; or (3) retarding very low density lipoprotein production (eg, free fatty acid restriction). The third mechanism is best supported, and we offer an expanded mechanistic hypothesis (Supplemental Figure 3, online). A dose of niacin rapidly suppresses hormone-sensitive lipase[32] by stimulating adipocyte GPR109A.[33-35] Thus, niacin restricts lipolysis of stored triglyceride to free fatty acid, prompting a precipitous decrease in adipose-derived plasma free fatty acid within minutes,[36] restricting free fatty acid delivery to the liver, largely via the portal vein.[16,32,33] Because the liver depends on adipose-derived free fatty acid for triglyceride synthesis, restricted free fatty acid supply suppresses triglyceride synthesis, halting very low density lipoprotein production as early as 1 hour post-dose.[37] With a half-life of 1 to 2 hours,[37] arrested very low density lipoprotein production takes several hours to shrink the very low density lipoprotein and total triglyceride pools, consistent with observed triglyceride suppression 4 hours post-dose.[16] Niacin-induced free fatty acid restriction is thought to initiate very

low density lipoprotein and plasma triglyceride suppression.[38,39] Sustained suppression during plasma free fatty acid rebound suggests that additional mechanisms perpetuate the initial halt in very low density lipoprotein production[37,40-42] or that restored production simply lags plasma free fatty acid rebound.

Regardless of how niacin suppresses very low density lipoprotein-triglyceride production, the resulting post-dose reduction in the very low density lipoprotein-triglyceride pool could be exploited clinically to reduce postprandial chylomicron triglyceride by simply taking extended-release niacin at mealtime. Catabolism of chylomicron/very low density lipoprotein triglyceride is rate-limited by lipoprotein lipase, facilitating dissolution of triglyceride to free fatty acid. Because chylomicron and very low density lipoprotein compete for lipoprotein lipase, post-dose restriction of very low density lipoprotein-triglyceride leaves more lipoprotein lipase available for chylomicron-triglyceride catabolism, facilitating postprandial triglycerides clearance. Moreover, free fatty acid inhibits lipoprotein lipase activity;[43] thus, restricted free fatty acid disinhibits lipoprotein lipase activity, another way mealtime niacin might accelerate triglyceride-rich lipoprotein catabolism. Accordingly, in our study restricted free fatty acid preceded postprandial triglycerides suppression during the clearance phase of the curve 5 to 7 hours post-niacin, with robust correlations between rapid free fatty acid restriction ($r = +0.58$) or hydroxybutyrate ($r = +0.52$) and subsequent postprandial triglycerides suppression, which to our knowledge are novel. Although free fatty acid restriction has long been invoked to explain triglyceride suppression by virtue of biological plausibility, strong correlations in our study advance the case for a causal relationship.

Plasma free fatty acid may not reflect the totality of hepatic exposure to free fatty acid by underrepresenting portal free fatty acid delivery to the liver.[44] Because hepatocytes convert free fatty acid to hydroxybutyrate, plasma hydroxybutyrate may thereby provide a more specific marker for hepatic (ie, portal) free fatty acid flux than peripheral vein free fatty acid.[44] Thus, hydroxybutyrate provides an important and novel corroboration of the concept that restricted free fatty acid mediates postprandial triglyceride suppression.

The major clinical implication is that the recommended dosing strategy for extended-release niacin undermines its efficacy, especially because our results are in accord with studies of periprandial immediate-release niacin, whereas the study of pre-fast extended-release niacin had no effect on postprandial triglycerides. We propose that dosing extended-release niacin at bedtime undermines efficacy by (1) ensuring the rapid decrease in free fatty acid is long gone by the time of the next day's meal, an opportunity cost; and (2) risking timing breakfast during the free fatty acid rebound, an active interference with benefit. Indeed, bedtime dosing increases fasting free fatty acid well into the next morning, reflecting nocturnal free fatty acid rebound, which may promote very low density lipoprotein production, thereby undermining triglyceride suppression.[45-47] Alternatively, pre-meal dosing of extended-release niacin could fully exploit a postprandial benefit and even forestall nocturnal free fatty acid rebound, deepening fasting triglyceride suppression. A theoretic benefit has been used to justify bedtime dosing of extended-release niacin[48] because type IV triglyceridemics exposed to a high-carbohydrate meal and niacin infusion had diminished nocturnal free fatty acid rebound and triglycerides.[49] A more practical reason to initiate extended-release niacin at bedtime is to time the disagreeable dermal response with sleep.[50] We propose that after developing tolerance to the latter, bedtime dosing is neither obligatory nor advantageous. Indeed, the results of Plaisance et al[17] and our group imply that nocturnal dosing undermines a potentially atheroprotective benefit of the extended-release formulation. If switching the timing conferred additional 24-hour efficacy, perhaps extended-release niacin would achieve similar fasting and postprandial efficacy as immediate-release niacin, a proposition worthy of additional study.

The African-American population has lower fasting triglycerides and postprandial triglycerides.[28] This may reflect increased lipoprotein lipase activity and superior triglyceride-rich lipoprotein clearance. Fasting and postprandial triglycerides did not vary by race on oral fat tolerance test + placebo in our study. Perhaps the expected racial differences depend on variations in metabolic defects, so selecting fit subjects abrogated differences. With extended-release niacin in African Americans, free fatty acid rebound quickly followed free fatty acid restriction, suggesting that free fatty acid rebound prevented niacin from accelerating triglyceride-rich lipoprotein clearance.[47] To our knowledge, this is the first study demonstrating significant inefficacy of extended-release niacin in African Americans, but it does not speak to the inefficacy of long-term therapy or fasting lipoproteins.

Study Limitations

Our study is subject to several limitations. We limited niacin to a single exposure in drug-naïve subjects to separate acute pharmacodynamic from chronic therapy effects, thus better representing pharmacodynamic effects at the expense of generalizability to chronic therapy. We limited intra-individual variability by enrolling healthy individuals at the expense of generalizability to dyslipidemia. We selected an oral fat tolerance test with minimal insulin effects.[51] Although this minimizes confounding by a second antilipolytic, it limits generalizability to mixed meals. Strengths include the randomized, double-blind, placebo-controlled design, larger sample size than prior studies,[11-14,17] high-resolution sampling, and robust participation of African Americans, which allowed us to detect interaction by race.

CONCLUSIONS

We found a single exposure to extended-release niacin suppressed postprandial triglyceridemia in drug-naïve subjects,

in contrast to a report in which bedtime extended-release niacin failed to suppress postprandial triglyceridemia at breakfast. This indicates niacin suppresses postprandial triglyceridemia by an acute pharmacodynamic effect, probably by restricted free fatty acid supply limiting very low density lipoprotein and accelerating chylomicron catabolism. Clinically, this challenges the conventional wisdom of dosing extended-release niacin before a prolonged fast, which may undermine lipid if not atherosclerosis benefits.

ACKNOWLEDGMENTS

The authors thank Lorraine Norfleet, RN, Rhoda Collick, RN, the nurses and nutritionists of the UPenn Clinical and Translational Research Centers, Andrew Cucchiara, PhD, for statistical assistance, Joseph Jalkiewicz of Good Word Communications, LLC, for editorial assistance, and especially the study participants.

References

1. Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation*. 2007;115:450-458.
2. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;3:213-219.
3. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA*. 2007;298:299-308.
4. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA*. 2007;298:309-316.
5. Sharrett AR, Chambless LE, Heiss G, Paton CC, Patsch W. Association of postprandial triglyceride and retinyl palmitate responses with asymptomatic carotid artery atherosclerosis in middle-aged men and women. The Atherosclerosis Risk in Communities (ARIC) Study. *Arterioscler Thromb Vasc Biol*. 1995;15:2122-2129.
6. Ryu JE, Howard G, Craven TE, Bond MG, Hagaman AP, Crouse JR III. Postprandial triglyceridemia and carotid atherosclerosis in middle-aged subjects. *Stroke*. 1992;23:823-828.
7. Boquist S, Ruotolo G, Tang R, et al. Alimentary lipemia, postprandial triglyceride-rich lipoproteins, and common carotid intima-media thickness in healthy, middle-aged men. *Circulation*. 1999;100:723-728.
8. Vogel RA, Corretti MC, Plotnick GD. Effect of a single high-fat meal on endothelial function in healthy subjects. *Am J Cardiol*. 1997;79:350-354.
9. Kolovou GD, Kostakou PM, Anagnostopoulou KK, Cokkinos DV. Therapeutic effects of fibrates in postprandial lipemia. *Am J Cardiovasc Drugs*. 2008;8:243-255.
10. Kolovou GD, Anagnostopoulou KK, Salpea KD, Daskalopoulou SS, Mikhailidis DP. The effect of statins on postprandial lipemia. *Curr Drug Targets*. 2007;8:551-560.
11. Nikkila EA. Effect of nicotinic acid on adipose lipoprotein lipase and removal rate of plasma triglycerides. In: Gey KF, Carlson LA, eds. *Metabolic Effects of Nicotinic Acid and its Derivatives*. Bern: Hanss Huber Publishers; 1971:487-496.
12. Froberg S, Boberg J, Carlson LA, Eriksson M. Effect of nicotinic acid on the diurnal variation of plasma levels of glucose, free fatty acids, triglycerides and cholesterol and of urinary excretion of catecholamines. In: Gey KF, Carlson LA, eds. *Metabolic Effects of Nicotinic Acid and its Derivatives*. Bern: Hanss Huber Publishers; 1971:167-181.
13. King JM, Crouse JR, Terry JG, Morgan TM, Spray BJ, Miller NE. Evaluation of effects of unmodified niacin on fasting and postprandial plasma lipids in normolipidemic men with hypoalphalipoproteinemia. *Am J Med*. 1994;97:323-331.
14. O'Keefe JH Jr, Harris WS, Nelson J, Windsor SL. Effects of pravastatin with niacin or magnesium on lipid levels and postprandial lipemia. *Am J Cardiol*. 1995;76:480-484.
15. Carlson LA, Oro L, Ostman J. Effect of nicotinic acid on plasma lipids in patients with hyperlipoproteinemia during the first week of treatment. *J Atheroscler Res*. 1968;8:667-677.
16. Carlson LA, Oro L, Ostman J. Effect of a single dose of nicotinic acid on plasma lipids in patients with hyperlipoproteinemia. *Acta Med Scand*. 1968;183:457-465.
17. Plaisance EP, Mestek ML, Mahurin AJ, Taylor JK, Moncada-Jimenez J, Grandjean PW. Postprandial triglyceride responses to aerobic exercise and extended-release niacin. *Am J Clin Nutr*. 2008;88:30-37.
18. The Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA*. 1975;231:360-381.
19. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986;8:1245-1255.
20. The AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365:2255-2267.
21. HPS2-Thrive: a randomized trial of the long-term clinical effects of raising HDL cholesterol with extended-release niacin/laropiprant. Available at: http://www.thrivestudy.org. Accessed June 8, 2012.
22. Cabezas MC, de Bruin TW, Jansen H, Kock LA, Kortlandt W, Erkelens DW. Impaired chylomicron remnant clearance in familial combined hyperlipidemia. *Arterioscler Thromb*. 1993;13:804-814.
23. Lairon D, Lopez-Miranda J, Williams C. Methodology for studying postprandial lipid metabolism. *Eur J Clin Nutr*. 2007;61:1145-1161.
24. Birjmohun RS, Hutten BA, Kastelein JJP, Stroes ESG. Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. *J Am Coll Cardiol*. 2005;45:185-197.
25. Insull W Jr, McGovern ME, Schrott H, et al. Efficacy of extended-release niacin with lovastatin for hypercholesterolemia: assessing all reasonable doses with innovative surface graph analysis. *Arch Intern Med*. 2004;164:1121-1127.
26. Vega GL, Cater NB, Meguro S, Grundy SM. Influence of extended-release nicotinic acid on nonesterified fatty acid flux in the metabolic syndrome with atherogenic dyslipidemia. *Am J Cardiol*. 2005;95:1309-1313.
27. Florez H, Mendez A, Casanova-Romero P, et al. Increased apolipoprotein C-III levels associated with insulin resistance contribute to dyslipidemia in normoglycemic and diabetic subjects from a triethnic population. *Atherosclerosis*. 2006;188:134-141.
28. Friday KE, Srinivasan SR, Elkasabany A, et al. Black-white differences in postprandial triglyceride response and postheparin lipoprotein lipase and hepatic triglyceride lipase among young men. *Metabolism*. 1999;48:749-754.
29. van Oostrom AJ, van WJ, Cabezas MC. Lipaemia, inflammation and atherosclerosis: novel opportunities in the understanding and treatment of atherosclerosis. *Drugs*. 2004;64(Suppl 2):19-41.
30. Fredrik K. Postprandial lipemia-effect of lipid-lowering drugs. *Atheroscler Suppl*. 2002;3:41-46.
31. Cabezas CM, Erkelens DW, Kock LA, de Bruin TW. Postprandial apolipoprotein B100 and B48 metabolism in familial combined hyperlipidaemia before and after reduction of fasting plasma triglycerides. *Eur J Clin Invest*. 1994;24:669-678.
32. Carlson LA. Studies on the effect of nicotinic acid on catecholamine stimulated lipolysis in adipose tissue in vitro. *Acta Med Scand*. 1963;173:719-722.
33. Tunaru S, Kero J, Schaub A, et al. PUMA-G and HM74 are receptors for nicotinic acid and mediate its anti-lipolytic effect. *Nat Med*. 2003;9:352-355.

34. Wise A, Foord SM, Fraser NJ, et al. Molecular identification of high and low affinity receptors for nicotinic acid. *J Biol Chem*. 2003;278: 9869-9874.
35. Soga T, Kamohara M, Takasaki J, et al. Molecular identification of nicotinic acid receptor. *Biochem Biophys Res Commun*. 2003;303:364-369.
36. Carlson LA, Oro L. The effect of nicotinic acid on the plasma free fatty acid; demonstration of a metabolic type of sympathicolysis. *Acta Med Scand*. 1962;172:641-645.
37. Wang W, Basinger A, Neese RA, et al. Effect of nicotinic acid administration on hepatic very low density lipoprotein-triglyceride production. *Am J Physiol Endocrinol Metab*. 2001;280:E540-E547.
38. Carlson LA. Nicotinic acid: the broad-spectrum lipid drug. A 50th anniversary review. *J Intern Med*. 2005;258:94-114.
39. Lukasova M, Hanson J, Tunaru S, Offermanns S. Nicotinic acid (niacin): new lipid-independent mechanisms of action and therapeutic potentials. *Trends Pharmacol Sci*. 2011;32:700-707.
40. Grundy SM, Mok HY, Zech L, Berman M. Influence of nicotinic acid on metabolism of cholesterol and triglycerides in man. *J Lipid Res*. 1981;22:24-36.
41. Ganji SH, Tavintharan S, Zhu D, Xing Y, Kamanna VS, Kashyap ML. Niacin non-competitively inhibits diacylglycerol acyltransferase-2 (DGAT2) but not DGAT1 activity in HepG2 cells. *J Lipid Res*. 2004;45:1835-1845.
42. Hernandez C, Molusky M, Li Y, Li S, Lin JD. Regulation of hepatic ApoC3 expression by PGC-1beta mediates hypolipidemic effect of nicotinic acid. *Cell Metab*. 2010;12:411-419.
43. Bengtsson G, Olivecrona T. Lipoprotein lipase. Mechanism of product inhibition. *Eur J Biochem*. 1980;106:557-562.
44. Miles JM, Haymond MW, Nissen SL, Gerich JE. Effects of free fatty acid availability, glucagon excess, and insulin deficiency on ketone body production in postabsorptive man. *J Clin Invest*. 1983; 71:1554-1561.
45. Lauring B, Taggart AK, Tata JR, et al. Niacin lipid efficacy is independent of both the niacin receptor GPR109A and free fatty acid suppression. *Sci Transl Med*. 2012 (in press).
46. Klein S, Young VR, Blackburn GL, Bistrian BR, Wolfe RR. Palmitate and glycerol kinetics during brief starvation in normal weight young adult and elderly subjects. *J Clin Invest*. 1986;78:928-933.
47. Sniderman AD, Cianflone K. Substrate delivery as a determinant of hepatic apoB secretion. *Arterioscler Thromb*. 1993;13:629-636.
48. Knopp RH, Alagona P, Davidson M, et al. Equivalent efficacy of a time-release form of niacin (Niaspan) given once-a-night versus plain niacin in the management of hyperlipidemia. *Metabolism*. 1998;47: 1097-1104.
49. Schlierf G, Dorow E. Diurnal patterns of triglycerides, free fatty acids, blood sugar, and insulin during carbohydrate-induction in man and their modification by nocturnal suppression of lipolysis. *J Clin Invest*. 1973;52:732-740.
50. Dunbar RL, Gelfand JM. Seeing red: flushing out instigators of niacin-associated skin toxicity. *J Clin Invest*. 2010;120:2651-2655.
51. van Oostrom AJ, van Dijk H, Verseyden C, et al. Addition of glucose to an oral fat load reduces postprandial free fatty acids and prevents the postprandial increase in complement component 3. *Am J Clin Nutr*. 2004;79:510-515.

Appendix

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjmed.2012.03.017.

Supplemental Table 1: Baseline characteristics

Baseline Characteristics for OFTT Participants				
Result	**Non-African American** n = 12	**African American** n = 10	**Significance**	**Pooled** n = 22
Intrinsic Characteristics				
Female	75% (9/12)	20% (2/10)	p = 0.0102	50% (11/22)
Asian	8.3% (1/12)	0% (0/10)	p = 0.3501	4.5% (1/22)
Hispanic	16.7% (2/12)	0% (0/10)	p = 0.1757	9.1% (2/22)
Physical Characteristics				
Age (years)	37.0 (10.2)	41.1 (12.4)	p = 0.3997	38.9 (11.2)
Systolic Blood Pressure (mmHg)	108.5 (12.9)	120.7 (7.0)	p = 0.0146	114.1 (12.1)
Diastolic Blood Pressure (mmHg)	68.5 (9.1)	78.2 (6.5)	p = 0.0102	72.9 (9.3)
Weight, Women (kg)	58.2 (11.1)	78.3 (13.2)	p = 0.0498	61.9 (13.5)
Weight, Men (kg)	83.3 (11.7)	85.2 (11.5)	p = 0.8083	84.7 (11)
Body Mass Index, Women (kg/m2)	21.9 (3.0)	27.8 (2.4)	p = 0.0319	23 (3.7)
Body Mass Index, Men (kg/m2)	26.5 (2.7)	27.9 (2.3)	p = 0.4212	27.5 (2.3)
Mean Abdominal Girth, Women (cm)	77.8 (73.5 to 78.9)	87.1 (87.1 to 87.1)	p = 1.0000	78.8 (73.9 to 79)
Mean Abdominal Girth, Men (cm)	95.8 (5.0)	93.2 (7.3)	p = 0.5961	93.9 (6.6)
Lifestyle Attributes				
Current Smoker	25.0% (3/12)	30.0% (3/10)	p = 0.7932	27.3% (6/22)
Doesn't Drink Alcohol	50.0% (6/12)	30.0% (3/10)	p = 0.3421	40.9% (9/22)
Drinks Alcohol < Weekly	33.3% (4/12)	40.0% (4/10)	p = 0.7462	36.4% (8/22)
Drinks Weekly	16.7% (2/12)	20.0% (2/10)	p = 0.8400	18.2% (4/22)
Drinks Daily	0.0% (0/12)	10.0% (1/10)	p = 0.2622	4.5% (1/22)
Exercises Monthly	8.3% (1/12)	0% (0/10)	p = 0.3501	4.5% (1/22)
Exercises Weekly	33.3% (4/12)	20% (2/10)	p = 0.4844	27.3% (6/22)
Exercises Several Times a Week	25% (3/12)	40% (4/10)	p = 0.4520	31.8% (7/22)
Exercises Daily	33.3% (4/12)	30% (3/10)	p = 0.8673	31.8% (7/22)
Laboratory Studies				
Mean LDL-c by ultracentrifugation (mg/dL)	93.8 (26.0)	90.5 (30.0)	p = 0.7877	92.3 (27.2)
Mean Non-HDL-c (mg/dL)	108.9 (30.2)	102.9 (34.5)	p = 0.6723	106.2 (31.6)
Mean HDL-c, Women(mg/dL)	64.1 (13.2)	79.3 (16.5)	p = 0.1864	66.9 (14.3)
Mean HDL-c, Men(mg/dL)	53.6 (16.7)	60.1 (11.1)	p = 0.4590	58.3 (12.3)
Mean VLDL-c (mg/dL)	14.8 (6.1)	13.2 (5.6)	p = 0.5325	14 (5.8)
Mean TG (mg/dL)	71.0 (29.8)	74.7 (17.9)	p = 0.7332	72.7 (24.6)
Glucose (mg/dL)	74.7 (8.5)	79.7 (6.8)	p = 0.1523	77 (8)
Creatinine, Women (mg/dL)	0.73 (0.11)	0.73 (0.04)	p = 0.9361	.73 (.1)
Creatinine, Men (mg/dL)	0.92 (0.85 to 1.03)	1.10 (0.96 to 1.13)	p = 0.2970	1.05 (.87 to 1.11)
Glomerular Filtration Rate, CKD-EPI (mL/min per 1.73m2)	102.7 (11.9)	106.5 (19.4)	p = 0.5697	104.4 (15.5)

Given expected differences in fasting and postprandial lipids, we present baseline characteristics by African American status in addition to the pooled results, and provide a statistical comparison between African Americans and Non-African Americans.

Note: continuous variables are presented as mean (SD), except skewed variables are presented as median (25th to 75th

percentile).

HDL-c = high-density lipoprotein cholesterol, LDL-c = low-density lipoprotein cholesterol, Non-HDL-c = non-high-density lipoprotein cholesterol, TG = triglyceride, VLDL-c = very low-density lipoprotein cholesterol.

Supplemental Table 2: Predictors of TG iAUC

Correlation Analysis for TG iAUC (0 to 12h)

	Spearman		Regression	
Explanatory Variable	**rho**	**p-value**	**r**	**p-value**
FFA iAUC (0 to 12h)	+0.48	0.0012	+0.49	0.051
FFA iAUC (0 to 4h)	+0.35	0.0308	+0.49	0.0223
FFA iNadir (0 to 12h)	+0.41	0.006	+0.58	0.0007
FFA Nadir Time (0 to 12h)	-0.19	0.2325	-0.44	0.2166
HBA iAUC (0 to 12h)	+0.03	0.8717	-0.47	0.3064
HBA iAUC (0 to 4h)	+0.12	0.4591	+0.37	0.2734
HBA iNadir (0 to 12h)	+0.43	0.0042	+0.52	0.0011
HBA Nadir Time (0 to 12h)	-0.39	0.0096	-0.50	0.0534

Unless otherwise indicated, parameters are from 0 to 12 hours. The Spearman's correlation coefficient, rho, indicates the direction and strength of the relationship between TG iAUC and each candidate explanatory variable. The linear regression does the same, but also incorporates the interaction by race as well as an adjustment term for race. As expected, regression models provided a better fit than Spearman's correlation, since the former adjusted for race and its interaction.

AUC = area under the curve, FFA = free fatty acids, HBA = hydroxybutyrate, iAUC = incremental area under the curve, iNadir = incremental nadir

Supplemental Table 3: Comparison to Other Studies

Study	Design	Population	N*	Protocol	Postprandial Triglyceride Total Area Under Curve (mg/dL*h)		Postprandial Triglyceride Incremental Area Under Curve (mg/dL*h)	
					OFTT vs OFTT + NA	% Change	OFTT vs OFTT + NA	% Change
Studies of Immediate-Release Niacin								
Froberg, 1971(1)	Parallel RCT	Healthy Men	6	IR NA 1g thrice daily, 15 samples/12h	1895±12 vs 1337±6 **	-29% p<0.01	n.r.	n.r.
King, 1994(2)	Random-order crossover	Men with Low HDL	12	IR NA 1 g thrice daily, 3 samples/8h (hours 0, 4, and 8)	2972±1200 vs 1736±800	-41% p<0.005	+1290±682 vs +709±409	-45% p<0.025
O'Keefe, 1995(3)	Parallel RCT	Adults with low HDL+ high TG	21	IR NA 1g thrice daily + pravastatin, 2 samples/8h (hours 0 and 8)	n.r	n.r	n.r. *** (+130±130 vs +88±114 mg/dL at 8 h)	-32% p=0.04
Studies of Extended-Release Niacin								
Plaisance, 2008(4)	Fixed-sequence crossover	Men with Metabolic Syndrome	15	ER NA 2g before bed, 5 samples/8h (hours 0, 2, 4, 6, and 8)	3063 vs 2365	-23% p<0.001	+1058 vs +1085	+3% NS
Usman, 2012 (Current study)	Random-order crossover, single dose	Adults with no elements of Metabolic Syndrome	22	ER NA 2g 1h prior, 15 samples/12h 12 Non-African Americans	1102±319 vs 918±313	-11.6% p=0.009	+270±196 vs +53.7±194	-47% p=0.0005
				10 African Americans	1125±307 vs 1145±307	+4% p=0.8	+363±196 vs +364±193	+6% p=1.0
				All 22 subjects pooled	1112±317 vs 1025±314	-26% p=0.11	+312±200 vs +199±200	-33% p=0.02

*Number of subjects exposed to niacin

**Originally reported as average TG for each time point: 1.80±0.14 mmol/L on placebo vs 1.27+0.007 on niacin. We multiplied by 38.7 to convert to mg/dL and then multiplied that result by 12h.

***Data shown are increment from baseline at hour 8 in units of mg/dL.

n.r. = not reported

Supplemental Table 3 Reference List

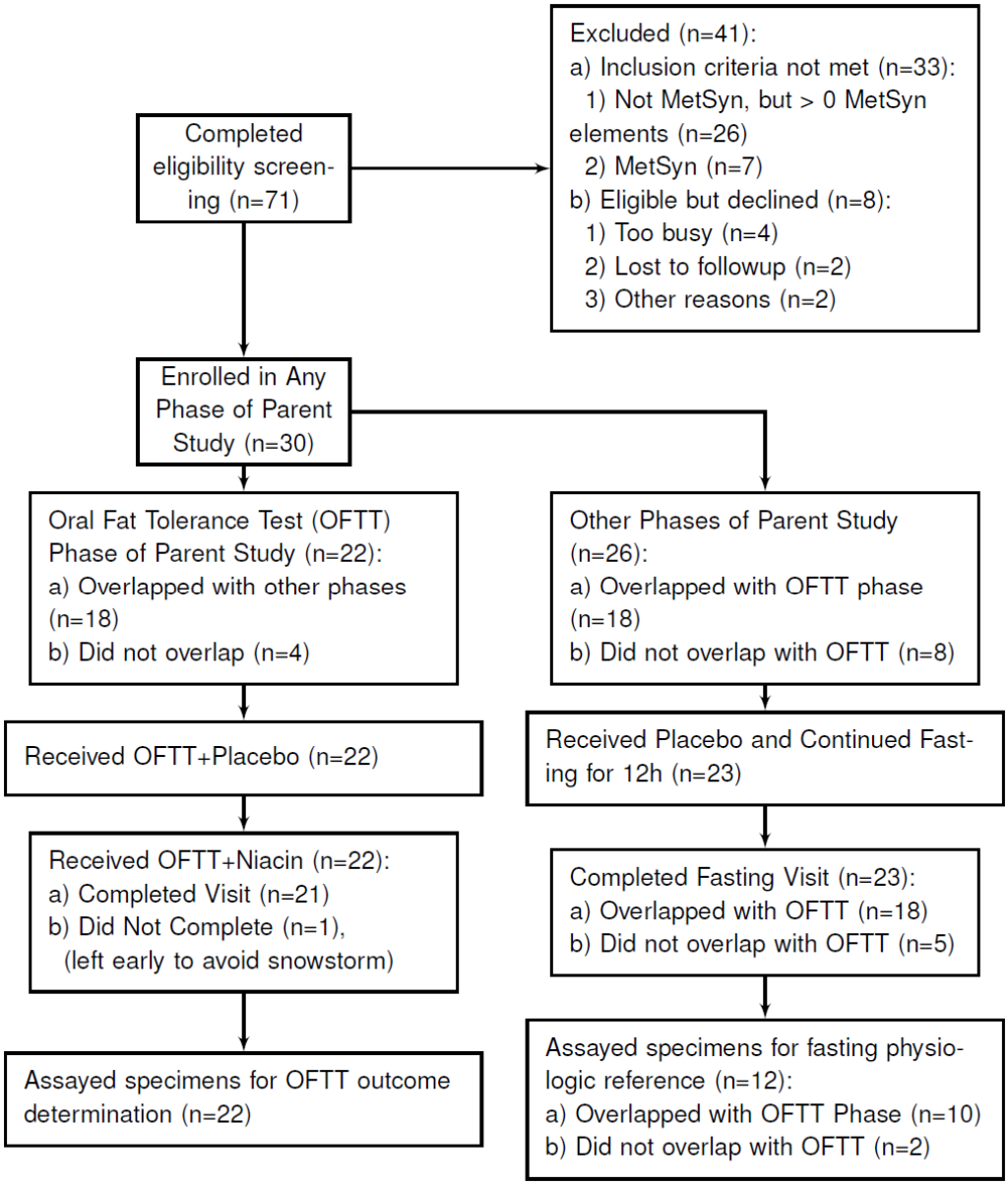
(1) Froberg S, Boberg J, Carlson LA, Eriksson M. Effect of nicotinic acid on the diurnal variation of plasma levels of glucose, free fatty acids, triglycerides and cholesterol and of urinary excretion of catecholamines. In: Gey KF, Carlson LA, editors. Metabolic Effects of Nicotinic Acid and its Derivatives. Bern: Hanss Huber Publishers; 1971. 167-181.

(2) King JM, Crouse JR, Terry JG, Morgan TM, Spray BJ, Miller NE. Evaluation of effects of unmodified niacin on fasting and postprandial plasma lipids in normolipidemic men with hypoalphalipoproteinemia. The American Journal of Medicine 1994; 97(4):323-331.

(3) O'Keefe JH, Jr., Harris WS, Nelson J, Windsor SL. Effects of pravastatin with niacin or magnesium on lipid levels and postprandial lipemia. Am J Cardiol 1995; 76(7):480-484.

(4) Plaisance EP, Mestek ML, Mahurin AJ, Taylor JK, Moncada-Jimenez J, Grandjean PW. Postprandial triglyceride responses to aerobic exercise and extended-release niacin. Am J Clin Nutr 2008; 88(1):30-37.

Supplemental Figure 1



Supplemental Figure 1: Recruitment, Randomization and disposition of study subjects

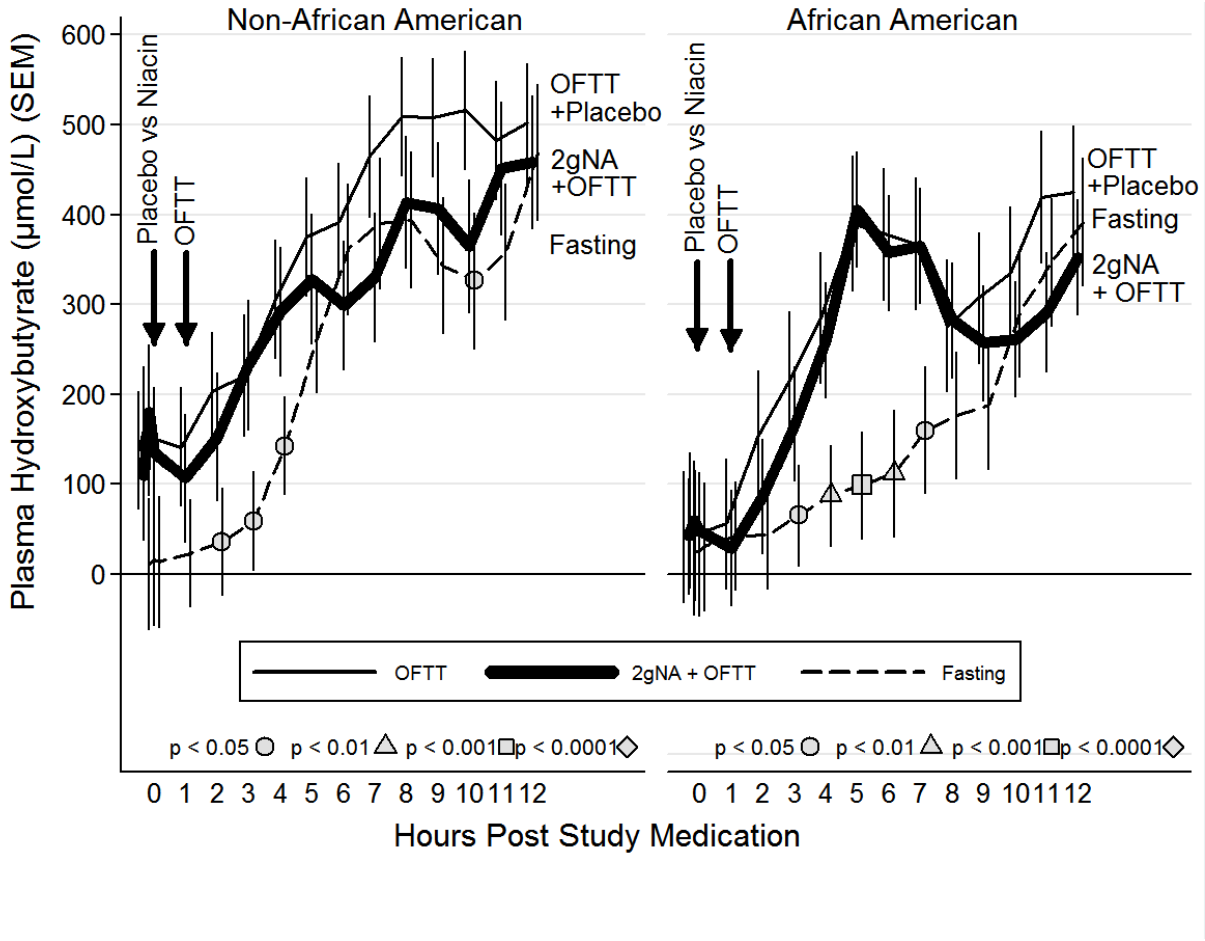
Between January 2006 and July 2010, we screened healthy adults aged 18 to 75 from the Philadelphia area by flyers and Penn recruitment databases, and included those with fasting triglyceride <150 mg/dL, HDL $\geq$40 mg/dL in men and $\geq$50 mg/dL in women, glucose <100 mg/dL, abdominal girth <102 cm in men (<89 cm for Asians) and <88 cm

in women (<79 cm in Asians) and blood pressure <130/85 mmHg. We excluded those on lipid-altering therapy, or who had atherosclerotic cardiovascular disease, congestive heart failure, diabetes, chronic kidney disease, chronic liver disease, serum albumin <2.5 mg/dL, serum creatinine >2.0 mg/dL, HIV, malignancy in the prior 5 years, uncontrolled thyroid disease, major active pulmonary, rheumatologic, dermatologic or inflammatory conditions, history of organ transplantation, alcohol or drug abuse, or major surgery in the previous 3 months, pregnant women, and subjects exposed to an investigational drug within 6 weeks.

Subjects received ER niacin 2 g or matching placebo in random order in each of two visits at least 7 days apart (n.b. since niacin was only given at one of the study visits, subjects were not on niacin prior to participation or between visits). The University of Pennsylvania (UPenn) Investigational Drug Service (IDS) over-encapsulated ER niacin and matching placebo. The IDS assigned treatment order electronically (www.randomization.com), dispensed blinded medication at each visit, and maintained the blinding information until analysis.

One subject left the visit early to avoid being stranded at the hospital during a brisk snowstorm, and did not complete the later blood draws. Since expected FFA nadir/peak and TG peak occurred before she left, these parameters were included in the analysis, but we did not include area parameters (i.e. AUC and iAUC).

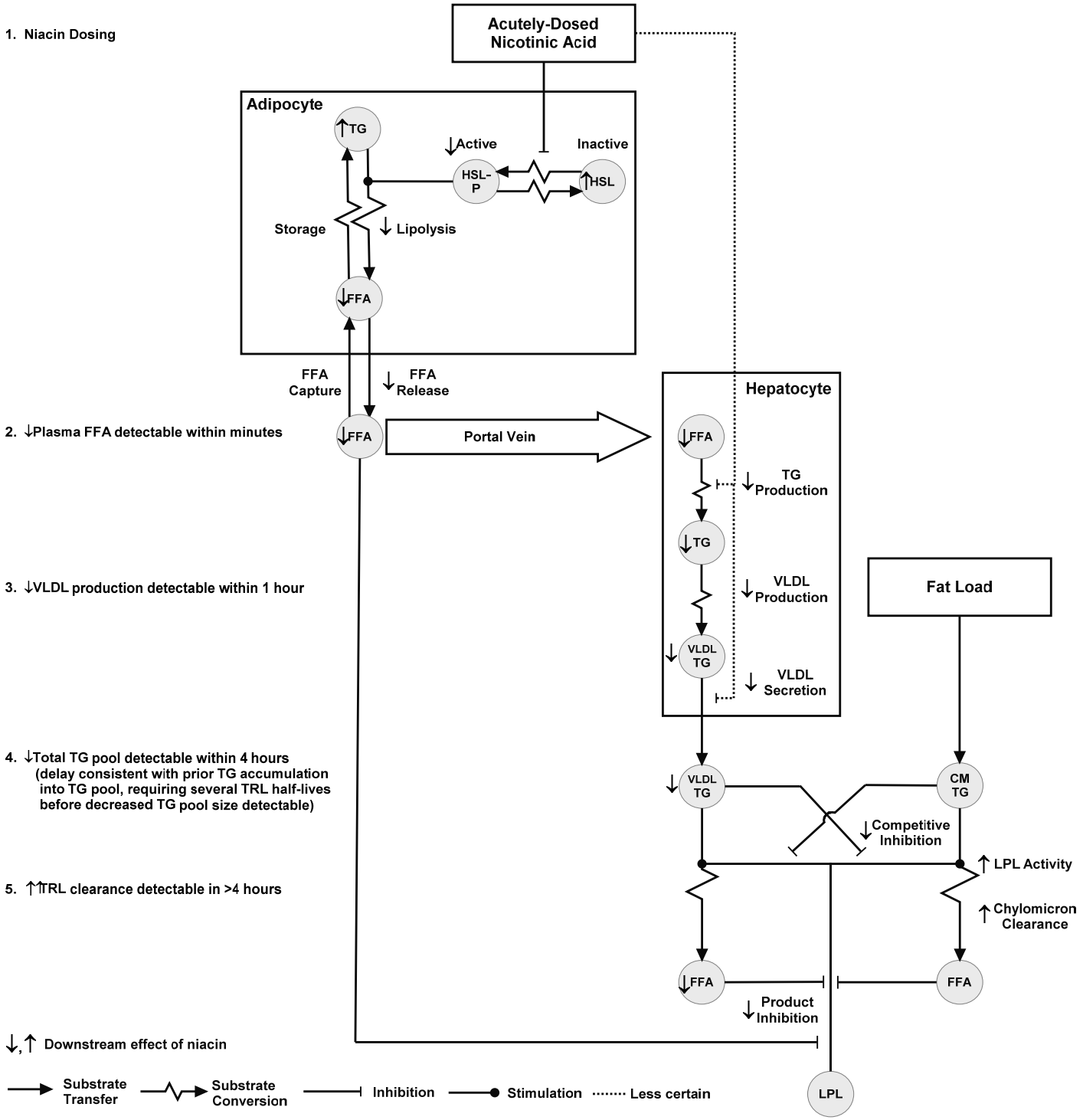
Supplemental Figure 2



Supplemental Figure 2: Effect of niacin on postprandial hydroxybutyrate

Data depicted in same manner as Figure 1.

Supplemental Figure 3: Proposed Mechanism of Niacin-Induced suppression of Postprandial Triglyceridemia



CM = Chylomicron FFA = Free fatty acids HSL = Hormone-sensitive lipase
LPL = Lipoprotein lipase TG = Triglyceride VLDL = Very low-density lipoprotein