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Effects of immediate-release niacin and dietary fatty acids on acute insulin and lipid status in individuals with metabolic syndrome

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Dedicated to the memory of Professor Jose Villar Ortiz who died on March 28th, 2016, and is a celebration of his work and contribution to the care and well being of people with MetS and any kind of person. He always hosted and guided our studies on olive oil and the postprandial metabolism of dietary fats. He has been and is an inspiration.

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ABSTRACT

Background: The nature of dietary fats profoundly affects postprandial hypertriglyceridemia and glucose homeostasis. Niacin is a potent lowering-lipid agent. However, limited data exist on postprandial triglycerides and glycemic control following co-administration of high-fat meals with a single-dose of niacin in subjects with metabolic syndrome (MetS). Thus, the study aim was to explore whether a fat challenge containing predominantly saturated (SFAs), monounsaturated (MUFAs) or MUFAs plus omega-3 long-chain polyunsaturated (LCPUFAs) fatty acids together with a single-dose of immediate-release niacin have a relevant role on postprandial insulin and lipid status in subjects with MetS.

Results: In a randomized crossover within-subject design, 16 subjects with MetS were given a single-dose of immediate-release niacin (2 g) and ~15 calorie per kilogram of body weight meals containing either SFAs, MUFAs, MUFAs plus omega-3 LCPUFAs or no fat. At baseline and hourly over 6 h, plasma glucose, insulin, C-peptide, triglycerides, free fatty acids (FFAs), total cholesterol, HDL-, and LDL-cholesterol were assessed. Co-administered with niacin, high-fat meals significantly increased the postprandial concentrations of glucose, insulin, C-peptide, triglycerides, FFAs, and postprandial indices of β-cell function. However, postprandial indices of insulin sensitivity were significantly decreased. These effects were significantly attenuated with MUFAs or MUFAs plus omega-3 LCPUFAs when compared with SFAs.

Conclusion: In the setting of niacin co-administration and compared to dietary SFAs, MUFAs limit the postprandial insulin, triglyceride, and FFA excursions and improve the postprandial glucose homeostasis in the MetS.

Keywords: niacin, dietary fatty acids, MUFAs, SFAs, postprandial, metabolic syndrome

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INTRODUCTION

The metabolic syndrome (MetS) is a constellation of interrelated and additive risk factors for cardiovascular disease (CVD) that comprises dysglycemia, dyslipidemia, hypertension, and central obesity.[1] The dyslipidemic state of MetS is characterized by raised triglycerides, low HDL-cholesterol, and abnormal elevation in postprandial, apolipoprotein B48 (apoB48)-containing triglyceride-rich lipoproteins (TRLs), mainly composed of dietary fatty acids. Subjects with MetS often have impaired glucose metabolism resulting from defects in insulin secretion, insulin action, or both.

Niacin (also commonly known as nicotinic acid or vitamin B3) is a water-soluble vitamin effective for lowering triglycerides and raising HDL-cholesterol.[2] Data from recent studies indicated that niacin has long-term benefits in lowering postprandial secretion of apoB48[3] and TRLs[4] in statin-treated patients with type 2 diabetes. Less evident are the long-term benefits of niacin on postprandial glucose homeostasis in dyslipidemic patients with or without type 2 diabetes.[5] Of interest, the extended-release form of niacin has been shown to acutely suppress postprandial hypertriglyceridemia in healthy subjects.[6] However, the role of immediate-release niacin dosed with a high-fat meal on postprandial insulin secretion or action and hypertriglyceridemia, particularly in subjects with MetS, remains largely unknown.

We have previously shown that the nature of the dietary fats in the meal influences on postprandial triglycerides and control of insulin secretion and sensitivity in subjects with normal[7] and high[8] fasting triglycerides. Our studies provided evidence that subjects had decreased postprandial β-cell function and became less insulin resistant postprandially as the proportion of MUFAs compared with SFAs in dietary fats increased. These effects were specifically associated to the content of MUFA oleic acid and SFA palmitic acid in the meal.[9]

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In addition, omega-3 long-chain PUFAs (LCPUFAs) have long-term benefits in lowering triglycerides,[10] notably when combined with extended-release niacin,[2] in individuals with MetS. Omega-3 LCPUFAs may also attenuate postprandial abnormalities in lipid metabolism associated with MetS.[11] However, recent trials have not produced evidence for additional clinical benefits of omega-3 PUFAs on glucose homeostasis in either the fasting or postprandial period.[10,12]

Here, we explored the impact of immediate-release niacin co-ingested with a meal rich in SFAs, MUFAs or MUFAs plus omega-3 LCPUFAs on postprandial insulinemic and lipemic responses as well as on postprandial parameters and indices of β-cell function and insulin sensitivity in subjects with MetS.

MATERIALS AND METHODS

Participants and design

Inclusion criteria for MetS consisted of at least 3 of the following components: waist circumference >102 cm, fasting plasma HDL-cholesterol ≤ 1.03 mmol/l, fasting plasma triglycerides ≥1.7 mmol/l, systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥85 mmHg, and fasting plasma glucose ≥5.6 mmol/l.[13] As shown in **Table 1**, the participants' average body mass index (BMI), waist circumference, waist-to-hip ratio, and blood pressure were above the standard values, while average HDL-cholesterol was below the standard value, reflecting characteristics of individuals with MetS. None of the participants had impaired renal, thyroid or liver function; none had cardiovascular disease or gastroparesis; none had anemia or pulmonary, psychiatric, immunological or neoplastic diseases; none used tobacco, consumed special diets or took medication known to alter gastric emptying, insulin secretion or insulin action. Ethics approval was obtained from the Human

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Clinical Research and Ethics Committee of the University Hospital Virgen del Rocio (UHVR, Seville), and the study complied with the current revision of the Declaration of Helsinki. All subjects gave written informed consent. This study was registered at the ClinicalTrials.gov registry and the clinical trial registration number is NCT02061267.

The study was designed as a within-subject crossover in which the participants attended the Clinic Experimental Research Unit for Vascular Risk at the UHVR on 4 separate occasions. Fasting blood samples ($t = 0$) were taken at 0800 after a 12-h overnight fast. The test meals in combination with a single 2 g dose of immediate-release niacin (Twinlab, American Fork, UT) were given in random order with an interval of ~1 wk between meals. The high-fat meals consisted in an emulsion prepared according to a method previously described,[14] with water, sucrose (30 g/m^2 of body surface area), and fat (50 g/m^2 of body surface area). Dietary fats were cow's milk cream, refined olive oil or refined olive oil plus a dose of omega-3 LCPUFAs, which consisted of 920 mg of EPA and 760 mg of DHA in the form of ethyl esters. The fatty acid compositions of dietary fats are described in **Table S1** in the Supporting Information. The participants also consumed a test meal prepared as indicated above, but not including fat, as a control meal. After the ingestion of the meals within 10 min, blood samples were collected each 60 min in tubes containing EDTA for the measurement of glucose, insulin, C-peptides, triglycerides, FFAs, total cholesterol, HDL-cholesterol, and LDL-cholesterol over 360 min. In this study, each participant served as his own control. Subject flow through the protocol is shown in **Figure S1** in the Supporting Information.

Biochemical analyses

Glucose was immediately measured using the glucose/oxidase method (Glucose GOD-PAP; Biolabo, Madrid, Spain). Insulin and C-peptide were measured by using ELISA (Diagnostic

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System Laboratories, Webster, TX). Total cholesterol and triglycerides were determined by enzymatic methods (CHOD-PAP and GPO-PAP, respectively; Roche Diagnostics, Basel, Switzerland). HDL-cholesterol was determined after precipitation with phosphotungstic acid. LDL-cholesterol was measured using an Advia 2400 Clinical Chemistry System (Siemens Healthcare Diagnostics, Erlangen, Germany). FFAs were measured with an ACS-ACOD assay (Wako Chemicals GmbH, Neuss, Germany). Glycated hemoglobin (HbA_{1c}) was measured according to the Standard Operating Procedure of the IFCC Reference, with an automated HPLC analyzer (Bio-Rad, Milan, Italy).

Calculations

Fasting β-cell function was estimated by 2 methods: *1)* the homeostasis model assessment of insulin secretion (HOMA-B), by using the formula HOMA-B = $I_0 \times 3.33/(G_0 - 3.5)$; and *2)* the basal disposition index (DI_0), which gives an adjusted measure by insulin sensitivity according to the HOMA-IR, by using the formula $DI_0 = HOMA\text{-}B \times (1/HOMA\text{-}IR)$.[15]

Fasting insulin resistance and its reciprocal (fasting insulin sensitivity) were estimated by 4 methods: *1)* HOMA-IR = $I_0 \times G_0$ divided by 22.5; *2)* the revised-quantitative insulin sensitivity check index [rQUICKI = $1/(\log I_0 + \log G_0 + \log FFA_0)$]; *3)* the basal insulin sensitivity index (ISI_0) for glycemia $\{ISI(G)_0 = 2/[(I_0 \times G_0) + 1]\}$; and *4)* the basal ISI_0 for blood FFAs $\{ISI(FFA)_0 = 2/[(I_0 \times FFA_0) + 1]\}$. I_0, G_0, and FFA_0 refer to fasting concentrations ($t = 0$) of insulin, glucose, and FFAs, respectively.

Postprandial β-cell function was estimated by 4 methods: *1)* the insulinogenic index (IGI), which is a surrogate measure of first-phase insulin secretion and was calculated by using the difference between the postprandial insulin peak ($t = 60$ min) and the fasting insulin in

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relation to the difference in glucose (IGI = $\Delta I_{0-60}/\Delta G_{0-60}$); *2)* the ratio of the IGI to the HOMA-IR, which gives an adjusted measure of β-cell function that accounts for variations in insulin sensitivity; *3)* the ratio of the insulin to glucose areas under the curve (AUC_{INS}/AUC_{GLU}), which significantly correlates with glucose sensitivity and early-phase insulin secretion, calculated by using the trapezoidal method from 0 to 120 min; and *4)* the total disposition index from 0 to 120 min (DI_{120}) by using the product of AUC_{INS}/AUC_{GLU} with the Matsuda insulin sensitivity index,[16] which incorporates both the hepatic and muscle components of insulin resistance and correlates well with the euglycemic insulin clamp.

Postprandial insulin sensitivity was estimated by 4 methods: *1)* the insulin sensitivity index $IS_{0\text{-}\infty}$; 2*)* the postprandial insulin sensitivity index ($ISI_{0\text{-}\infty}$) for glycemia [$ISI(G)_{0\text{-}\infty}$]; and *3)* the $ISI_{0\text{-}\infty}$ for blood FFAs [$ISI(FFA)_{0\text{-}\infty}$]. The infinity symbol represents the values at any postprandial time. The details of the equations and additional references using this multisampling protocol were previously described.[7]

Statistical analyses

The summary data (the fasting and postprandial response) were analyzed by using one-factor repeated-measures ANOVA. The incremental AUC (iAUC) was calculated by the trapezoidal rule. The postprandial time courses after the test meals were analyzed by using 2-factor repeated-measures ANOVA, and Bonferroni correction was applied for the post hoc detection of significant pairwise differences. When indicated, hypothesis testing for differences between groups was performed by the one-sample *t* test for independent samples. The data were analyzed by using STATVIEW for WINDOWS (SAS Institute, Cary, NC). $P < 0.05$ was considered significant.

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3 174 **RESULTS**
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5 175 **Basal conditions of participants**
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7 176 There were no significant differences between fasting values for plasma glucose, insulin, C-
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9 177 peptide, triglycerides, and FFAs at the beginning of each of the four intervention periods
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11 178 (**Table S2** in the Supporting Information). Neither were differences in fasting plasma total
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13 179 cholesterol, HDL-cholesterol, and LDL-cholesterol (data not shown). Likewise, we found no
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15 180 significant differences in the basal values for HOMA-B, DI_0, HOMA-IR, rQUICKI, and the
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17 181 basal Belfiore indices for glycemia and blood FFAs (**Table S3** in the Supporting Information).
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19 182 These data indicated that all of the participants had similar basal β-cell function and insulin
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21 183 sensitivity prior to the ingestion of the high-fat meals and the pharmacological dose of
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23 184 immediate-release niacin.
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27 186 **Effect of co-ingestion of immediate-release niacin with meals on plasma lipids, glucose,**
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29 187 **insulin, and C-peptide**
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31 188 The plasma concentrations of postprandial glucose, insulin, C-peptide, triglycerides, FFAs,
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33 189 total cholesterol, HDL-cholesterol, and LDL-cholesterol after the meal with no fat and the
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35 190 meals enriched in SFAs, MUFAs or MUFAs+omega-3 LCPUFAs plus niacin are shown in
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37 191 **Figures 1A-1H**. As expected, no changes in plasma triglycerides were observed when fat was
38
39 192 not included in the meal. The plasma total cholesterol, HDL-cholesterol, and LDL-cholesterol
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41 193 were also not affected during the postprandial period. The high-fat meals markedly increased
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43 194 ($P < 0.05$) plasma triglycerides to a peak at 60 min (3.02 ± 0.26 mmol/l with SFAs, 3.05 ±
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45 195 0.18 mmol/l with MUFAs, and 2.87 ± 0.23 mmol/l with MUFAs+omega-3 LCPUFAs vs.
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47 196 1.79 ± 0.16 mmol/l with no fat), and the iAUC values (0-6 h) for triglycerides also increased
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49 197 (+544% with SFAs, +428% with MUFAs, and +408% with MUFAs+omega-3 LCPUFAs vs.
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51 198 no fat, 100%) (Table S2 in the Supporting Information). All of the meals co-administered
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with niacin induced a decrease in plasma FFAs at 240 min (174 ± 32 μmol/l with SFAs, 173 ± 25 μmol/l with MUFAs, and 159 ± 64 μmol/l with MUFAs+omega-3 LCPUFAs vs. 138 ± 22 μmol/l with no fat, $P < 0.05$). Thereafter, plasma FFAs rebounded but not reaching basal values. The high-fat meals increased ($P < 0.05$) the iAUC values (0-6 h) for FFAs (+120% with SFAs, +111% with MUFAs, and +110% with MUFAs+omega-3 LCPUFAs vs. no fat, 100%) (Table S2 in the Supporting Information). The postprandial glucose response was similar after ingestion of any of the meals plus niacin, increasing from a basal concentration to a peak at 60 min (7.94 ± 1.39 mmol/l with SFAs, 8.51 ± 1.14 mmol/l with MUFAs, and 8.15 ± 1.01 mmol/l with MUFAs+omega-3 LCPUFAs vs. 8.11 ± 0.86 mmol/l with no fat, $P > 0.05$) and returning to basal values between 120 and 180 min. However, the high-fat meals markedly increased ($P < 0.05$) plasma insulin to a peak at 60 min (452 ± 44 pmol/l with SFAs, 353 ± 15 pmol/l with MUFAs, and 352 ± 23 pmol/l with MUFAs+omega-3 LCPUFAs vs. 301 ± 26 pmol/l with no fat), and the iAUC values (0-6 h) for insulin also increased (+812% with SFAs, +474% with MUFAs, and +493% with MUFAs+omega-3 LCPUFAs vs. no fat, 100%) (Table S2 in the Supporting Information). These effects of fat-enriched meals on insulin were close to those observed on C-peptide, with a marked increase ($P < 0.05$) to a peak at 60 min (2608 ± 229 pmol/l with SFAs, 2219 ± 120 pmol/l with MUFAs, and 2235 ± 155 pmol/l with MUFAs+omega-3 LCPUFAs vs. 2029 ± 136 pmol/l with no fat), and the iAUC values (0-6 h) for C-peptide also increased (+442% with SFAs, +271% with MUFAs, and +253% with MUFAs+omega-3 LCPUFAs vs. no fat, 100%) (Table S2 in the Supporting Information).

Effect of co-ingestion of immediate-release niacin with meals on β-cell function and insulin sensitivity

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223 Estimates of postprandial β-cell function, including IGI (0-60 min), IGI/HOMA-IR,
224 AUC_{INS}/AUC_{GLU} (0-120 min), and DI_{120} (0-120 min) were higher ($P < 0.05$) after the high-fat
225 meals than after the meal containing no fat plus niacin, and these estimates were higher ($P <$
226 0.05) after the SFA meal when compared to the MUFA and MUFA+omega-3 LCPUFA meals
227 (**Table 2**). In addition, estimates of postprandial insulin sensitivity, including $IS_{0-\infty}$ (0-480
228 min) and the postprandial Belfiore indices for glycemia and blood FFAs (0-480 min), were
229 lower ($P < 0.05$) after the high-fat meals than after the meal containing no fat plus niacin.
230 These estimates were also lower ($P < 0.05$) after the SFA meal when compared to the MUFA
231 and MUFA+omega-3 LCPUFA meals.
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233 **DISCUSSION**

234 This randomized and within-subject crossover study is the first to demonstrate the time course
235 of changes in plasma glucose, insulin, C-peptide, and lipids —triglycerides, FFAs, total
236 cholesterol, HDL-cholesterol, and LDL-cholesterol— and the extent of β-cell function and
237 insulin sensitivity dysregulation after a single pharmacological dose of immediate-release
238 niacin in combination with SFA, MUFA or MUFA+omega-3 LCPUFA meals in individuals
239 with MetS. All of the participants had similar fasting β-cell function and insulin sensitivity,
240 and all of the meals co-administered with niacin elicited similar postprandial glucose
241 responses. However, the high-fat meals increased postprandial β-cell function and decreased
242 postprandial insulin sensitivity compared to the meal containing no fat. Most importantly, our
243 results showed that individuals with MetS had lower insulinemic and lipemic responses and
244 were less insulin resistant postprandially when given a meal containing MUFAs or
245 MUFAs+omega-3 LCPUFAs rather than SFAs in the setting of niacin co-ingestion.
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3 247 The treatment targeted at postprandial glucose homeostasis, which is involved in the
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5 248 prediction of CVD and all-cause mortality, has been reported to reduce the progression of
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7 249 atherosclerosis and CVD events.[17] Previous studies have demonstrated the potential of high-
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9 250 fat meals to induce β-cell dysfunction and insulin resistance in healthy subjects[7,18] and in
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11 251 individuals with high fasting plasma triglycerides,[8] type 2 diabetes[19] or MetS.[20] The evolution
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13 252 of type 2 diabetes may be related to the progressive deterioration of glucose homeostasis,
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15 253 starting during the postprandial period in subjects whose glycemic profiles are normal at
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17 254 fasting.[21] It is also hypothesized[22] that the nature of the postprandial lipid excursions may
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19 255 influence the transition from normal to impaired glucose tolerance and to overt diabetes.
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21 256 However, little is currently known about the postprandial insulin secretion and action
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23 257 following specific fatty acid intake co-administered with niacin in humans. In earlier studies
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25 258 of patients with type 2 diabetes,[23] insulin release was found to be stimulated by dietary SFAs
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27 259 but not by dietary MUFAs. More recent studies found higher postprandial plasma insulin
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29 260 following a SFA meal when compared with a MUFA meal in healthy subjects[7] or individuals
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31 261 with high fasting triglycerides.[8] Until now, it was only addressed the impact of a SFA meal on
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33 262 parameters of postprandial glucose metabolism after long-term pharmacological use of
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35 263 extended-release niacin to establish that niacin is innocuous on fasting insulin action in statin-
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37 264 treated patients with type 2 diabetes.[4] The limited relevance of niacin on glucose homeostasis
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39 265 was also assessed in dyslipidemic patients with or without type 2 diabetes[5] or MetS,[24] and in
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41 266 sedentary, nondiabetic postmenopausal women.[25] The mechanisms underlying the link
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43 267 between the predominant class of fatty acid in high-fat meals, niacin, and acute insulin
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45 268 hypersecretion (or impaired insulin sensitivity) require further elucidation. This is of
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47 269 particular importance in individuals with MetS.[26] The present study contributes to the
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49 270 understanding of this issue and reveals that postprandial β-cell function and insulin sensitivity
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51 271 are improved with dietary MUFAs, with or without omega-3 LCPUFAs, when compared to
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3 272 dietary SFAs, therefore extending metabolic benefits of MUFA-rich meals to a population of
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5 273 individuals with MetS in the setting of co-administration with immediate-release niacin.
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10 275 Postprandial hypertriglyceridemia is considered an important and residual risk factor of CVD
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12 276 and all-cause mortality, particularly in patients with MetS.[27] However, the relative effects of
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14 277 SFA, MUFA or MUFA+omega-3 LCPUFA meals on postprandial triglycerides and FFAs
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16 278 have been investigated in only a small number of studies to date,[7,8,28-30] and none of these
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18 279 studies included the co-administration of high-fat meals with a single-dose of immediate-
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20 280 release niacin or subjects with MetS. Our study showed a significant attenuation of
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23 281 incremental triglyceride and FFA responses following the MUFA and MUFA+omega-3
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25 282 LCPUFA meals compared to the SFA meal, particularly at the late postprandial period where
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27 283 more atherogenic remnant particles are formed.[31] Our new data extend the interplay between
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29 284 MUFA-rich meals and immediate-release niacin, and emphasize their acute benefits on acute
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32 285 TRL and FFA metabolism to a population of men with MetS. In line with this notion, recent
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34 286 studies have shown the short-term benefits of extended-release niacin in lowering
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36 287 postprandial secretion of TRLs in healthy subjects,[6] and the long-term benefits of extended-
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38 288 release niacin in lowering postprandial secretion of apoB48[3] and TRLs[4] in statin-treated
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41 289 patients with type 2 diabetes and in increasing the fractional catabolic rate of apoB48 in
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43 290 subjects with combined hyperlipidemia.[32] It is also likely that the suppression of adipose
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45 291 tissue lipolysis by the early postprandial hyperinsulinemia[7,8,33] was only partial and that niacin
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47 292 cooperated to further prevent FFA appearance due to its efficacy at suppressing adipocyte
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50 293 intracellular lipolysis.[34] We do not exclude the possibility of niacin also acting as a promoter
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52 294 of FFA clearance in the postprandial period because of an insulin-mediated translocation of
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54 295 fatty acid transport proteins and favorable concentration gradient for adipocyte FFA uptake
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56 296 and storage.[35] This mechanism of FFA clearance has been reported to be less efficient in
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adipose tissue of obese than lean men.[36] In addition, the content of multiple transferable apoCs in postprandial TRLs have been proposed to be pivotal in postprandial triglycerides and FFAs via their roles in regulating TRL lipolysis and hepatic removal of remnant TRLs.[37] Because each participant served as his own control and no differences were found in fasting triglycerides prior to ingestion of the high-fat meals and immediate-release niacin, we excluded any influence of fasting triglycerides on postprandial lipid concentrations and clearly established that MUFAs, with or without omega-3 LCPUFAs, are superior to SFAs in reducing the dysregulation of postprandial lipid metabolism in individuals with MetS and that this effect may be facilitated by the co-ingestion of niacin.

The study had several limitations. First, because the participants were men, our results may not be generalizable to women. Second, our analyses were restricted to the fat tolerance test used. Third, we do not exclude the possibility that participants perceived the taste of any dietary fat in the meals.

In summary, this study demonstrates that the co-administration of immediate release niacin and dietary MUFAs, compared to dietary SFAs, improves the postprandial glucose and lipid homeostasis by reducing postprandial insulin (and C-peptide), triglyceride, and FFA responses and insulin resistance in individuals with MetS.

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CONFLICT OF INTEREST

The authors declare no competing financial interest.

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Table 1. Baseline clinical and biochemical characteristics of participants.

	Value
Participants, *n*	16
Age (y)	38.5 ± 4.3
Examination	
Body mass index (kg/m^2)	31.8 ± 4.2
Waist circumference (cm)	124.5 ± 16.1
Waist-to-hip ratio	1.18 ± 0.12
Systolic blood pressure (mmHg)	134.1 ± 8.2
Diastolic blood pressure (mmHg)	84.9 ± 8.8
Investigations	
Total cholesterol (mmol/l)	5.2 ± 0.5
HDL-cholesterol (mmol/l)	1.01 ± 0.11
LDL-cholesterol (mmol/l)	3.49 ± 0.28
Triglycerides (mmol/l)	1.49 ± 0.16
Glucose (mmol/l)	5.34 ± 0.65
Insulin (pmol/l)	135 ± 18
C-peptide (pmol/l)	1192 ± 120
HbA_{1c} (%)[a]	5.2 ± 0.4

Data are mean ± SD. These values were not statistical different when compared with those obtained in each occasion before the ingestion of the dose of immediate-release niacin and the corresponding high-fat meal or the meal with no fat. [a]33.0 ± 0.2 in mmol/mol.

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Table 2. Postprandial indices of β-cell function (IGI, IGI/HOMA-IR, AUC_{INS}/AUC_{GLU}, and DI_{120}) and insulin sensitivity [$IS_{0-\infty}$, $ISI(G)_{0-\infty}$, and $ISI(NEFA)_{0-\infty}$] after the test meals co-administered with a single-dose of immediate-release niacin.

	Meal with no fat	**SFA meal**	**MUFA meal**	**MUFA + omega-3 LCPUFA meal**
IGI 0-60 min[a]	60.4 ± 6.5	130.1 ± 15.9*	75.8 ± 10.2*†	85.2 ± 11.1*†
IGI/HOMA-IR[b]	1.89 ± 0.19	4.46 ± 0.55*	2.52 ± 0.26*†	2.78 ± 0.37*†
AUC_{INS}/AUC_{GLU} 0-120 min[a]	31.4 ± 2.8	46.2 ± 4.1*	34.7 ± 2.5*†	37.2 ± 3.9*†
DI_{120} 0-120 min[c]	85.3 ± 6.1	106.9 ± 8.5*	92.0 ± 5.6*†	94.8 ± 7.9*†
$IS_{0-\infty}$ 0-360 min[d]	486 ± 37	138 ± 13*	225 ± 16*†	216 ± 20*†
Postprandial-Belfiore index for glycemia [$ISI(G)_{0-\infty}$] 0-360 min[c]	1.00 ± 0.08	0.68 ± 0.06*	0.80 ± 0.07*†	0.78 ± 0.08*†
Postprandial-Belfiore index for blood NEFA [$ISI(NEFA)_{0-\infty}$] 0-360 min[c]	1.00 ± 0.09	0.55 ± 0.05*	0.68 ± 0.06*†	0.69 ± 0.09*†

Data are mean ± SD (n = 16). Statistical differences are based on repeated-measures ANOVA with a Bonferroni correction. *$P < 0.05$ vs. meal with no fat; †$P < 0.05$ vs. SFA meal; [a]pmol/mmol; [b]l/mmol; [c]no units; [d]$min^{-1} \times dl \times kg^{-1}/\mu U/ml$.

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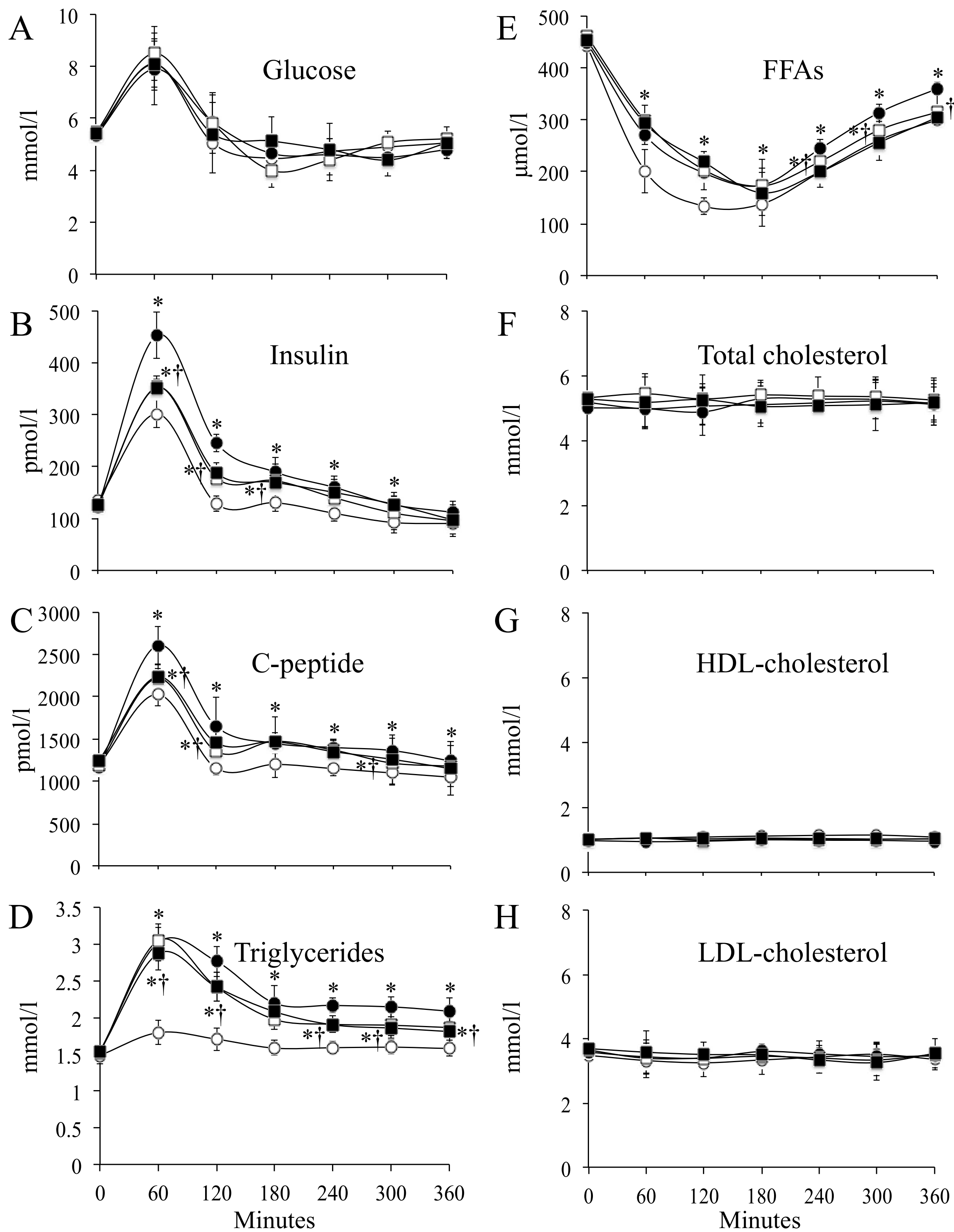

Figure 1. Postprandial graphs for (A) glucose, (B) insulin, (C) C-peptide, (D) triglycerides, (E) FFAs, (F) total cholesterol, (G) HDL-cholesterol, and (H) LDL-cholesterol after the ingestion of the dose of immediate-release niacin and the meal with no fat, control meal

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3 (white circle), rich in SFAs (black circle), rich in MUFAs (white square) or rich in
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5 MUFAs+omega-3 LCPUFAs (black square). *P < 0.05 between the high-fat meals and the
6
7 control meal; †P < 0.05 between the MUFA meals and the SFA meal. The time effect and
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9 meal × time interaction were significant (P < 0.05), except for glucose, total cholesterol,
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11 HDL-cholesterol, and LDL-cholesterol.
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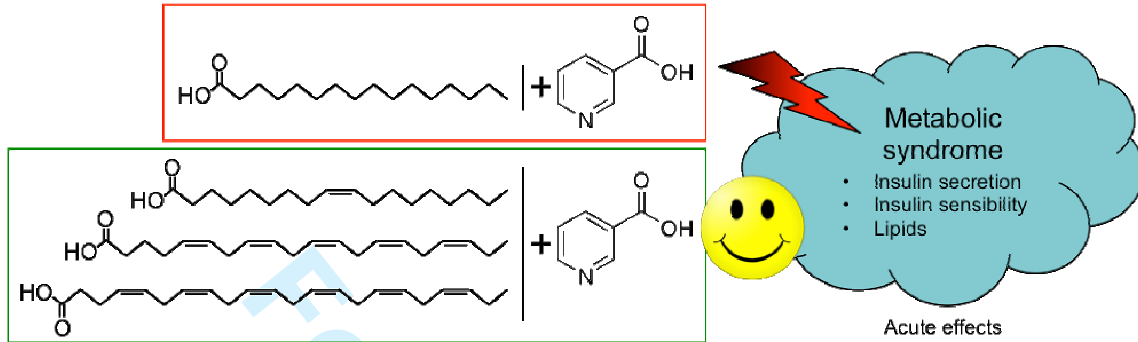

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SUPPORTING INFORMATION

- Fatty acid composition of dietary fats.
- Fasting values on triglycerides, free fatty acids, glucose, insulin, and C-peptide.
- Fasting values on β-cell function and insulin action.

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3 **ONLINE SUPPORTING INFORMATION**
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8 **Supporting Table 1.** Fatty acid composition of dietary fats.

	Cow's milk cream	**Olive oil**	**Olive oil + omega-3 LCPUFAs**
Fatty acid		g/100 g of fatty acid	
4:0, butyric	0.83 ± 0.16	-	-
6:0, caproic	0.25 ± 0.02	-	-
8:0, caprylic	0.61 ± 0.07	-	-
10:0, capric	2.47 ± 0.13	-	-
12:0, lauric	3.09 ± 0.42	-	-
14:0, myristic	10.9 ± 0.91	-	-
16:0, palmitic	35.50 ± 0.82	20.44 ± 0.89	20.48 ± 0.64
16:1(ω-7), palmitoleic	3.60 ± 0.32	0.97 ± 0.17	0.82 ± 0.12
18:0, stearic	11.54 ± 0.75	5.70 ± 0.11	4.49 ± 0.36
18:1(ω-9), oleic	25.33 ± 0.71	61.90 ± 1.23	61.51 ± 0.97
18:2(ω-6), linoleic	4.27 ± 0.82	7.97 ± 0.65	8.04 ± 0.53
18:3(ω-3), α-linolenic	0.39 ± 0.05	1.04 ± 0.13	0.94 ± 0.03
20:5(ω-3), eicosapentaenoic	-	-	0.92 ± 0.09
22:6(ω-3), docosahexaenoic	-	-	0.72 ± 0.10
Others	0.96 ± 0.42	2.05 ± 1.08	2.01 ± 0.88

44 Data are mean ± SD (n = 3).
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Supporting Table 2. Fasting values on the day of administration of the test meals and responses (iAUC) to the test meals[1] co-administered with a single-dose of immediate-release niacin at early (0-t_1 min), late (t_1-t_2 min), and complete (t_2-360 min) postprandial periods for triglycerides, FFAs, glucose, insulin, and C-peptide.

	Meal with no fat	SFA meal	MUFA meal	MUFA + omega-3 LCPUFA meal
Fasting triglycerides[2]	1.49 ± 0.16	1.53 ± 0.23	1.51 ± 0.18	1.53 ± 0.22
Triglycerides $iAUC_{0\text{-}60\ min}$[3]	18.6 ± 2.4	89.0 ± 12.5*	90.9 ± 10.1*	80.4 ± 9.6*
Triglycerides $iAUC_{60\text{-}360\ min}$[3]	35.4 ± 4.2	204.7 ± 28.6*	140.2 ± 19.6*†	139.7 ± 22.5*†
Triglycerides $iAUC_{0\text{-}360\ min}$[3]	54.0 ± 5.0	293.7 ± 49.2*	231.1 ± 30.0*†	220.1 ± 28.1*†
Fasting FFAs[4]	441 ± 35	447 ± 45	462 ± 37	453 ± 69
FFA $iAUC_{0\text{-}120\ min}$[5]	–60177 ± 7203	–50226 ± 5195*	–51348 ± 4070*	–50148 ± 6052*
FFA $iAUC_{120\text{-}360\ min}$[5]	–20490 ± 2451	–14670 ± 1318*	–20790 ± 1455†	–22218 ± 2433†
FFA $iAUC_{0\text{-}360\ min}$[5]	–80667 ± 7550	–64896 ± 6001*	–72138 ± 6512*†	–72366 ± 7091*†
Fasting glucose[2]	5.34 ± 0.65	5.36 ± 0.63	5.48 ± 1.01	5.44 ± 0.86
Glucose $iAUC_{0\text{-}60\ min}$[3]	166 ± 19	152 ± 21	171 ± 36	159 ± 24
Glucose $iAUC_{60\text{-}360\ min}$[3]	–144 ± 13	–129 ± 15	–147 ± 21	–135 ± 23
Glucose $iAUC_{0\text{-}360\ min}$[3]	21.5 ± 2.9	23.7 ± 2.9	23.8 ± 4.2	23.5 ± 3.6
Fasting insulin[6]	135 ± 18	122 ± 14	122 ± 19	127 ± 14
Insulin $iAUC_{0\text{-}60\ min}$[7]	10000 ± 1289	46853 ± 4650	26377 ± 4615*†	26996 ± 3778*†
Insulin $iAUC_{60\text{-}360\ min}$[7]	–5896 ± 702	13514 ± 1784	6259 ± 924*†	6734 ± 578*†
Insulin $iAUC_{0\text{-}360\ min}$[7]	4104 ± 507	33339 ± 4010	19458 ± 3173*†	20262 ± 2182*†
Fasting C-peptide[6]	1192 ± 86	1169 ± 153	1194 ± 75	1242 ± 142
C-peptide $iAUC_{0\text{-}60\ min}$[7]	50244 ± 4094	73830 ± 8456*	61526 ± 6383*†	59580 ± 7642*†
C-peptide $iAUC_{60\text{-}360\ min}$[7]	–14029 ± 1231	86317 ± 11002*	36599 ± 3193*†	32225 ± 3115*†
C-peptide $iAUC_{0\text{-}360\ min}$[7]	36215 ± 2722	160147 ± 19891*	98125 ± 10775*†	91805 ± 11872*†

[1]Participants ingested either a control meal (containing no fat) or a meal enriched in SFAs, MUFAs or MUFAs+omega-3 LCPUFAs. Data are mean ± SD (n = 16). Statistical differences are based on repeated-measures ANOVA with a Bonferroni correction. *$P < 0.05$ vs. meal

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3 with no fat, †$P < 0.05$ vs. SFA meal; [2]mmol/l; [3]mmol/min/l; [4]µmol/l; [5]µmol/min/l; [6]pmol/l;
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Supporting Table 3. Fasting indices of β-cell function (HOMA-B and DI_0), insulin resistance (HOMA-IR and rQUICKI), and insulin sensitivity (ISI_0 for glycemia and ISI_0 for blood NEFAs) on the day of administration of the test meals and a single-dose of immediate-release niacin.[1]

	Prior to the meal with no fat	**Prior to the SFA meal**	**Prior to the MUFA meal**	**Prior to the MUFA + omega-3 LCPUFA meal**
HOMA-B[2]	244 ± 29	219 ± 30	208 ± 30	218 ± 34
DI_0[3]	7.6 ± 0.8	7.5 ± 0.9	6.9 ± 0.8	7.1 ± 1.0
HOMA-IR[4]	32.0 ± 3.4	29.2 ± 3.9	30.1 ± 4.3	30.6 ± 4.2
rQUICKI[5]	0.60 ± 0.07	0.61 ± 0.08	0.60 ± 0.09	0.60 ± 0.10
Basal-Belfiore index for glycemia [$ISI(G)_0$][6]	1.00 ± 0.09	1.10 ± 0.13	1.06 ± 0.14	1.04 ± 0.12
Basal-Belfiore index for blood NEFAs [$ISI(NEFA)_0$][6]	1.00 ± 0.07	1.08 ± 0.11	1.04 ± 0.09	1.04 ± 0.14

[1]Data are mean ± SD (n = 16). Statistical differences are based on repeated-measures ANOVA with a Bonferroni correction. There were no significant differences between the groups for all of the indices; [2]pmol/mmol; [3]$mmol^{-2} \times l^{-2}$; [4]$pmol \times mmol \times l^{-2}$; [5]$pmol \times mmol \times l^{-2}$; [6]no units.

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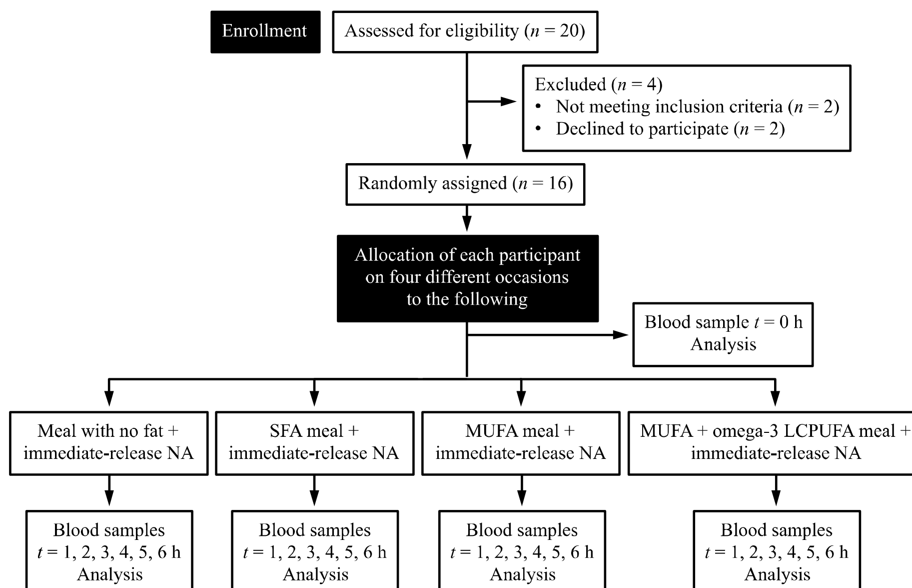

Supporting Figure 1. Overview of subject recruitment and flow through the protocol. NA, niacin

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