Omega-3 fatty acids supplementation decreases metabolic syndrome prevalence after lifestyle modification program

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ABSTRACT

The additional effect of omega-3 supplementation in association with lifestyle modification program (LSMP) in free living-adults was evaluated. We studied 39 adults (control group with LSMP (G1, n = 16) and LSMP plus supplementation of 3 g of fish oil per day (360 mg of docosahexaenoic acid and 540 mg of eicosapentaenoic acid) (G2, n = 23)) during 20 weeks. The fish oil group showed a significant decrease in waist circumference (1.3%) followed by metabolic syndrome reduction (29%) mainly due to normalization of blood pressure (33.3%) and triacylglycerol (27.3%). Omega-3 supplementation provided additional benefits to LSMP in the resolution of metabolic syndrome.

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1. Introduction

The metabolic syndrome (MS) has usually been defined as a clustering of numerous factors that increase cardiovascular risk (Takahashi et al., 2011), such as dyslipidemia, abdominal obesity, hypertension, and high fasting glycemia, which increases prothrombotic and proinflammatory markers (Grundy, 2006; Orsatti et al., 2012). MS prevalence has increased significantly over the last years, reaching pandemic proportions worldwide (Ford, Giles, & Mokdad, 2004) and the etiology includes several genetic, metabolic and environmental factors (Mirmiran, Noori, & Azizi, 2008). Among environmental factors, diet and exercise are the main factors related to the increase in MS rates (Buckland, Salas-Salvado, Roure, Bullo, & Serra-Majem, 2008). Recently our research group has shown that MS is related to a higher intake of saturated fat and low diet variety and fruit intake (de Oliveira, McLellan, Vaz de Arruda Silveira, & Burini, *Corresponding author. Centre for Physical Exercise and Nutrition Metabolism, Public Health Department, UNESP School of Medicine, Botucatu, SP, Brazil. Tel.: +55 14 3811 6128; fax: +55 14 3811 6128.
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The omega-3 supplementation has an effect on reducing the omega-6 to omega-3 ratio and increasing resolvin and protectin that have important anti-inflammatory effects (Goldberg & Katz, 2007) and also can reduce the risk factors for MS, with significant effects in all MS components (Poudyal et al., 2011; Stanley et al., 2007). We have already shown that lifestyle change and physical exercise associated with a proper diet can reduce the prevalence of MS by 24% (Mecca et al., 2012) but the additional effect of omega-3 supplementation was not yet observed. Therefore, the objective of this study was to investigate the additional benefit of omega-3 supplementation in association with lifestyle modification program (LSMP) on the resolution of the MS and its components in overweight adults.

2. Methods

2.1. Subjects

This is a clinical, prospective study with 39 adults aged 36 to 64 years, 33 females and 6 males, clinically selected for the LSMP from August 2009 to July 2010. Initially, 123 adults were assessed. Of these, 64 did not start the program and 20 did not complete the 20-week intervention protocol. The LSMP offered to patients with chronic non-communicable diseases in Botucatu city (São Paulo, Brazil) consists of supervised exercise and nutritional counseling (Mecca et al., 2012). The studied subjects were part of a subgroup (convenience sample) of participants clinically screened for the lifestyle change program “Mexe-se Pró-Saúde” [Exercise for Health]. All individuals signed an informed-consent form, which, conjointly with the project, was approved by the Research Ethics Committee (document no. OF. 364/2009 – CEP) of the Botucatu School of Medicine (FMB – UNESP). The anthropometric, biochemical, dietary, and physical assessments were done at baseline and after 20 weeks of intervention (after LSMP).

3. Study design

3.1. Nutritional intervention

The participants were divided into two groups. The control group with LSMP, n = 16; and another group receiving omega-3 PUFA supplementation and LSMP, n = 23. The omega-3 PUFA was instructed to take 3 capsules (1 g each) of fish oil daily (Naturalis®). Each capsule contained 120 mg of DHA and 180 mg of EPA. The participants of the supplemented group were asked to consume the capsules together with the main meals (2 during lunch and 1 during supper). The opportunity to join the omega-3 PUFA group was given to all participants and adherence was spontaneous. The study lasted 20 weeks.

3.2. Exercise intervention

All participants were submitted to supervised exercise of 80 minutes, including warm up (20 min) walking (40 min)/stretching (20 min), 3 times/week complemented with 60 min (2 times/week) of resistance training (40 min), and stretching (10 min) at a gym. Only participants with a minimum attendance of 3 times/week were included in the study.

3.3. Body composition

Body weight was measured by a platform-type anthropometric scale (Filizola®) with a maximum capacity of 150 kg and an accuracy of 0.1 kg. Height was measured by a portable Seca® stadiometer with accuracy of 0.1 cm (Heyward & Stolarczyk, 2000). The body mass index (BMI) was calculated by dividing the body weight by the square of the height.

Waist circumference (WC) was measured at the midpoint between the last rib and the iliac crest. A steel Sanny® anthropometric tape measure (without a lock) was used for all measurements.

A bioelectrical impedance device (Biodynamics®, model 450, Seattle, WA, USA) was used to determine percentage of body fat (% body fat) (Segal, Van Loan, Fitzgerald, Hodgdon, & Van Itallie, 1988).

3.4. Dietary intake

Dietary intake was assessed using a single 24-hour dietary recall at baseline and M1. The diet was documented by trained professionals, and in order to obtain accurate information, the subjects were asked how often they usually ate during the day, what foods were consumed, how the food was prepared, what the serving size was, and what food/meal brands were consumed. The diets were analyzed by NutWin® software (2002), version 1.5 (NutWin, 2002), and the main nutrients of interest were energy, protein, fat (saturated, monounsaturated and polyunsaturated), cholesterol, carbohydrates, and fiber. Mean individual nutrient intakes per day were computed using the NutWin database and Brazilian food tables (IBGE, 1999; NEPA/UNICAMP, 2004; Philippi, 2002). The Healthy Eating Index (HEI) modified for the Brazilian population was used to assess diet quality (Mota et al., 2008). The original HEI was based on a 10-component system of five food groups with a total possible index score of 100. This method was adapted for the Brazilian population based on the Brazilian food guide, which has eight food groups and 12 components to measure diet variety. Each of the 12 components has a score ranging from 0 to 10; therefore the total possible index score is 120.
3.5. Cardiorespiratory fitness

Cardiorespiratory fitness was determined by maximum oxygen consumption (VO2max) using an electric treadmill (model QMCTM90) according to the Balke protocol (Balke & Ware, 1959). The respiratory indices were continually measured by an open circuit ergospirometric system (model QMCTM90 Metabolic Cart, Quinton®, Bothell, WA, USA) with the mix-chamber method and with constant monitoring of the heart and respiratory rates and blood pressure.

3.6. Blood pressure

Systolic (SBP) and diastolic (DBP) blood pressure (BP) was evaluated with the individual in the seated position according to the procedures described by the VI Brazilian Guidelines on Arterial Hypertension (Sociedade Brasileira de Cardiologia, & Sociedade Brasileira de Hipertensão, 2010), using properly sized cuffs for arm circumference, considering the width/length proportion of 1:2, and the width of the cuff’s rubber bag, which should correspond to 40% of arm circumference, and length, to at least 80%.

3.7. Biochemical analyses

Blood samples were collected by vacuum venous puncture, after a 10 to 12-h fasting period, and centrifuged to obtain serum and plasma samples which were stored at −80 °C until the end of the study. The individuals were previously advised to not perform vigorous physical exercises 24 h and/or consume alcohol 72 h prior to blood collection. Plasma triacylglycerol, total cholesterol (Total-c), high-density lipoprotein cholesterol (HDL-c), uric acid (UA), creatinine (Cr), and gamma-glutamyl transpeptidase (gGT) were assayed by dry-chemistry (Systems Vitros chemistry 950 Xr). Plasma low-density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald equation (Friedewald, Levy, & Fredrickson, 1972), malondialdehyde (MDA) was assayed by high-performance liquid chromatography and high-sensitivity C-reactive protein (hs-CRP) by chemiluminescence (Immulite, 2000).

3.8. Metabolic syndrome

Diagnosis of the MS was performed according to the NCEP-ATP III criteria (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001) with adaptation for glucose values (American Diabetes Association, 2004). The 5 components used were hypertension, abnormal WC, high plasma levels of triglycerides and glucose, and low levels of HDL-c. The metabolic syndrome was diagnosed when 3 or more of these components were abnormal.

3.9. Statistical analysis

The data were analyzed by the software SAS version 9.2 for Windows. Descriptive statistics were performed for the study and continuous variables, presented as means ± standard deviation. Categorical variables were presented as percentages. Samples were tested for normal distribution (Shapiro–Wilk) and groups were compared by either the ANOVA two-way or Kruskal–Wallis test. The chi-square test compared the differences between the prevalence of metabolic syndrome components. The results were discussed based on a significance level of 5% (p < 0.05).

### Table 1 – Dietary intake of control group and omega-3 PUFA group at baseline and after LSMP.

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>W-3 PUFA group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Mean ± SD</td>
<td>After LSMP Mean ± SD</td>
</tr>
<tr>
<td>Total calories (kcal)</td>
<td>1051 ± 371 *a</td>
<td>1214 ± 336 *a</td>
</tr>
<tr>
<td>Carbohydrates (g/kg)</td>
<td>2.3 ± 0.8 *a</td>
<td>2.6 ± 0.9 *a</td>
</tr>
<tr>
<td>Carbohydrates (%)</td>
<td>56.5 ± 11.6 *a</td>
<td>56.3 ± 8.7 *a</td>
</tr>
<tr>
<td>Proteins (g/kg)</td>
<td>0.6 ± 0.3 *a</td>
<td>0.8 ± 0.4 *a</td>
</tr>
<tr>
<td>Proteins (%)</td>
<td>15.4 ± 5.2 *a</td>
<td>16.2 ± 5.1 *a</td>
</tr>
<tr>
<td>Total lipids (g/kg)</td>
<td>0.48 ± 0.3 *a</td>
<td>0.63 ± 0.32 *a</td>
</tr>
<tr>
<td>Total lipids (%)</td>
<td>28 ± 8.9 *a</td>
<td>29.2 ± 6.8 *a</td>
</tr>
<tr>
<td>Monounsaturated lipids (g)</td>
<td>10.2 ± 8.4 *a</td>
<td>13.2 ± 6.5 *a</td>
</tr>
<tr>
<td>Monounsaturated lipids (%)</td>
<td>8.2 ± 3.8 *a</td>
<td>9.4 ± 3 *a</td>
</tr>
<tr>
<td>Polysaturated lipids (g)</td>
<td>7.4 ± 5.9 *a</td>
<td>12.1 ± 5.3 *a</td>
</tr>
<tr>
<td>Polysaturated lipids (%)</td>
<td>5.9 ± 3 *a</td>
<td>8.7 ± 2.6 *a</td>
</tr>
<tr>
<td>Saturated lipids (g)</td>
<td>10.9 ± 7.7 *a</td>
<td>11.2 ± 6.6 *a</td>
</tr>
<tr>
<td>Saturated lipids (%)</td>
<td>8.8 ± 4 *a</td>
<td>8 ± 2.8 *a</td>
</tr>
<tr>
<td>Fiber (g)</td>
<td>12.5 ± 5.7 *a</td>
<td>15.4 ± 7.3 *a</td>
</tr>
</tbody>
</table>

LSMP: Lifestyle modification program.

Values were significant when p < 0.05. We considered a > b > c. A and B are different at basal moment. Weight = adjusted for sex and age; BMI = sex, age, and total caloric intake; other variables adjusted for sex, age, BMI, and total caloric intake.

4. Results

At baseline, groups had different energy intakes but at the end of the study the energy intake was similar between the groups. Macronutrient and fiber intake at baseline and end of the study did not vary between the groups, except for polysaturated

...
fatty acid intake, which was higher in the group receiving omega-3 supplementation (Table 1).

Body weight, BMI, and % of body fat did not change in either group with the intervention. Cardiorespiratory fitness behaved similarly in both groups, with an increase in VO\textsubscript{max} and time on treadmill by the end of the study, showing the benefit of exercise in both groups. Furthermore, malondialdehyde of control group (oxidative stress) increased, while omega-3 did not change. No changes were detected for other variables (Table 2).

Regarding the MS components, HDL-c increased significantly in both groups, showing the benefits of a lifestyle modification program intervention regardless of omega-3 PUFA supplementation. We observed additional effects of omega-3 supplementation in omega-3 PUFA group. Systolic and diastolic blood pressures and WC values reduced after LSMP with omega-3 supplementation. In control group we did not observe these differences (Table 3).

When analyzing changes in the prevalence of MS and its components, we observed a significant decrease in MS prevalence in the omega-3 PUFA group (from 48 to 19%). Furthermore, we observed a significant decrease in the prevalence of hypertension (SBP from 43 to 10% and DBP from 33 to 10%) and high triacylglycerol (from 50 to 23%) in the omega-3 PUFA group (Table 3).

### 5. Discussion

The main finding of the present study was that LSMP in addition with supplementation of 3 g of fish oil during 20 weeks...
showed a decrease in systolic and diastolic blood pressure and waist circumference values and decreased the prevalence of high triacylglycerol, probably reflecting on resolution of MS, which did not occur in the control group. Interestingly, some variables decreased in values and others when analyzing the prevalence of alteration. It can be explained because some individuals presented some variables values too much higher than cut-off point and results in reduction of mean values, but not in classification. The contrary was also observed; TG did not decrease mean values, but diminished the prevalence of alteration because TG values were near the normal cut-off value.

The proper intake is 3 to 3.5 g of fish oil per day (Carpentier, Portois, & Malaisse, 2006), which corresponds to the study dosage (Carpentier et al., 2006). Some studies have shown that omega-3 can prevent weight gain (Buckley & Howe, 2010; Krebs et al., 2006; Ryan & Seeley, 2013). Omega-3 seems to reduce the activity of some nuclear receptors, among them peroxisome proliferator-activated receptor γ (PPAR γ). This nuclear receptor regulates the transcription of important genes for lipid metabolism. High PPAR γ activity increases the lipid reserves in the adipose tissue and acts on the brain causing hyperphagia, both factors related to an increase in body fat (Lu et al., 2011; Ryan et al., 2011). Based on these factors, low PPAR γ activity causes less storage of fat in the adipose tissue and brain, reducing the stimulus to consume high-fat diets (Lu et al., 2011; Ryan et al., 2011; Ryan & Seeley, 2013).

The SBP and DBP decreased in omega-3 PUFA group after 20 weeks whereas blood pressure of control group did not change. Many clinical trials and meta-analyses have found that supplements with high omega-3 dosages can lower blood pressure in hypertensives (Appel, Miller, Seidler, & Whelton, 1993; Morris, Sacks, & Rosner, 1993). Supplementation with 1.9 g/day of omega 3 PUFA improved vasodilator function (Hill, Buckley, Murphy, & Howe, 2007) and results can be confirmed in two meta-analyses of controlled studies, whereas 3 g/day and 6 g/day of omega-3 resulted in a decrease of 4/3 mmHg in hypertensive individuals (Appel et al., 1993; Morris et al., 1993). The probable mechanism for blood pressure reduction after omega-3 intake could be the antagonistic effect of angiotensin receptors (Poudyal et al., 2011).

Although triacylglycerol did not decrease quantitatively, high triacylglycerol prevalence decreased significantly. Other studies have shown similar effects of omega-3 supplementation on dyslipidemia parameters (Kelley, Siegel, Yemuri, & Mackey, 2007; Khandelwal et al., 2013; Munro & Garg, 2011). Kelley et al. (2007) found a reduction of triacylglycerol in men aged 39 to 66 years with high triacylglycerol after 45 days of taking 3 g of fish oil per day. Another study found that the prevalence of high triacylglycerol decreased by 27% in individuals taking 6 g/day of fish oil (n = 17) (Munro & Garg, 2011), similar to the present study.

Some theories have been proposed to explain how omega-3 reduces triacylglycerol. The strongest evidence is the reduction in hepatic lipogenesis, reducing hepatic secretion of VLDL (Jacobson, 2008). Furthermore, omega-3 inhibits certain enzymes involved in the hepatic synthesis of triacylglycerol, reducing its plasma level (Agerholm-Larsen, Nordestgaard, Steffensen, Jensen, & Tjøbaerg-Hansen, 2000). HDL-c increased in both groups, possibly because of physical activity, since the groups did not differ otherwise. Other studies have already reported that physical activity increases HDL-c (Couillard et al., 2001; Kraus et al., 2002), and that individuals submitted to aerobic training showed a reduction in total cholesterol and an increase in HDL-c (Kelley, Kelley, & Tran, 2004). Data regarding HDL-c are still divergent. While some studies found that HDL-c increased (Kesavulu, Kameswararao, Apparao, Kumar, & Harinarayan, 2002; Pedersen et al., 2003), others have found that omega-3 did not change it (Luo et al., 1998; Moore et al., 2006). More studies are necessary to determine the effect of omega-3 on HDL-c. LDL-c also did not change with the intervention in either group. Some studies did not find changes in total cholesterol or LDL-c (Kesavulu et al., 2002; Petersen, Pedersen, Major-Pedersen, Jensen, & Marckmann, 2002).

One of the most interesting result of this study was the resolution of MS by 29% due to omega-3 supplementation, which corroborated with another study and reinforces the importance of this oil in MS prevention and treatment (Baik, Abbott, Curb, & Shin, 2010). The prevalence of nearly all MS components decreased (waist circumference, high blood pressure, high triacylglycerol, and increase in HDL-c), which has already been mentioned and justifies the resolution of MS in this group. Furthermore, this study provides new insights regarding the interaction between exercise and diet in the MS resolution once we observed additional effects of omega-3 PUFA in a LSMP.

The only component that was not affected by supplementation in the present study was plasma glucose. However, another study found that omega-3 supplementation reduced glycemia and improved insulin resistance (Ebbesson, Risica, Ebbesson, Kennish, & Tejero, 2005). Our population presented values related to glucose intolerance, so the values were not high and the subjects would probably not benefit from supplementation.

Although physical activity (measured by VO2max and treadmill time) and physical fitness (measured by dynamometry) improved in both groups after 20 weeks, these variables did not differ significantly between the groups, indicating the benefit of the lifestyle modification program regardless of supplementation. It has been shown that a strong relationship between physical inactivity and the presence of cardiovascular risk factors, such as high blood pressure, insulin resistance, diabetes, dyslipidemia, and obesity and that regular physical activity is important to prevent MS (Rennie, McCarthy, Yazdgerdi, Marmot, & Brunner, 2003), however the exercise without omega-3 was not efficient to reduce MS in our study.

While malondialdehyde of controls increased after 20 weeks, omega-3 supplementation did not change. The literature has shown that omega-3 can lower C-reactive protein and malondialdehyde concentrations (Kremer, 2000), but the present study found no reduction in C-reactive protein, probably because of the low basal concentration of this parameter.

A strong point of our study was the correct control of diet and exercise. Both groups did not change the intake of macronutrients and the only intervention and change was polyunsaturated fat intake because of omega-3 supplementation. Furthermore, all individuals realized the same protocol of exercise, which show that difference between groups occurred only because of additional intervention with omega-3 supplementation.
6. Study limitations

The study population consisted of a convenience sample where the participants chose to participate in the lifestyle change program. This study was realized with individuals joining a lifestyle modification program (healthy diet and exercise), so these results cannot be extrapolated to other populations (sedentary individuals). Also, an important limitation of this study was the absence of measuring fatty acid concentrations in the bloodstream.

7. Conclusion

We concluded that omega-3 PUFA supplementation during 20 weeks provides additional benefits to a lifestyle modification program protocol in the resolution of MS by reducing blood pressure, waist circumference and high triacylglycerol prevalence.

Authors’ contributions

LCT and RCB designed the study. EPO and LCT wrote the manuscript. FM did part of the lab work. FM, KCPM, and RCB contributed to revised and draft manuscript. All authors had substantial contributions to the manuscript, read, and agreed to the final version.

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