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Randomized control trials

Modification in a single meal is sufficient to provoke benefits in inflammatory responses of individuals at low-to-moderate cardiometabolic risk

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SUMMARY

Background & aims: Postprandial state is characterized by metabolic changes which may elevate circulating inflammatory biomarkers, used to assess cardiometabolic risk. It is unclear if biological benefits of certain food components could be obtained by a short-term change in a single meal of Brazilian's habitual diet. We investigated the postprandial effects of 2 fat tolerance tests (FTT) with different isocaloric meals (a typical Brazilian and a modified meal) differing by type of fatty acids and fiber contents, prior to and after breakfast interventions.

Methods: This crossover clinical trial included 80 overweight individuals with at least one cardiometabolic risk factor, *(35–69 years)* who received two isocaloric breakfast interventions for 4 weeks, with a 2-week washout. The Brazilian breakfast was saturated fat-enriched while the modified one was rich in unsaturated fatty acids and fibers. Before and after intervention periods, individuals underwent two FTT with meals with similar composition to the interventions breakfasts but higher energy content. Variables were compared by repeated-measures ANOVA. Correlations were assessed by Pearson's coefficient.

Results: At the end of both interventions, participants did not change plasma glucose or triglycerides. The higher IL-6 and IL-8 responses to the FTT with the Brazilian meal compared to that with the modified meal was accentuated after the interventions (p-diet <0.01; p-time <0.01). Acutely, E-selectin, TNF-α, IFN-γ, IL-10 and IL-17 concentrations did not increase in response to the FTTs, but showed higher values only after the Brazilian intervention. In contrast, intervention with the modified breakfast induced reductions in fasting and postprandial cytokines (p-diet <0.01). Changes in MUFA and PUFA intakes were inversely correlated to changes in inflammatory markers, while changes in saturated fat intake were directly correlated to IFN-γ and IL-6.

Conclusion: Isocaloric meals with distinct nutrient composition elicit different postprandial inflammatory responses after a relatively short intervention in a single meal. Each saturated fat-enriched meal consumed, as well as each unsaturated fat and fiber-enriched meal may induce pro- or anti-inflammatory responses that could impact on the cardiometabolic risk profile.

1. Introduction

Modern dietary habits, characterized by high-energy and high-density food intake, have been associated with cardiometabolic diseases, and low-grade inflammation plays a key role in their natural history [1]. In particular, postprandial biochemical changes are associated with morbidities [2] which are relevant since most of the time humans are in a postprandial state. Each meal induces increases in plasma glucose, triglycerides (TG), hormones, and cytokines, whose magnitude and duration depend on their composition and individual characteristics [3]. An unhealthy diet in combination with sedentary behavior can negatively influence postprandial response, generating inflammation and predisposing to insulin resistance.

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List of abbreviations

BMI	body mass index
CRP	C-reactive protein
FTT	fat tolerance test
HOMA-IR	homeostasis model assessment
IFN-γ	interferon gamma
IL	interleukin
MUFA	monounsaturated fatty acids
PUFA	polyunsaturated fatty acids
SD	standard deviation
SFA	saturated fatty acids
TG	triglycerides
TLR4	toll like receptor 4
TNF-α	tumor necrosis factor alpha

The clinical relevance of postprandial lipids in predicting cardiovascular disease is recognized, although the role of hypertriglyceridemia, independently of other risk factors, is still a matter a discussion [3,4]. Despite no standard fat tolerance test (FTT) to evaluate postprandial lipemia, this seems to be useful to orient how aggressive lifestyle modification should be in individuals at risk, since dietary habits may influence circulating levels of metabolites and cytokines [4]. In fact, postprandial hyperlipemia has been shown to be associated with impaired endothelial function and inflammation [3,4].

Distinct dietary fatty acids compositions have different impacts on cell signaling pathways. Saturated fatty acids (SFA) are shown to stimulate adipose tissue inflammation by a process that involves toll-like receptor 4 (TLR4) that plays a key role in the innate immune response [5]. The observation that TLR4 deficiency protected against insulin resistance in SFA-induced obesity suggested that TLR4 was the link between an unhealthy diet, low-grade inflammation, and insulin resistance [5]. On the other hand, n-3 polyunsaturated (PUFA) and monounsaturated fatty acids (MUFA) were associated with anti-inflammatory effects [6–8]. Evidence on the effects of MUFA on the expression of anti-inflammatory genes and circulating cytokines is limited to interventions with Mediterranean style diet and these studies are commonly conducted in Mediterranean populations [6]. The long-term cardiovascular benefits of the Mediterranean has been mostly attributed to high contents of unsaturated fat, mainly from olive oil, nuts, phenolic compounds, and fibers [8,9]. How long these dietary habits take to assure benefits and underlying mechanisms is still under investigation.

Despite the recognized cardioprotection conferred by the Mediterranean diet, marked changes in dietary habits of non-Mediterranean populations are difficult to sustain in the long term. Brazil is characterized by a rich agriculture and a high admixture of the population. Therefore, this unique condition represents an opportunity to implement sustained modification in dietary habits. It is unknown whether small changes in dietary habits, including Mediterranean food components, could induce metabolic benefits. We hypothesized that biological benefits of certain food components could be obtained by a short-term change in a single meal of Brazilian's habitual diet.

This study compared the postprandial effects of two FTTs based on isocaloric meals (a typical Brazilian and a modified meal) differing by type of fatty acids and fiber contents, before and after a 4-week intervention in the breakfasts of individuals at cardiometabolic risk.

2. Material & methods

This study was registered at the Brazilian Registry of Clinical Trials (ReBEC ID: RBR-98 × 6b5) and conducted from April, 2013 to May, 2014 at the Research Center of the University Hospital of the University of São Paulo. The study was approved by the Ethics Committee of the School of Public Health of the University of São Paulo, and individuals provided written consent.

2.1. Subjects

Individuals were invited to participate by posters at the University of São Paulo campi and by newspaper ads. From 543 individuals screened, 142 fulfilled eligibility criteria and 96 were randomly allocated to the interventions. To be included, participants had to meet the following criteria: age between 35 and 69 years, body mass index (BMI) between 25 and 40 kg/m^2, and at least one additional cardiovascular risk factor such as blood pressure $\geq$ 140/90 mmHg or stable antihypertensive treatment, fasting plasma glucose between 100 and 124 mg/dL, TG concentrations $\geq$ 150 mg/dL, or total cholesterol $\geq$ 230 mg/dL or LDL-c > 100 mg/dL or HDL-c < 45 mg/dL for women, or < 40 mg/dL for men. Exclusion criteria were pregnancy, medical history of neurological or psychiatric disorders, diabetes mellitus, thyroid, renal or liver diseases, neoplasia, infectious and rheumatic diseases, use of lipid-lowering agents, and body weight variation $\geq$5% during the last six months.

A sample size calculation (P = 0.05; power = 0.8) for 10% total cholesterol changes revealed that 71 participants were sufficient to demonstrate significant differences after intervention with the modified breakfast. The flowchart of participants of the study is shown in Fig. 1.

2.2. Design and research protocol

This 10-week crossover clinical trial involved two 4-week interventions in breakfast, with a 2-week washout period (Fig. 2). Participants received one of two breakfasts in random order, a Brazilian breakfast or a modified one. The breakfasts were isocaloric, differing by the distribution of fatty acids types and fiber content. The prepared Brazilian breakfast included 3% fat milk (180 mL), coffee (60 mL), sugar (10 g), French bread (50 g), salted butter (15 g), and mozzarella cheese (32 g). The modified breakfast was created including some components of the Mediterranean diet as following: 1% fat milk (180 mL), coffee (60 mL), sugar (10 g), whole-grain French bread (50 g), ricotta cheese (40 g) with extra-virgin olive oil (16 g), and peanuts (10 g). These preparations were similar in energy (around 500 kcal) and macronutrient distribution (46% fat, 38% carbohydrates, and 16% protein), but differed by the relative amounts of fatty acids. Participants were instructed to maintain their daily intake during the day, as well as their regular physical activities. They received weekly phone calls in order to reinforce compliance with the experimental protocol.

One week prior the start of study, as well as at the last week of consumption of each breakfast, two 24-h food recalls were collected. One food recall was obtained face-to-face and the other by telephone by a trained dietitian.

At the beginning and on the last day of each intervention period, participants underwent FTTs.

2.3. Fat tolerance test (FTT)

Participants were instructed to abstain from alcohol intake during the preceding three days. After a 12-h overnight fast, participants were cannulated and blood samples were taken for several determinations prior to the test meal.

The compositions of the Brazilian and modified meal used in the FTTs were similar to the breakfasts consumed during the 4-week interventions, but with a higher total energy (850 kcal) and fat

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