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Original article

Immediate-release niacin and a monounsaturated fatty acid-rich meal on postprandial inflammation and monocyte characteristics in men with metabolic syndrome

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SUMMARY

Background & aim: When considered separately, long-term immediate-release niacin and fatty meals enriched in monounsaturated fatty acids (MUFA) decrease postprandial triglycerides, but their effects on postprandial inflammation, which is common in individuals with metabolic syndrome, are less known. Moreover, successful combination is lacking and its impact on acute disorders of the innate immune cells in the metabolic syndrome remains unclear. Here, we aimed to establish the effects from combination with niacin of different fats [butter, enriched in saturated fatty acids (SFA), olive oil, enriched in MUFA, and olive oil supplemented with eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids] on plasma inflammatory markers and circulating monocyte subsets, activation and priming at the postprandial period in individuals with metabolic syndrome.

Methods: A random-order within-subject crossover experiment was performed, in which 16 individuals with metabolic syndrome and 16 age-matched healthy volunteers took 2 g immediate-release niacin together with the corresponding fatty meal or a meal with no fat as control. In total, 128 postprandial curves were analysed. We sampled hourly over 6 h for plasma concentrations of soluble inflammatory markers and triglycerides. Circulating monocyte subsets (CD14/CD16 balance), activation (CCL2/CCR2 axis) and priming (M1/M2-like phenotype) at the time of postprandial hypertriglyceridemic peak were also addressed.

Results: Dietary SFA (combined with niacin) promote postprandial excursions of circulating IL-6, IL-1β, TNF-α and CD14/CCR2-rich monocytes with a pro-inflammatory M1-like phenotype, particularly in individuals with metabolic syndrome. In contrast, dietary MUFA (combined with niacin) postprandially increased circulating CD16-rich monocytes with an anti-inflammatory M2-like phenotype. Omega-3 PUFA did not add to the effects of MUFA.

Conclusion: The co-administration of a single-dose of immediate-release niacin with a fatty meal rich in MUFA, in contrast to SFA, suppresses postprandial inflammation at the levels of both secretory profile and monocyte response in individuals with metabolic syndrome. These findings highlight a potential role of combining niacin and dietary MUFA for the homeostatic control of inflammation and the innate immune system, identifying a new search direction for the management of disorders associated with the metabolic syndrome.

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Abbreviations

CCL2	C–C motif chemokine ligand 2/monocyte chemoattractant protein-1 (MCP-1)
CCR2	C–C chemokine receptor type 2/cluster of differentiation 192 (CD192)
CD200R	CD200 receptor
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
FFAR4	Free Fatty Acid Receptor 4/G protein-coupled receptor 120 (GPR120)
GPR109A	G protein-coupled receptor 109A/hydroxycarboxylic acid 2 receptor (HCA2)
HLA-DR	human leucocyte antigen
HDL-C	high-density lipoprotein cholesterol
iAUC	incremental area under the curve
IRN	immediate-release niacin
LDL-C	low-density lipoprotein cholesterol
MFI	mean fluorescence intensity
MRC1	C-type mannose receptor 1
MUFA	monounsaturated fatty acid
PPARγ	peroxisome proliferator-activated receptor gamma
qRT-PCR	quantitative real-time reverse transcription polymerase chain reaction
SFA	saturated fatty acid
TC	total cholesterol
TG	triglyceride
TNF-α	tumour necrosis factor-α
PUFA	polyunsaturated fatty acid

1. Introduction

Metabolic syndrome is a worldwide epidemic and a cluster of interconnected physiological, biochemical, clinical and metabolic factors [1]. Therefore, understanding the aetiology of metabolic syndrome is critical for developing effective prevention and intervention strategies. Increasing evidence suggest that chronic, subclinical inflammation is part of metabolic syndrome [2]. Activated leukocytes, especially monocytes, selectively traffic to the sites of inflammation and produce inflammatory cytokines that contribute to sustain the local and systemic inflammation [3]. Human monocytes are traditionally divided into three subsets. The major subset consists of $CD14^{++}CD16^{-}$ (classical) monocytes, while the CD16 expressing monocytes are usually divided into a $CD14^{++}CD16^{+}$ (intermediate) and $CD14^{+}CD16^{++}$ (non-classical) subsets. Classical $CD14^{++}CD16^{-}$ monocytes contribute to the secretion of proinflammatory cytokines, phagocytosis and production of reactive oxygen species; the intermediate $CD14^{++}CD16^{+}$ monocytes also exhibit inflammatory functions; while non-classical $CD14^{+}CD16^{++}$ monocytes are responsible for an immunomodulatory and tissue-reparative response, thereby aiding in resolving the inflammation [4].

The postprandial hypertriglyceridemia is considered a metabolic condition with inflammatory consequences due to the transient increase of plasma proinflammatory biomarkers and to the defective immune response of circulating leukocytes in the period that follows a fatty meal [5–7]. Previous studies have reported that the predominant class of dietary fatty acids in the meals can play a role on postprandial metabolic factors associated with cardiovascular disease. Dietary monounsaturated fatty acids (MUFA) and omega-3 long-chain polyunsaturated fatty acids (PUFA) as compared to saturated fatty acids (SFA) have been found to be beneficial in terms of reducing atherogenic and diabetogenic disorders in healthy individuals and in individuals at risk of metabolic syndrome [8–10]. Niacin, also commonly known as nicotinic acid or vitamin B3, is currently the most potent available agent to increase plasma HDL-cholesterol and to lower plasma triglycerides (TG) [11,12]. Higher intake of niacin is known to be associated with reduced risk of metabolic syndrome [13]. In addition, the benefits of immediate-release niacin and dietary MUFA on susceptibility of bone marrow-derived macrophages to inflammation [14] and of adipose tissue to expansion [15] in a mouse model of high-fat diet (HFD)-induced metabolic syndrome have been noticed. However, there is no evidence on the potential effects of niacin in combination with dietary MUFA and omega-3 long-chain PUFA on postprandial inflammation, including the balance of proinflammatory and immunomodulatory monocytes, in the metabolic syndrome with a focus on humans.

2. Aim

The study aim was to evaluate the effects of a single-dose of immediate-release niacin co-administered with high-fat meals enriched in SFA, MUFA or MUFA plus omega-3 long-chain PUFA on postprandial soluble inflammatory markers and on plasma markers and circulating monocyte subsets including their activation state and priming at the postprandial hypertriglyceridemic peak in men with metabolic syndrome and in age-matched healthy men.

3. Materials & methods

3.1. Participants, meals and study design

This study included 16 healthy men and 16 men with metabolic syndrome. Inclusion criteria for metabolic syndrome 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 ≥130 mmHg or diastolic blood pressure ≥85 mmHg, and fasting plasma glucose ≥5.6 mmol/L [16]. As shown in Table 1, the participants' average 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 metabolic syndrome. None of the participants had impaired renal, thyroid or liver function; none had cardiovascular disease or gastroparesis; none had anaemia 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 Clinical Research and Ethics Committee of the University Hospital Virgen del Rocio (Seville), and the study complied with the current revision of the Declaration of Helsinki (The Code of Ethics of the World Medical Association). 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

Table 1
Baseline clinical and biochemical characteristics of participants.[a]

Characteristics	Healthy individuals	Individuals with metabolic syndrome	p value
	$n = 16$	$n = 16$	
Age, y	35.2 (6.7)	38.5 (4.3)	0.11
Men	16 (100%)	16 (100%)	1.00
BMI, kg/m^2	22.1 (1.3)	31.8 (4.2)	<0.001
Waist circumference, cm	85.3 (7.0)	124.5 (16.1)	<0.001
Waist-to-hip ratio	0.87 (0.1)	1.18 (0.12)	<0.001
Systolic blood pressure, mmHg	127.3 (5.0)	134.1 (8.2)	0.009
Diastolic blood pressure, mmHg	81.4 (7.4)	84.9 (8.8)	0.24
Plasma TC, mmol/L	4.51 (0.44)	5.24 (0.53)	<0.001
Plasma HDL-C, mmol/L	1.69 (0.16)	1.01 (0.11)	<0.001
Plasma LDL-C, mmol/L	2.43 (0.14)	3.49 (0.28)	<0.001
Plasma TG, mmol/L	0.50 (0.46, 0.54)	1.49 (1.37, 1.62)	<0.001
Plasma glucose, mmol/L	4.50 (0.36)	5.34 (0.65)	<0.001
Plasma insulin, pmol/L	44 (5)	135 (18)	<0.001
Plasma C-peptide, pmol/L	632 (112)	1192 (120)	<0.001
HbA_{1c}, %	5.1 (0.2)	5.2 (0.4)	0.39

[a] Values are presented as mean (SD) for normally distributed continuous measures, median (interquartile ranges) for skewed distributed continuous variables and count (percentage) for categorical measures. 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. Continuous measures were compared between groups using ANOVA, while categorical measures were compared using Wilcoxon rank-sum test. Abbreviations: TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, total triglycerides.

crossover in which the participants attended the Clinic Experimental Research Unit for Vascular Risk at the University Hospital Virgen del Rocio on 4 separate occasions. For randomization, we used a random number generation method with no restriction. The randomization schedule was used to allocate subject identification numbers in a 1:1:1:1 ratio into the four-meal sequence interventions. 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, USA) were given in random order with an interval of ~1 week between meals. The high-fat meals consisted in an emulsion prepared according to a method previously described [17], 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 (SFA meal), olive oil (MUFA meal) or olive oil plus a dose of omega-3 long-chain PUFAs, which consisted of 920 mg of eicosapentaenoic acid (EPA) and 760 mg of docosahexaenoic acid (DHA) in the form of ethyl esters (referred to as PUFA meal). Olive oil was devoid of minor constituents as obtained by physical refining of virgin olive oil in a discontinuous deodorizer that used nitrogen as stripping gas at the Core Facilities for Oil Extraction and Refining of the Instituto de la Grasa (Seville). The method for measurement of fatty acids in dietary fats (Supplemental Table 1) is described in the Supplemental material. The participants also consumed a test meal prepared as indicated above, but not including fat, as a control meal. After co-administration of niacin and the corresponding meal within 10 min, blood samples were collected hourly into K_3EDTA-containing tubes (Becton Dickinson, NJ, USA) over 6 h. The blood samples taken at the 4-h time point, which corresponded to all the individuals and all the meals, were lost by accident. In this study, each participant served as his own control. Subject flow through the protocol is presented in Fig. 1.

3.2. Anthropometric and biochemical determinations

A precision scale of easy calibration was used for weight measurement with participants in underwear, height was measured with a Harpenden stadiometer (Holtain, Crymych Pembs, UK), BMI was calculated as weight (kg)/height^2 (m) and body surface area (m^2) was calculated as $0.007184 \times \text{height (cm)}^{0.725} \times \text{weight (kg)}^{0.425}$. Waist circumferences were measured at a level midway between the lowest rib and the iliac crest. Brachial systolic and diastolic blood pressures were measured using an automated oscillometer device (Omron M6 Comfort; Omron Healthcare, Kyoto, Japan) in the right arm, with participants lying in the supine position for 10 min by a trained observer. Three blood pressure readings were taken at 2-min interval, and the mean was used for data analysis. Total cholesterol was determined by an enzymatic method (CHODPAP; Roche Diagnostics, Basel, Switzerland). HDL-cholesterol was determined after precipitation with phosphotungstic acid. LDL-cholesterol was calculated by the Friedewald formula (LDL-cholesterol = total cholesterol − HDL-cholesterol − triglycerides/5). Total triglycerides were determined by an enzymatic method (GPO-PAP; Roche Diagnostics). Glucose was measured with a DAX-96 autoanalyzer (Bayer Diagnostics, Milan, Italy) by using commercially available reagents and an enzyme-based kit. Insulin and C-peptide were measured by using specific enzyme-linked immunosorbent assays (Diagnostic System Laboratories, Webster, TX, USA). HbA_{1c} was measured according to the Standard Operating Procedure of the IFCC Reference, with an automated high-performance liquid chromatography analyser (Bio-Rad, Milan, Italy). IL-6, IL-1β, tumour necrosis factor-α (TNF-α) and IL-10 were determined by using enzyme-linked immunosorbent assay kits (Diaclone, Besancon, France).

3.3. Identification, isolation and phenotyping/genotyping of monocytes

Flow cytometry analysis (FACSCanto II flow cytometer, BD) of monocyte composition (CD14, CD16) and activation [C–C chemokine receptor type 2 (CCR2)/cluster of differentiation 192 (CD192)] in each monocyte subset was performed in whole blood samples at fasting and at the postprandial hypertriglyceridemic peak. Peripheral blood monocytes were isolated using Ficoll-Histopaque (Sigma, Madrid, Spain) gradient centrifugation and immunomagnetic negative isolation. After RNA isolation and reverse transcription, messenger RNA of proinflammatory (IL-6, IL-1β, TNF-α), anti-inflammatory (IL-10), activation [C–C motif chemokine ligand 2 (CCL2)/monocyte chemoattractant protein-1 (MCP-1)] and priming [M1-like phenotype: CD64, CD80; M2-like phenotype: CD200 receptor (CD200R), C-type mannose receptor 1 (MRC1)] genes was measured in the monocyte fraction at fasting and at the

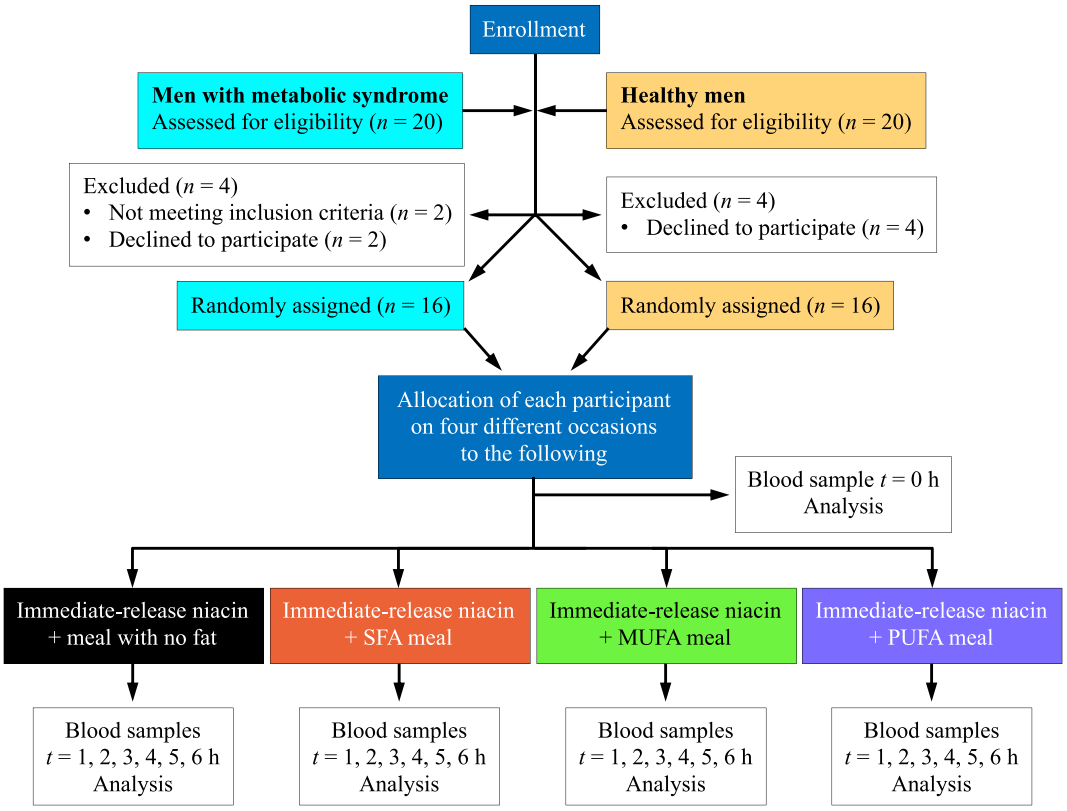

Fig. 1. Overview of subject recruitment and flow through the protocol. Blood samples from time hour 4 were lost. Abbreviations: SFA meal, meal enriched in saturated fatty acids; MUFA meal, meal enriched in monounsaturated fatty acids (MUFA); PUFA meal, meal enriched in MUFA plus a dose of omega-3 long-chain polyunsaturated fatty acids (PUFA) [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)].

postprandial hypertriglyceridemic peak using quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR) analysis. Details, including sequences of qRT-PCR primers (Supplemental Table 2), are shown in the Supplemental material.

3.4. Statistical analysis

Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test. Categorical measures were compared using Wilcoxon rank-sum test. Changes over time per group were determined by 1-way analysis of variance, and changes over time between interventions (niacin + control meal/niacin + SFA meal/niacin + MUFA meal/niacin + PUFA meal) were determined by 2-way analysis of variance. Bonferroni multiple comparisons test as post hoc test was used. The 6-h incremental area under the curve (iAUC; ignoring the area below fasting level) was calculated using the trapezoidal rule. p Values <0.05 were considered significant. Data were evaluated with Graph Pad Prism Version 6 software (GraphPad, CA, USA).

4. Results

4.1. The impact of niacin co-administered with high-fat meals enriched in SFA, MUFA or PUFA on plasma inflammatory profile during the postprandial period

IL-6, IL-1β and TNF-α levels were higher in fasting plasma of individuals with metabolic syndrome verifying pro-inflammatory status (Fig. 2A–F). After niacin plus test meals, postprandial plasma levels of pro-inflammatory markers were increased by the SFA meal but not by the MUFA or PUFA meal when compared to the co-administration of niacin and the control meal with no fat. This effect was more prominent in individuals with metabolic syndrome than in healthy men. In contrast, IL-10 levels were postprandially lower after the SFA meal than after the MUFA or PUFA meal both in individuals with metabolic syndrome (Fig. 2G) and in healthy men (Fig. 2H). In an additional kinetic analysis, IL-6 and IL-1β iAUCs only increased after the SFA meal (Fig. 2I and J). Remarkably, TNF-α iAUC was particularly increased by the SFA meal but reduced by the MUFA and the PUFA meals in individuals with metabolic syndrome (Fig. 2K). IL-10 iAUC was reduced by the SFA meal but remained unaltered after the MUFA or PUFA meal (Fig. 2L).

4.2. The impact of niacin co-administered with high-fat meals enriched in SFA, MUFA or PUFA on circulating TG during the postprandial period and on monocyte phenotyping/genotyping at postprandial hypertriglyceridemic peak

Postprandial changes in plasma triglyceride levels among different study groups are shown in Supplemental Fig. 1. After niacin plus test meals, postprandial TG increased in the form of a bell-shaped curve showing a peak at 1 h both in individuals with metabolic syndrome and in healthy individuals. No changes in plasma TG were observed after niacin and the control meal with no fat. The gating scheme for identification of monocyte subsets, including an additional human leucocyte antigen (HLA-DR) gating strategy to avoid any overestimation of non-monocytes $CD16^{+}$ cells are shown in Supplemental Figs. 2 and 3, respectively. At fasting, $CD14^{++}CD16^{-}$ classical monocytes were more abundant while $CD14^{+}CD16^{++}$ non-classical monocytes were less abundant in individuals with metabolic syndrome than in healthy men. After niacin plus test meals (at the time of postprandial

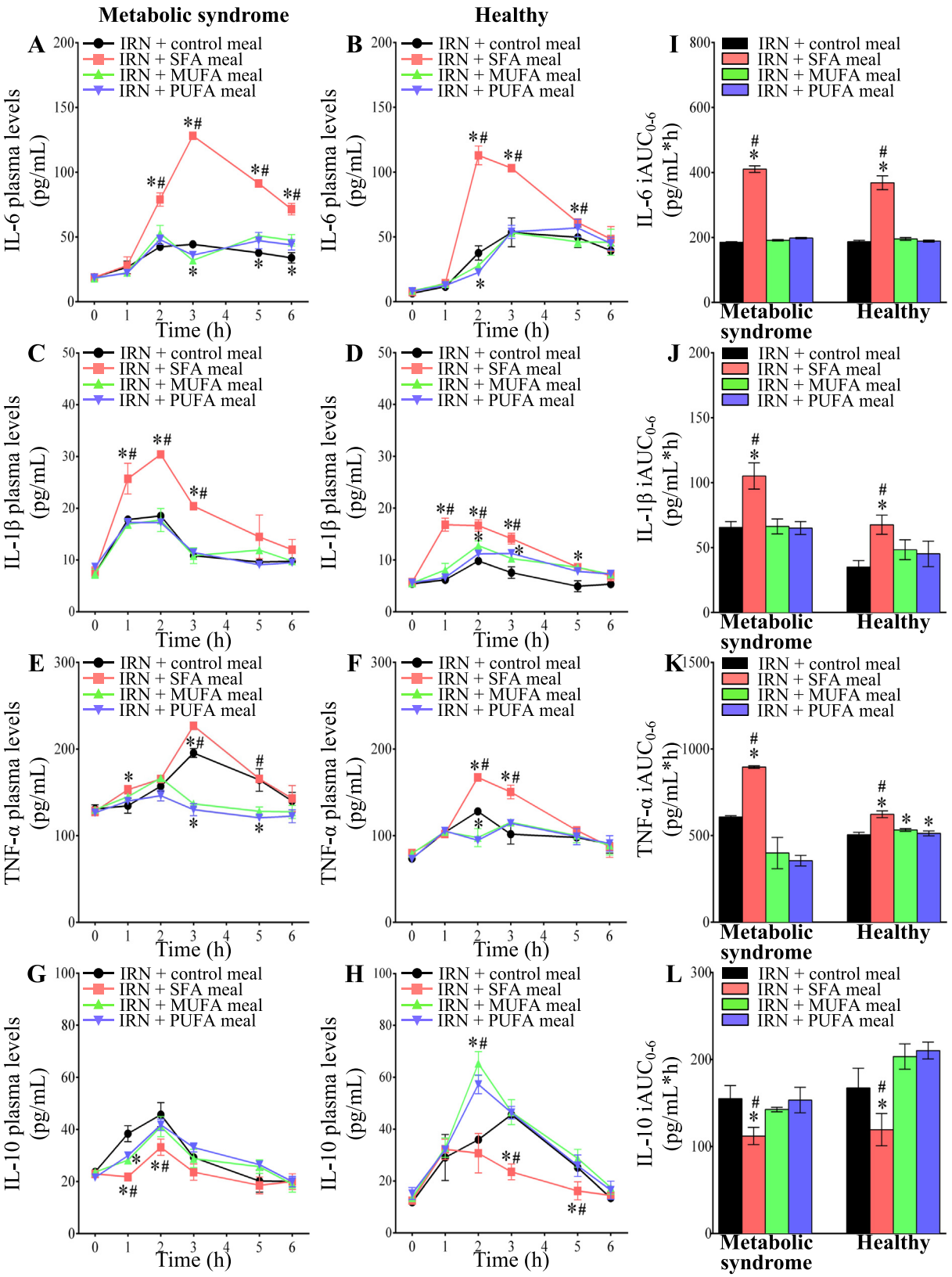

Fig. 2. Inflammatory markers in plasma at fasting and at postprandial. **A**, **C**, **E** and **G**, Time course of IL-6, IL-1β, TNF-α and IL-10 in individuals with metabolic syndrome. **B**, **D**, **F** and **H**, Time course of IL-6, IL-1β, TNF-α and IL-10 in healthy individuals. **I**, **J**, **K** and **L**, Area under the curve of IL-6, IL-1β, TNF-α and IL-10 in individuals with metabolic syndrome and in healthy individuals. Values are expressed as the mean ± SD. *Statistical difference ($p < 0.05$) vs fasting. #Statistical difference ($p < 0.05$) vs other high-fat meal. Abbreviations: IRN, immediate-release niacin; SFA meal, meal enriched in saturated fatty acids; MUFA meal, meal enriched in monounsaturated fatty acids (MUFA); PUFA meal, meal enriched in MUFA plus a dose of omega-3 long-chain polyunsaturated fatty acids (PUFA) [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)].

hypertriglyceridemic peak), classical and intermediate postprandial monocytes increased while non-classical postprandial monocytes decreased by the SFA meal when compared to fasting values, to niacin alone (co-administered with the control meal) and to the MUFA and PUFA meals both in individuals with metabolic syndrome (Fig. 3A–C) and in healthy individuals (Fig. 3D–F). In contrast, niacin and the MUFA or PUFA meal promoted an increase of CD16 expression in circulating postprandial monocytes, resulting in a lower number of classical and a higher number of non-classical monocytes both in individuals with metabolic syndrome and in healthy individuals. Niacin alone (administered with the control meal with no fat) had no postprandial effects on any monocyte subset.

In the context of our experimental design, the chemokine receptor CCR2 was markedly increased by the SFA meal in classical and intermediate postprandial monocytes when compared to fasting values, to niacin alone (co-administered with the control meal) and to the MUFA and PUFA meals at the postprandial

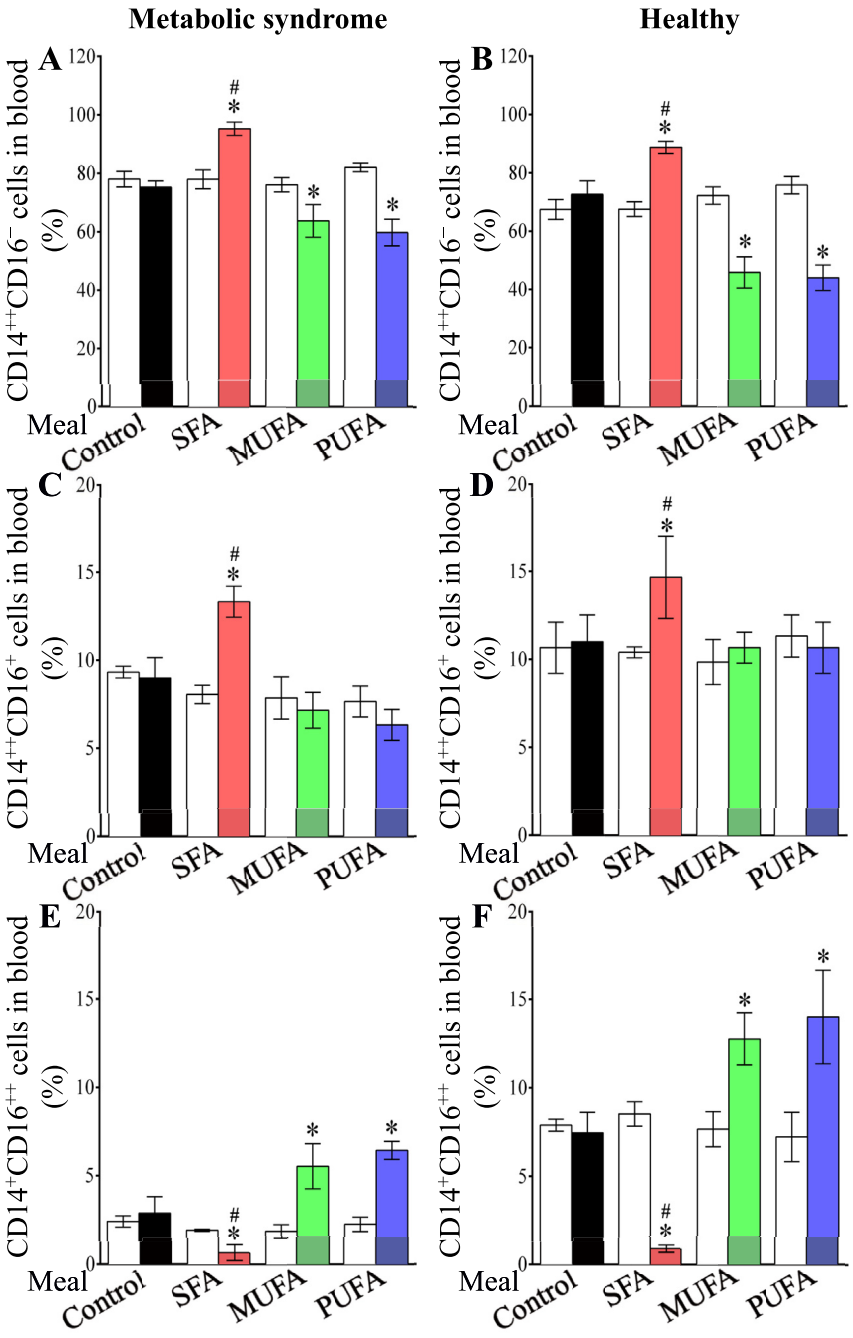

Fig. 3. FACS analysis of CD14 and CD16 in fasting (white bars) and postprandial (coloured bars) monocytes. **A**, **C** and **E**, Percentages of classical $CD14^{++}CD16^{-}$, intermediate $CD14^{++}CD16^{+}$ and non-classical $CD14^{+}CD16^{++}$ monocytes in individuals with metabolic syndrome. **B**, **D** and **F**, Percentages of classical $CD14^{++}CD16^{-}$, intermediate $CD14^{++}CD16^{+}$ and non-classical $CD14^{+}CD16^{++}$ monocytes in healthy individuals. Values are expressed as the mean ± SD. *Statistical difference ($p < 0.05$) vs fasting. #Statistical difference ($p < 0.05$) vs other high-fat meal. Abbreviations: SFA meal, meal enriched in saturated fatty acids; MUFA meal, meal enriched in monounsaturated fatty acids (MUFA); PUFA meal, meal enriched in MUFA plus a dose of omega-3 long-chain polyunsaturated fatty acids (PUFA) [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)].

hypertriglyceridemic peak in individuals with metabolic syndrome (Fig. 4A, C and E) and in all monocyte subsets in healthy subjects (Fig. 4B, D and F). In contrast, CCR2 expression was postprandially reduced by MUFA and PUFA meals in non-classical postprandial monocytes more prominently in individuals with metabolic syndrome. Interestingly, niacin alone reduced CCR2 expression in intermediate and non-classical postprandial monocytes both in individuals with metabolic syndrome and in healthy individuals. Representative mean fluorescence intensity plots for CCR2 on circulating monocyte subsets in fasting and postprandial periods are shown in Supplemental Fig. 4. Regarding CCL2, the principal CCR2 ligand, its mRNA expression in the pool of postprandial monocytes was markedly increased by the SFA meal when compared to fasting values, to niacin alone (co-administered with the control meal) and to the MUFA and PUFA meals in the monocyte fraction at the postprandial hypertriglyceridemic peak both in individuals with metabolic syndrome (Fig. 4G) and in healthy individuals (Fig. 4H). Niacin alone reduced mRNA levels of CCL2 gene in healthy individuals (Fig. 4H).

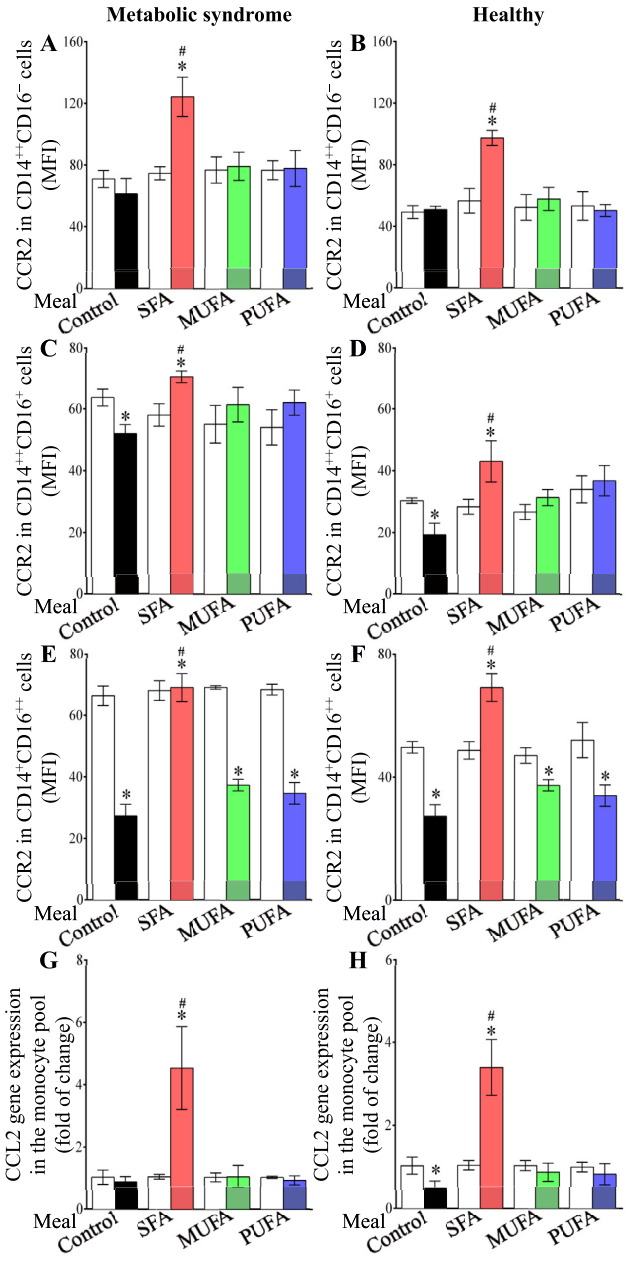

Fig. 4. FACS analysis of CCR2 and transcriptomic analysis of CCL2 in fasting (white bars) and postprandial (coloured bars) monocytes. **A**, **C** and **E**, Mean fluorescence intensity of CCR2 in classical $CD14^{++}CD16^{-}$, intermediate $CD14^{++}CD16^{+}$ and non-classical $CD14^{+}CD16^{++}$ monocytes in individuals with metabolic syndrome. **B**, **D** and **F**, Mean fluorescence intensity of CCR2 in classical $CD14^{++}CD16^{-}$, intermediate $CD14^{++}CD16^{+}$ and non-classical $CD14^{+}CD16^{++}$ monocytes in healthy individuals. **G**, Fold of changes of the expression of CCL2 mRNA in the pool of monocytes from individuals with metabolic syndrome. **H**, Fold of changes of the expression of CCL2 mRNA in the pool of monocytes from healthy individuals. Values are expressed as the mean ± SD. *Statistical difference ($p < 0.05$) vs fasting. #Statistical difference ($p < 0.05$) vs other high-fat meal. Abbreviations: CCR2, C–C chemokine receptor type 2/cluster of differentiation 192 (CD192); CCL2, C–C motif chemokine ligand 2/monocyte chemoattractant protein-1 (MCP-1); MFI, mean fluorescence intensity; SFA meal, meal enriched in saturated fatty acids; MUFA meal, meal enriched in monounsaturated fatty acids (MUFA); PUFA meal, meal enriched in MUFA plus a dose of omega-3 long-chain polyunsaturated fatty acids (PUFA) [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)].

We also asked whether the combination of niacin and test meals had any effect on priming of circulating monocytes to a M1 pro-inflammatory (CD64 and CD80 markers) or M2 anti-inflammatory (CD200R and MRC1 markers) phenotype (M1/M2 pre-activation status), which can express pro-inflammatory (IL-6, IL-1β and TNF-α) or anti-inflammatory (IL-10) cytokines in the pool of postprandial monocytes at transcriptional level. After niacin plus test meals, mRNA expression of CD64 and CD80 genes markedly increased while that of CD200R gene decreased by the SFA meal when compared to fasting values, to niacin alone (co-administered with the control meal) and to the MUFA and PUFA meals in the monocyte fraction at the postprandial hypertriglyceridemic peak both in individuals with metabolic syndrome (Fig. 5A, C, E and G) and in healthy individuals (Fig. 5B, D, F and H). However, mRNA expression of CD64 and CD80 genes decreased while that of CD200R and MRC1 genes markedly increased by the MUFA and PUFA meals when compared to fasting values and to the SFA meal in the monocyte fraction at the postprandial hypertriglyceridemic peak both in individuals with metabolic syndrome (Fig. 5A, C, E and G) and in healthy individuals (Fig. 5B, D, F and H). Next, mRNA expression of IL-6, IL-1β and TNF-α genes markedly increased while that of IL-10 gene was not affected by the SFA meal when compared to fasting values, to niacin alone (co-administered with the control meal) and to the MUFA and PUFA meals in the monocyte fraction at the postprandial hypertriglyceridemic peak in individuals with metabolic syndrome (Fig. 6A, C, E and G). Healthy individuals showed a similar pattern, but a decreased IL-10 gene expression (Fig. 6B, D, F and H). In contrast, mRNA expression of IL-1β and TNF-α genes markedly decreased while that of IL-10 increased by the MUFA and PUFA meals when compared to fasting values and to the SFA meal in the monocyte fraction at the postprandial hypertriglyceridemic peak in individuals with metabolic syndrome (Fig. 6A, C, E and G). Healthy individuals showed a similar pattern (Fig. 6B, D, F and H). It was interesting to note that niacin alone induced almost identical effects on M1/M2 marker and cytokine genes as the MUFA and PUFA meals (co-administered with niacin) in individuals with metabolic syndrome, except for IL-6 gene expression that decreased.

5. Discussion

In line with well-known clinical observations on metabolic benefits of Mediterranean-type diets rich in MUFA and omega-3 PUFA in individuals at risk of metabolic syndrome when compared to Western-type diets rich in SFA [18–20] and of niacin particularly for patients with statin intolerance [21,22], niacin/dietary MUFA combination improved plasma inflammatory cytokine levels, hypertriglyceridemia and phenotype of circulating monocytes during the postprandial period not only in a cohort of healthy

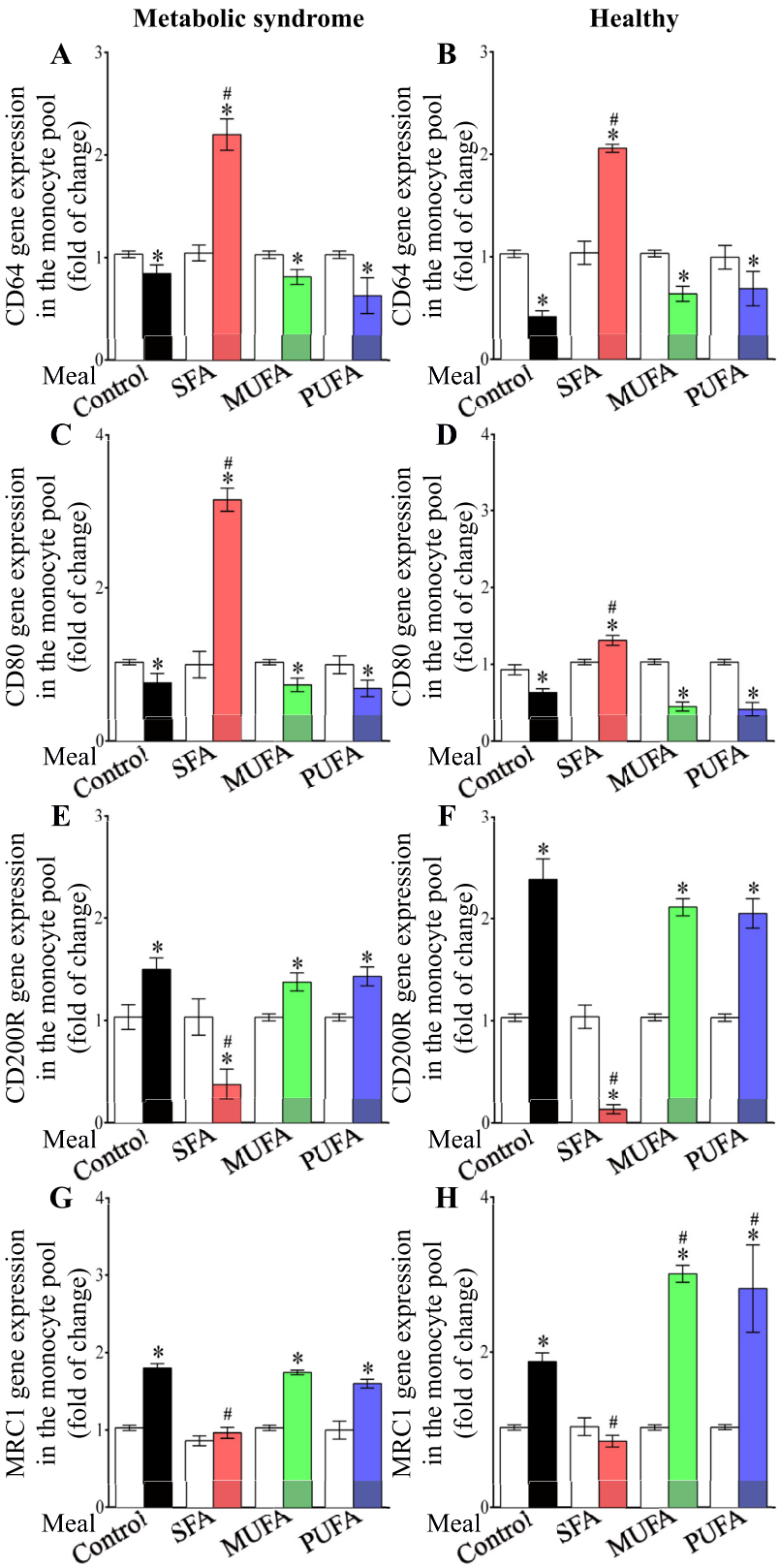

Fig. 5. Transcriptomic analysis of M1/M2-related gene markers in fasting (white bars) and postprandial (coloured bars) monocytes. **A**, **C**, **E** and **G**, Fold of changes of the expression of CD64, CD80, CD200R and MRC1 mRNA in the pool of monocytes from individuals with metabolic syndrome. **B**, **D**, **F** and **H**, Fold of changes of the expression of CD64, CD80, CD200R and MRC1 mRNA in the pool of monocytes from healthy individuals. Values are expressed as the mean ± SD. *Statistical difference ($p < 0.05$) vs fasting. #Statistical difference ($p < 0.05$) vs other high-fat meal. Abbreviations: CD200R, CD200 receptor; MRC1, C-type mannose receptor 1; SFA meal, meal enriched in saturated fatty acids; MUFA meal, meal enriched in monounsaturated fatty acids (MUFA); PUFA meal, meal enriched in MUFA plus a dose of omega-3 long-chain polyunsaturated fatty acids (PUFA) [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)].

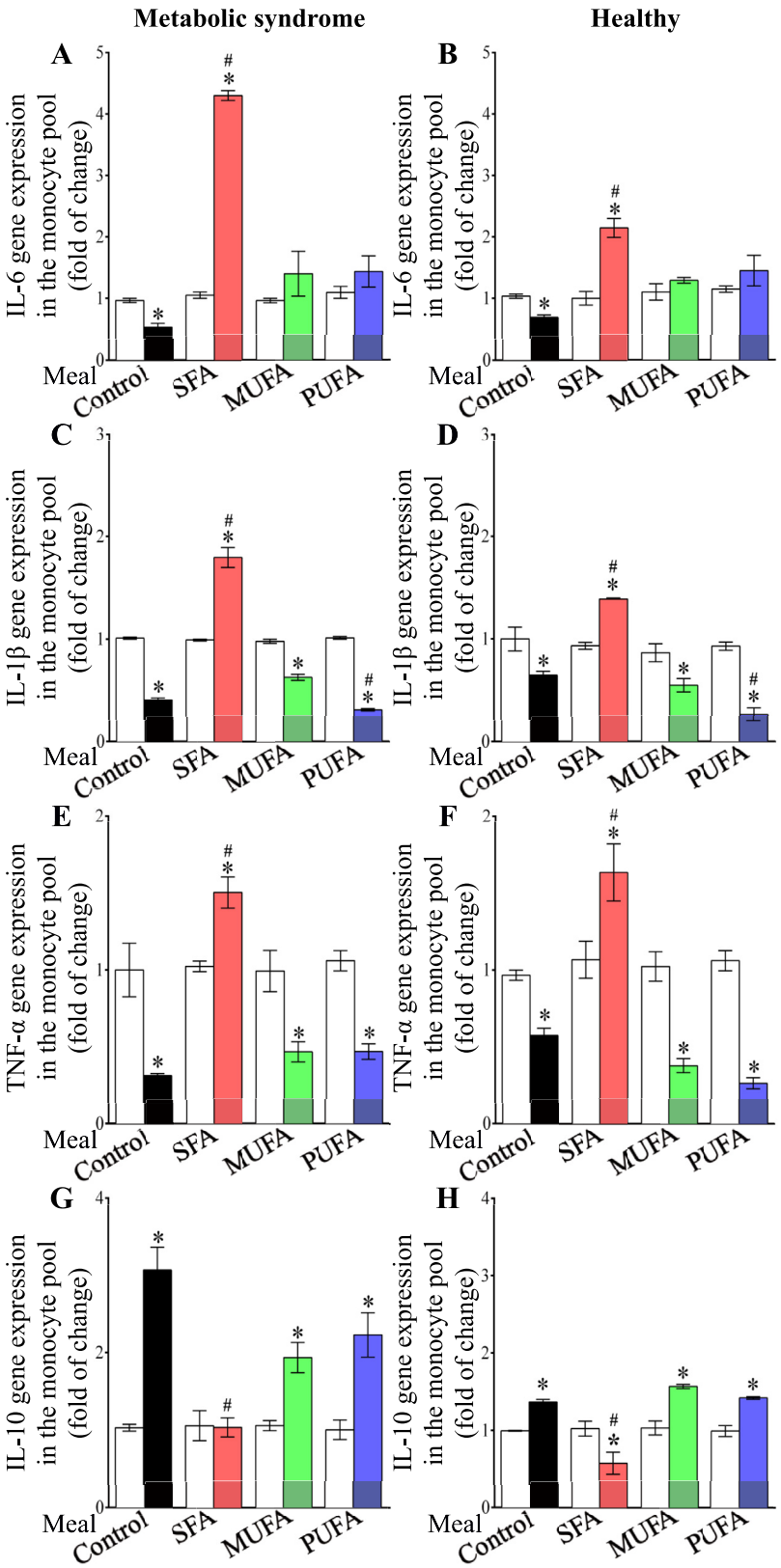

Fig. 6. Transcriptomic analysis of inflammation-related gene markers in fasting (white bars) and postprandial (coloured bars) monocytes. **A**, **C**, **E** and **G**, Fold of changes of the expression of IL-6, IL-1β, TNF-α and IL-10 mRNA in the pool of monocytes from individuals with metabolic syndrome. **B**, **D**, **F** and **H**, Fold of changes of the expression of IL-6, IL-1β, TNF-α and IL-10 mRNA in the pool of monocytes from healthy individuals. Values are expressed as the mean ± SD. *Statistical difference ($p < 0.05$) vs fasting. #Statistical difference ($p < 0.05$) vs other high-fat meal. Abbreviations: TNF-α, tumour necrosis factor-α; SFA meal, meal enriched in saturated fatty acids; MUFA meal, meal enriched in monounsaturated fatty acids (MUFA); PUFA meal, meal enriched in MUFA plus a dose of omega-3 long-chain polyunsaturated fatty acids (PUFA) [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)].

men but also, and with more intensity, in a cohort of men with metabolic syndrome. These findings, which should not be extended to women, could be of importance because the appearance of a higher grade of inflammation each time we eat foods rich in SFA can be regarded as a risk factor for future major cardiovascular and metabolic events in asymptomatic individuals [5,23,24] and for further deterioration of cardiovascular and metabolic traits among individuals with metabolic syndrome [25,26], who often exhibit chronic inflammation and, as shown here, exacerbated postprandial inflammatory response.

In earlier studies, we demonstrated that a meal rich in dietary MUFA postprandially increased the soluble forms of intercellular and vascular adhesion molecules 1 as surrogate markers of endothelial activation and vascular inflammation in hypertriglyceridemic individuals when compared to the fasted state, but these postprandial effects were markedly less pronounced after a meal rich in dietary SFA [27]. Now we show that the replacement in the meal of dietary SFA with an isocaloric amount of dietary MUFA or dietary MUFA supplemented with EPA and DHA resulted in an undetectable impact on the iAUC of IL-6 and IL-1β when compared to the control meal with no-fat in individuals with metabolic syndrome co-treated with niacin. Under these experimental conditions, EPA and DHA had no observable effects. Importantly, the meals enriched in MUFA even reduced the iAUC of TNF-α below the control level. As all the test meals were provided in combination with a single 2 g dose of niacin, these findings represent novel evidence of potential clinical benefits from the use of a pharmacological dose of niacin in combination with dietary MUFA by individuals with metabolic syndrome to prevent postprandial excursions of the inflammatory markers IL-6, IL-1β and TNF-α, and to promote postprandial excursions of IL-10. We also previously documented that combined administration of niacin with dietary MUFA was highly effective in ameliorating the glycaemic response during the postprandial period in individuals with metabolic syndrome [28] and in protecting against white fat dysfunction in mice with high-fat induced metabolic syndrome [15]. We hypothesised that a diet rich in MUFA would improve inflammatory conditions associated with high IL-6, IL-1β and TNF-α secretion, and/or with low IL-10 secretion in niacin-treated individuals, with metabolic syndrome or other disease modalities. Such a nutritional strategy could also help to reduce the dose of niacin while having equivalent pharmacological efficacy and to minimize the undesirable effect of cutaneous flushing [29,30] that is less common at lower doses [31].

The role of combination of niacin and dietary fatty acids on immune cells concerned with inflammation in humans has not been described so far to the best of our knowledge. We studied this combination on circulating monocytes including their activation state and priming towards a migratory endpoint and an M1-or M2-like phenotype at the postprandial hypertriglyceridemic peak. First, based on surface makers expression of CD14 and CD16 receptors, we found a profile of circulating monocytes characterized by an increased frequency of classical $CD14^{++}CD16^{-}$ and a decreased frequency of non-classical $CD14^{+}CD16^{++}$ monocytes at fasting in individuals with metabolic syndrome compared to healthy individuals. In addition, we observed that dietary SFA in combination with niacin postprandially induced an increase of classical and intermediate monocytes but a decrease of non-classical $CD14^{+}CD16^{++}$ monocytes both in individuals with metabolic syndrome and in healthy individuals. The contrary effects on classical and non-classical monocytes were observed with dietary MUFA (supplemented or not with EPA and DHA) in combination with niacin, further suggesting that dietary MUFA could rapidly switch the phenotype of circulating monocytes to be anti-inflammatory rather than proinflammatory in niacin-treated individuals. These observations are consistent with previous reports on decreasing the inflammatory state of human monocytes by olive oil-based intravenous lipid emulsions [32] and on restoring the proportions of classical monocytes (diminishing) and non-classical monocytes (enhancing) at sites of inflammation in mice with peritonitis or sepsis that were given lipid emulsions containing omega-3 PUFA [33]. Here we show no acute effects of niacin alone on the profile of circulating monocyte subsets, compatible with the results of a recent short-term study in mice in which niacin was, however, able to reverse deficient remyelinating activity of monocyte-derived macrophages in the aging central nervous system [34]. Niacin has also been recently reported to give human monocytes some immune abilities, for example, those related to a resilient phenotype against growth of cancerous cells [35]. Remarkably, the skewing of monocytes into the classical subset in parallel to depletion of the non-classical subset is evocative of monocyte exhaustion seen in patients with severe inflammation, which is a condition associated with a decline of cellular NAD^{+} levels [36]. To establish whether the same mechanism operates in monocytes of individuals with metabolic syndrome on the basis of our niacin/dietary fatty acid approach would be worth to take under consideration in future studies, particularly given that the disruption of metabolic reprogramming of immune cells by a drop of NAD^{+} reserves may contribute to the occurrence and development of inflammatory diseases of the central nervous system [37] and other pathological processes, such as cancer [38]. Pointing in the same direction is the fact that classical (or intermediate) monocytes and non-classical monocytes have antagonistic effects on the severity of atherosclerosis [39], neurological disorders [40–42] and tumour progression and metastasis [43]. Therefore, our study reinforces the idea that dietary MUFA, in contrast to dietary SFA, have the potential to beneficially exploit the multifaceted influence of niacin on immune system in individuals with metabolic syndrome, which is conductive to reset the balance of monocyte subsets and thereby could prevent or delay progression of health outcomes associated with classical and intermediate monocytes when they are present at high levels in blood.

Monocyte mobilisation and recruitment to inflammatory sites is known to be mediated by several chemokine systems. Among them, the receptor CCR2 and its ligand CCL2 have been recognized as one of the most important regulatory pathways in the orchestration of such monocyte trafficking [44]. We evaluated the postprandial effects of niacin and dietary fatty acids on CCR2 protein expression in the different monocyte subsets and on CCL2 gene expression in the monocyte pool. It was noticeable that dietary SFA, but not MUFA or MUFA + EPA + DHA, in combination with niacin postprandially induced an increase of CCR2 protein expression in classical and intermediate monocytes both in individuals with metabolic syndrome and to a less extent in healthy individuals. This shape shift has been reported to strongly promote the proinflammatory functions of those CCR2-enriched monocyte subsets [45], which are nowadays considered key targets for next generation of anti-inflammatory treatments against many diseases including atherosclerosis [46] and ischaemic stroke [47]. We additionally observed that only the combination of niacin and dietary SFA led to an increased expression of CCL2 gene in the postprandial monocyte pool of individuals with metabolic syndrome and of healthy individuals, suggesting an overstimulation of the CCL2/CCR2 axis. Previous studies in the absence of niacin showed that omega-3 PUFA have no effects on postprandial serum levels of CCL2 in healthy individuals [48] and in individuals with overweight or obesity [49], and that olive oil (the major source of MUFA in the diet) slightly increases the postprandial levels of CCL2 in subcutaneous adipose tissue of individuals with obesity [50] and has no effect on postprandial levels of CCL2 in peripheral blood mononuclear cells of elderly subjects [51]. Postprandial studies on the

role of dietary SFA in circulating CCL2 have shown no treatment effect in individuals with metabolic syndrome [52]. Of note, niacin alone induced a marked decrease of CCR2 protein expression in postprandial intermediate and non-classical monocytes both in individuals with metabolic syndrome and in healthy individuals. Although CCR2 is better expressed in intermediate monocytes but less expressed in non-classical monocytes [53], this is the first time that niacin has been shown to have such a role. It can be reasoned that niacin could be a useful addition to anti-migratory and anti-inflammatory armamentarium in individuals with metabolic syndrome who have high levels of circulating intermediate monocytes. This decrease of surface CCR2 expression was likely not due to internalization of the CCL2-CCR2 signalling complex, as CCL2 expression was unaffected in individuals with metabolic syndrome or reduced in healthy individuals by niacin. Recent literature has reported that niacin reduces the transcriptional activity of CCL2 gene in monocyte-derived macrophages recruited to the epididymal white adipose tissue both in global adiponectin null mice with HFD-induced obesity and in lean wild-type mice [54]. Therefore, we do not rule out the possibility that the mechanisms underlying dual effects of niacin on CCR2 and CCL2 could be functional after differentiation of monocytes into macrophages at sites of inflammation in individuals with metabolic syndrome. From all this evidence, the concept has arisen that niacin guides a homeostatic program in postprandial monocytes of individuals with metabolic syndrome by targeting the CCL2/CCR2 axis, but a very important remark is that this effect can be suppressed and even reversed on diets rich in SFA instead of MUFA.

Of major interest was that niacin alone or in combination with dietary MUFA biased the priming of postprandial monocytes to an M2-like phenotype by the down-regulation of CD64 and CD80 genes accompanied by the up-regulation of CD200R and MRC1 genes both in individuals with metabolic syndrome and in healthy individuals. This reprogramming of gene expression was reversed to an M1-like phenotype by niacin in combination with dietary SFA. Our observations are in concert with recent reports showing ex vivo that niacin and dietary MUFA orientate bone marrow-derived macrophages to M2 polarisation while the combination of niacin with dietary SFA promotes the polarisation into the M1 phenotype in mice with HFD-induced metabolic syndrome [14] and in vitro that TG-rich lipoproteins isolated at the postprandial peak from blood of healthy volunteers after the ingestion of a meal rich in MUFA or MUFA + EPA + DHA, particularly in combination with niacin, enhanced the competence of autologous circulating monocytes to be differentiated and polarised into M2 macrophages; in sharp contrast with the addition of postprandial TG-rich lipoproteins containing a high concentration of dietary SFA combined with niacin that skewed naïve macrophages toward M1 macrophages [55]. In humans, the ability of niacin to switch the circulating leukocytes from an M1-to M2-like state has recently been documented to be associated with an improvement of neuroinflammation in Parkinson disease, probably via GPR109A [56,57]. The transcription factor termed peroxisome proliferator-activated receptor gamma (PPARγ) has also been shown to be involved in the priming of circulating monocytes by suppressing M1 markers and enhancing M2 markers [58,59]. It is known that MUFA and PUFA, but not SFA, are endogenous ligands for PPARγ [60]. Interestingly, niacin has been reported to stimulate the PPARγ signalling pathway in human monocyte (THP-1)-derived macrophages [61]. Therefore, it is plausible that activation of GPR109A by niacin and of PPARγ by niacin and/or dietary MUFA could at least in part explain the patterned expression of genes encoding proinflammatory (decreasing IL-6, IL-1β and TNF-α) and anti-inflammatory (enhancing IL-10) cytokines in postprandial monocytes when niacin alone or in combination with dietary MUFA is given to individuals with metabolic syndrome. Based on these propositions, the priming of circulating monocytes before differentiation during acute phase of niacin treatment combined with the ingestion of dietary MUFA might skew monocyte-derived macrophages to retain an M2 polarisation in inflammatory sites, which could be of value for the continuous proinflammatory pre-activated state of circulating monocytes and other cells (in circulation or in tissues) in the metabolic syndrome [62].

6. Conclusion

In summary, this pilot study provides novel and useful data to demonstrate that the combination of niacin and dietary MUFA has a beneficial impact on inflammatory and immune mechanisms at multiple levels in individuals with metabolic syndrome during the postprandial period, decreasing circulating inflammatory signals and diminishing the inflammatory activation state and the migratory phenotype via the CCL2/CCR2 axis of circulating monocytes. However, these findings should need to be confirmed in a chronic condition. Our observations could considerably aid in informing meaningful and clinically relevant advices for precision health by the dynamic and co-operative contribution of niacin and dietary MUFA in the management of the metabolic syndrome.

Author contributions

SM, BB, RA, FJGM: designed research and had primary responsibility for final content; SM, MCN, SL, MCML, ARD, SMJC, BB, FJGM: coordinated the participant recruitment and data collection; SM, BB: conducted the statistical analysis; BB, FJGM: drafted the manuscript of the article; SM, MCN, SL, MCML, ARD, SMJC, RA, FJGM, BB: contributed to the discussion and critical revision of the manuscript. All authors have read and approved the final manuscript.

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Conflicts of interest

The authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.08.017.

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