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Effects of Coenzyme Q10 Supplementation in Women with Metabolic Syndrome and Non-Alcoholic Fatty Liver Disease Evaluated by Magnetic Resonance Imaging—Coenzyme Q10 in Metabolic Syndrome and NAFLD

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Abstract: (1) Introduction: Coenzyme Q10 (CoQ10) is a component present in the transport chain of mitochondrial electrons with antioxidant property. Currently, there are limited studies which indicate the effects of its supplementation on Metabolic Syndrome (MetS) and Non-Alcoholic Fatty Liver Disease (NAFLD). (2) Objective: This work was conducted to determine the effects of CoQ10 supplementation in women with MetS and NAFLD. (3) Methodology: This double-blind randomized clinical-controlled trial was performed among 22 women with MetS and NAFLD. Patients were randomized into two groups: group A (n = 11), which received 200 mg/day of CoQ10; and group B (n = 11), which received a placebo medication for 12 weeks. The hepatic steatosis present in NAFLD, the volume of abdominal fat, and visceral fat volume were evaluated by Magnetic Resonance Imaging (MRI). Anthropometric, blood pressure, and marker serums that compound the MetS were also analyzed. (4) Results: A decrease in visceral fat volume (p = 0.02), abdominal circumference (p = 0.03/CI = 0.19–3.80), and increase in HDL-cholesterol (p = 0.01/CI = −9.80: −1.44) was observed in the CoQ10-supplemented group. We did not find significant changes in any of the other variables evaluated. (5) Conclusions: Supplementation with CoQ10 for 12 weeks, even if discreetly, brought some benefits for the supplemented group whereas no changes were observed in the control group.

Keywords: coenzyme Q10; metabolic syndrome X; non-alcoholic fatty liver disease; liver steatosis; magnetic resonance imaging

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1. Introduction

Metabolic syndrome (MetS) is a complex group of interrelated risk factors for cardiovascular disease and type 2 diabetes mellitus (DM2) represented by hyperglycemia, arterial hypertension, dyslipidemia, and abdominal obesity [1]. The prevalence of MetS has been increasing due to obesity and sedentary lifestyle [2]. Recent studies demonstrate the constant evolution of MetS, with some prevalence ranging from 25% in Middle Eastern countries [3], 35% in the United States [4], 50% in India [5], and up to 43% in Latin American countries [2]. In Brazil, the prevalence is estimated at 38.4% [6]. It is worth noting that there is some progressive age-related increasing prevalence of MetS [7], and it is more common in females.

The criteria that encompass MetS are strongly linked to hepatic steatosis and are considered primary predisposing factors for hepatic steatosis, a term that characterizes

Non-Alcoholic Fatty Liver Disease (NAFLD). NAFLD is the most common form of diffuse liver disease, and it is characterized by fatty infiltration of the liver, which can be diagnosed in imaging tests. It may or may not be associated with necro-inflammatory changes and fibrosis, which may progress to cirrhosis and hepatocellular carcinoma [8]. It occurs in individuals with no history of significant alcohol intake, who do not have any other liver disease that could justify steatosis. In most cases, it is associated with MetS [9]. Recently, some guidelines have suggested renaming the NAFLD terminology to Metabolic-Associated Fatty Liver Disease (MAFLD) to improve disease management and awareness. In clinical practice, both terminologies are used [10]. NAFLD or MAFLD affects 25% of the world population [11] and is forecasted to become one of the main causes of hepatocellular carcinoma (HCC) in the world. In the United States, it is projected that cases of HCC will increase by 122% by 2030 [12].

Coenzyme Q10 is a benzoquine present in almost every cell in the body and is found mainly in the inner membrane of mitochondria, where it participates in the processes of electron transport and adenosine triphosphate (ATP) production [13]. Mitochondria plays a key role in the differentiation and maturation of adipocytes and in the generation of sufficient ATP to support the lipogenic processes that consume energy during preadipocyte differentiation [14]. Clinical evidence demonstrates that mitochondrial dysfunction and decrease in CoQ10 levels can be found in obese individuals and patients with MetS and NAFLD who show an increase in body fat deposits [15].

Previous studies have highlighted interesting results after CoQ10 supplementation in patients with MetS and NAFLD. A meta-analysis evaluated the effects of CoQ10 and found that supplementation was able to increase HDL-cholesterol and significantly decrease total cholesterol levels [16]. Another effect attributable to CoQ10 supplementation is its ability to reduce hyperglycemia levels [15]. Farsi et al. (2016) administered 100 mg/day of CoQ10 fasting plasma glucose for 12 weeks, concluding that that amount was sufficient to promote some decrease in NAFLD in patients evaluated by ultrasound [17]. Evidence suggests that CoQ10 may improve the metabolic and steatotic profiles in patients with MetS and NAFLD.

To date, data on the effects of CoQ10 supplementation in women with MetS and NAFLD using magnetic resonance as an analytical tool are scarce in the literature. In light of this, the present study was conducted with the aim of investigating and elucidating the effects of CoQ10 supplementation on markers that compose the MetS and quantifying the percentage of hepatic fat fraction, abdominal, and visceral after analyses with magnetic resonance.

2. Methodology

2.1. Participants

This study was a double-blind randomized placebo-controlled trial, approved by the Research Ethics Committee of the Hospital of Faculty of Medicine of Ribeirão Preto of the University of São Paulo, Brazil (11234/2017) and registered in the Brazilian Registry of Clinical Trials (RBR-26cq7n—21 June 2018). Female patients who were overweight or obese, sedentary, non-menopausal, BMI $\leq$ 50 kg/m^2, MetS, and NAFLD were selected at the Hospital of Ribeirão Preto, Brazil. Individuals with any history of chronic liver disease, renal failure, gastrointestinal diseases, polycystic ovary syndrome, use of Ginkgo biloba, anticoagulants, or statins and who had been supplemented with vitamin E or CoQ10 in the last three months were excluded. In all patients, MetS was confirmed following the criteria proposed by the International Diabetes Federation [1], which is characterized by the presence of three of the following criteria: central obesity measured by measurement of waist circumference (WC) according to sex and ethnicity, with values in Brazil of 80 cm for women; serum levels of triglycerides $\geq$ 150 mg/dL (1.7 mmol/L); cholesterol HDL < 50 mg/dL (1.29 mmol/L) for women; blood pressure $\geq$ 130/85 mmHg; and blood glucose fasting rate of $\geq$100 mg/dL (5.6 mmol/L). The diagnosis of NAFLD was confirmed by the chronic elevation of liver enzymes, the absence of alcohol consumption, an ultrasound of the liver being compatible with NAFLD, and the exclusion of any other etiologies of liver disease.

2.2. Study Design

With a convenience sample calculation, 22 patients were selected in 2019 and randomly divided into two groups: 11 in the intervention group and 11 in the placebo group. All participants at the beginning of the study received instructions to maintain the diet and the usual level of physical activity throughout the duration of the protocol. The CoQ10 capsules were manipulated and cataloged by Homeocenter Ltd.—Epp (CNPJ: 65,567,935/0001-08). Capsules with CoQ10 were composed of 200 mg of powder in oxidized form and maltodextrin placebo. The intervention period was 12 weeks with presupplementation and postsupplementation analyses. Volunteers were advised to use the supplement after lunch to increase absorption in the small intestine due to the presence of fat in the diet. We contacted patients weekly to remind them about supplementation, and they were instructed to report any adverse effects.

2.3. Anthropometric Assessment

Height was determined by a graduated and inextensible rod in centimeters (cm). The body mass index (BMI) was calculated using the Quetelet formula [BMI = weight in kg/(height in m)^2]. The classification of each individual followed the criteria established by the World Health Organization: eutrophic (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (ÿ30 kg/m^2) [18]. The WC was obtained using an inelastic, inextensible anthropometric measurement tape that was 2.0 m in length and had a precision of 0.1 cm. The measurement was performed on an imaginary horizontal line that passes through the midpoint between the lower edge of the last rib and the iliac crest, at the end of a not-forced expiration.

2.4. Blood Pressure Assessment

Blood pressure was measured using a pressure device with the appropriate calibrated cuffs. Volunteers were in a sitting position with their legs uncrossed, feet flat on the floor, back leaning against the chair, and were not talking, with the left arm supported at heart level after five minutes of rest.

2.5. Biochemical Assessment

Blood samples were collected after a 12-h fast before and after intervention. When necessary, analysis was performed in duplicate. At each step, 7 mL of blood was collected by venipuncture in a sterile vacuum tube (Vacutainer—BD® with yellow cap, New Jersey, NY, USA) containing coagulation activator, stored in a thermal box, and protected from heat. After collection, the separation of whole blood to obtain the serum was performed in a Universal 320R Hettich® centrifuge (Andreas Hettich GmbH & Co, Tuttlingen, Germany) for 10 min at 4° and 3500 revolutions/minute. The supernatant (serum) was separated and transferred to Ependorf tubes and the sediment was discarded. After centrifugation, the samples were stored in a −80° freezer until the time of analysis. The blood glucose analyses of fasting, lipid profile (total cholesterol, high-density lipoprotein (HDL), and triglycerides (TG) were quantified by the enzymatic-colorimetric method provided by specific kits of the Labtest® brand (Labtest Diagnóstico SA Lagoa Santa—Minas Gerais, Brazil), following manufacturer recommendations. The equipment used for reading was the Epoch microplate spectrophotometer with an absorbance capacity between 200–999 nm (Bioteck®,Santa Clara, CA, USA).

2.6. Imaging Exams

The quantification of liver fat fractions was determined by magnetic resonance imaging. A high-field instrument with magnitude 1.5 Tesla with 16-channel model XL Torso coil (model ACHIEVA; Philips Medical Systems, Low) allowed for the construction of T2 and T1 sequences: (a) plane-weighted T2 sequence coronal, breath-suppressed turbo-spin-echo (TSE) sequence [TR (time to repeat) = 737 msec, TE (echo time) = 80 msec, slack angle = 90°, echo-train length = 121, section thickness = 6 mm, gap = 8%, (30 sections in 22 s of suppressed breathing) used as locator]; (b) T1-weighted sequence in the axial

plane, in-phase (TE = 4.6 msec) and out-of-phase (TE = 2.3 msec) double echo with breathing suppressed, spoiled gradient echo (SGE) (TR = 111 msec, clearance angle = 80°, thickness of section = 6 mm, gap = 7%, 30 sections per echo during 29 s of breathing suppressed), with acquisitions in the abdomen, including the liver and umbilical regions.

For the analysis of visceral and subcutaneous fat, an axial slice obtained from the T1 sequence at the umbilicus level was used, with manual segmentation subcutaneous and visceral fat and area calculation in mm2. The sum of areas of visceral fat and subcutaneous tissue in the same section was considered for the total area of abdominal fat. The amount of fat in these areas was calculated by obtaining the number and size of the segmented voxels (mm). For the analysis of liver fat, points were chosen in the liver parenchyma and eight regions of interest (ROI) measuring 1 cm^2 were selected in segments II, III, IVa, IVb, V, VI, VII, and VIII. All ROIs were positioned to avoid large intrahepatic vessels and hepatic lesions of any other nature. The mean of the eight measurements allowed for the calculation of the liver fat fraction. This method is based on the loss of signal strength on MRI by the gradient-echo technique of chemical shift by the following formula:

$$\mathrm{FG} = 100 * \frac{SIinphase - SIoutphase}{2 * SIinphase}$$

where FG is the liver fat fraction and SI is the signal intensity of the in-phase and out-of-phase images obtained at a specific point in the parenchyma [19]. From the measurement of the signal strength of the eight ROIs, the signal strength average was calculated. For image interpretation, all exams were prospectively read by an experienced radiologist. The examiner evaluated the images for the presence and pattern of fibrosis, presence and pattern of fatty infiltration, pattern of liver parenchyma, and other morphological aspects. The images were determined through the Osirix software (MD ANVISA).

2.7. Statistical Analyses

The Shapiro–Wilks test was applied to verify normality. After this verification, Student's *t* test was applied for independent samples. To compare both between times and between groups, a linear regression model was used with mixed model. The estimated differences with their respective *p* values are presented in 95% confidence intervals. We adopted $p \leq 0.05$ as a significance level in all analyses. The software used was SAS Statistical Software (version 9.3; SAS Institute, Inc., Cary, NC, USA).

3. Results

In general, no variable rejected the normality hypothesis by the Shapiro–Wilks test. On them, we applied the *t* test for independent samples. After statistical analysis between the groups, considering the variables of the basal characteristics, it was observed that the groups were similar due to the fact that no statistical difference was found.

The mean age in the CoQ10 group was 41.5 years old (±5.94) and 38.8 (±6.91) in the placebo group. Anthropometric variables including weight, BMI, and waist circumference are described in Table 1. When comparing abdominal circumference, there was a difference intragroup after CoQ10 supplementation ($p = 0.03$; CI = 0.19–3.80), with a 2 cm decrease in mean abdominal circumference. In the analysis between groups, there was no statistical significance of this variable. After 12 weeks of supplementation, no differences were found between the CoQ10 and placebo groups in regards to arterial blood pressure. Although the 8% reduction in fasting glucose in the CoQ10 group was not significant, we noticed a tendency to decrease ($p = 0.06$). In the placebo group, the decrease was 2.7%.

Table 1. Anthropometric, pressure, and biochemical evaluation according to each group after intervention [1].

	Coenzyme Q10	Placebo	*p*-Value [3]
Weight (kg)—Baseline	90.82 (12.75)	93.09 (13.73)	
Weight (kg)—12 weeks	90.17 (18.62)	93.37 (19.13)	0.49
p-value [2]	0.39	0.50	
BMI (kg/m^2)—Baseline	32.88 (5.50)	36.93 (7.20)	
BMI (kg/m^2)—12 weeks	32.48 (5.52)	36.82 (7.68)	0.16
p-value [2]	0.44	0.48	
Waist Circumference (cm)—Baseline	107.55 (10.32)	108.73 (8.85)	
Waist Circumference (cm)—12 weeks	105.55 (11.12)	108.91 (9.07)	0.09
p-value [2]	0.03	0.66	
SBP (mmHg)—Baseline	126.18 (13.26)	129.09 (11.91)	
SBP (mmHg)—12 weeks	127.27 (10.67)	126.09 (12.34)	0.73
p-value [2]	0.69	0.21	
DBP (mmHg)—Baseline	84.00 (5.5)	80.00 (11.32)	
DBP (mmHg)—12 weeks	80.00 (11.32)	80.00 (9.32)	0.26
p-value [2]	0.82	0.86	
Blood Glucose (mg/dL)—Baseline	103.55 (25.22)	106.68 (58.86)	
Blood Glucose (mg/dL)—12 weeks	95.22 (18.98)	103.83 (54.5)	0.56
p-value [2]	0.06	0.85	
HDL-cholesterol (mg/dL)—Baseline	32.10 (7.30)	35.64 (7.89)	
HDL-cholesterol (mg/dL)—12 weeks	37.73 (7.34)	39.89 (3.97)	0.69
p-value [2]	0.01	0.12	
Triglycerides (mg/dL)—Baseline	133.80 (52.64)	165.32 (79.35)	
Triglycerides (mg/dL)—12 weeks	166.13 (64.05)	193.45 (83.69)	0.45
p-value[2]	0.15	0.27	

[1] Data presented as mean ± SD. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure. Linear regression model with mixed effects. [2] *p*-value: result of comparison between intragroup moments. [3] *p*-value: result of interaction between groups.

In relation to lipids, in the intragroup analysis, HDL cholesterol showed a significant increase in both groups, but with statistical significance only in the group supplemented with CoQ10 (p = 0.01; CI = −9.80: −1.44). However, in the analysis between groups, there was no statistical significance. No significant changes were observed in triglyceride levels. Although LDL is not part of the criteria that encompass MetS, an interesting result was found as this lipid was analyzed. In the CoQ10 group, a reduction of 25.6% occurred, while an increase of 3.6% was observed in the placebo group. To calculate LDL-cholesterol, we used the Friedewald formula (LDL = total cholesterol − HDL − Triglycerides/5) [20].

The evaluation of variables obtained by MRI are described in Table 2. Visceral fat volume showed a significant difference after supplementation in the CoQ10 group with a reduction of about 21% (p = 0.02; CI = 1.67: 25.98), but there was no statistical significance between the groups (p = 0.10). Despite it being insignificant, we noticed a decrease of approximately 13% in the average percentage of liver fat fraction in the CoQ10 group, while in the placebo group no change was found. In the other variables, although not statistically significant, we noticed an improvement in all parameters after supplementation with CoQ10. The volume of subcutaneous fat and total abdominal area showed a slight decrease in the CoQ10 group, while there was a small increase in the placebo group.

Table 2. MRI assessment according to each group after intervention [1].

	Coenzyme Q10	Placebo	*p*-Value [3]
% Liver Fat Fraction—Baseline	17.14 (8.75)	16.34 (13.52)	
% Liver Fat Fraction—12 weeks	14.89 (11.87)	16.43 (13.40)	0.77
p-value [2]	0.10	0.96	
Subcutaneous Fat Volume (cm^2)—Baseline	44.82 (13.54)	46.56 (21.64)	
Subcutaneous Fat Volume (cm^2)—12 weeks	42.21 (7.98)	49.11 (14.44)	0.52
p-value [2]	0.28	0.95	
Visceral Fat Volume (cm^2)—Baseline	14.20 (3.40)	11.86 (1.32)	
Visceral Fat Volume (cm^2)—12 weeks	11.23 (4.32)	11.94 (3.25)	0.10
p-value [2]	0.02	0.83	
Total Abdominal Area (cm^3)—Baseline	418.72 (114.41)	416.81 (99.87)	
Total Abdominal Area (cm^3)—12 weeks	390.05 (82.32)	418.82 (104.11)	0.56
p-value [2]	0.13	0.91	

[1] Data presented as mean ± SD. Linear regression model with mixed effects. [2] *p*-value: result of comparison between intragroup moments. [3] *p*-value: result of interaction between groups.

4. Discussion

MetS is the subject of several studies due to its repercussions on morbidity and mortality along with its great impact on the health system. Moreover, it is also studied for its clinical and laboratory components, which are good risk predictors for the development of important diseases such as diabetes mellitus and cardiovascular diseases [14]. The ability of CoQ10 to improve some markers present in MetS, with few apparent side effects, suggests a possible role for supplementation in women with MetS and NAFLD [15]. So far, few studies have investigated the role of CoQ10 in MetS and NAFLD, and although some have satisfactory results, a series of questions are necessary to answer if the supplementation with Coenzyme Q10 may have a therapeutic action, particularly in these patients.

In this study, we noticed a trend towards improvement in fasting blood glucose levels, with decreases and consequent normalization according to the cut off proposed for these [1]. Gholnari et al. (2017) and Raygan et al. (2016) found results similar in their analyses [21,22]. After supplementing 100 mg/day for 12 and 8 weeks, respectively, the authors noted improvements in fasting glucose, but with no statistical significance. Fallah et al. (2018) did not show any correlation between levels of found glycemic control [23]. Zahedi et al. (2014) found an improvement in CoQ10 glycemia and fasting after 12 weeks of supplementation with 150 mg of CoQ10 [24]. Two meta-analyses, which were carried out to analyze the effects of CoQ10 on markers of diabetes mellitus type 2 (fasting glucose, HOMA IR and HOMA β, HbA1c, QUICKI, and insulin), found that supplementation can help control fasting blood glucose and HbA1c despite not significantly reducing any of the other glycemic control-related markers [15,25]. Emerging data shows that oxidative stress contributes to hyperglycemia, insulin resistance, and beta cell dysfunction [26]. People with MetS are more susceptible to metabolic abnormalities, elevated systemic inflammation, and oxidative stress. High concentrations of H_2O_2 promote insulin signaling and induce an increase in hepatic gluconeogenesis, increased glucose uptake by adipocytes, stimulation of GLUT4 translocation, and lipid synthesis by adipocytes, raising serum lipid and glucose levels [27]. CoQ10 acts through mechanisms that include the reduction of oxidative stress, anti-inflammatory actions, and the regulation of glucose and lipid metabolism. By modulating the Nrf2/Keap1/ARE (antioxidant response element) pathway, CoQ10 can improve oxidative stress induced by hyperglycemia and subsequently stimulate the production of antioxidant enzymes [26].

The markers which compound the lipid profile impair the mitochondrial function when altered, triggering an increase in free radicals and reactive oxygen species with consequent chronic inflammation and endothelial dysfunction [28]. Although not significant between the groups, when analyzing the lipid profile, we noticed an increase in the HDL-cholesterol and, despite not being part of the criteria that compounds the MetS, we

found an interesting result in the 25.6% decrease in LDL-cholesterol only in the group supplemented with CoQ10. Some studies have shown that there is a relationship among the total cholesterol, LDL, and CoQ10 levels. In LDL, the antioxidant function of CoQ10 proved to be effective, as it was the first antioxidant to be depleted when the lipoproteins were exposed to oxidative stress [29].

The main reason as to why CoQ10 affects the lipid profile is not yet well described, and several mechanisms are involved. As an intracellular antioxidant, it protects both the phospholipid membrane and mitochondrial membrane protein against free radical-induced damage. In addition, CoQ10 can increase fatty acid oxidation in pre-3T3-L1 adipocytes and increase PPARα in protein and mRNA levels [28]. A meta-analysis that evaluated only patients with NAFLD observed a trend towards decreasing the lipid profile of these patients [30]. Another meta-analysis carried out with more than 520 patients evaluated the effects of CoQ10 in patients with coronary heart disease, and it was found that supplementation was able to increase HDL cholesterol and lower total cholesterol levels significantly [16]. However, supplementation with 100 mg/day for 8 weeks in patients with MetS showed no effect [22]. In other clinical trials conducted with diabetic patients with altered lipid profiles, supplementation with doses of 100 and 120 mg/day of CoQ10 for 12 weeks was not enough to change lipid profile markers [23,31]. Regarding triglyceride levels, in [16], no relationship was found between CoQ10 supplementation and CoQ10 decrease, similar to our findings.

In recent years, several studies have documented the antihypertensive action of CoQ10, demonstrating its possible ability to induce vasodilation through effects on the endothelium, decreasing peripheral resistance by preserving nitric oxide and vascular smooth muscle. In some forms of hypertension, the superoxide radicals that inactivate nitric oxide are produced in excess and the antioxidant CoQ10 effects can prevent this inactivation [32]. Regarding blood pressure, this study did not find changes after supplementation, corroborating with Young et al. (2012) [33], who evaluated the effects of CoQ10 supplementation in patients with MetS and uncontrolled blood pressure, and contradicting Zhao D et al. (2022) [34], who stated CoQ10 would have hypotensive action in blood pressure. The subgroup analysis revealed a significant reduction in SBP in patients with diabetes and dyslipidemia, but not in CVD and MetS subjects. Yet, the same authors have reported antihypertensive effects of CoQ10 in studies with longer durations (>12 weeks) [33]. The Cochrane Hypertension Group [35] carried out a selective analysis of this subject, and it was concluded that whether CoQ10 reduces blood pressure in primary hypertension in the long-term is uncertain. Significant changes in blood pressure after CoQ10 supplementation may be relevant at the population level, whether associated with other therapies or not. However, for this scenario, we highlight the need of more clinical trials with well-described designs.

In this study, the effectiveness of CoQ10 without energy intake restriction or physical activity increasing, in isolation, did not influence weight loss and BMI. The main regulator of body weight is the energy balance between the energy intake from diet and the energy spent on daily activities [36]. The literature describes that patients with high BMI values have lower plasma CoQ10 rates [37]. The effects of CoQ10 supplementation on weight control and BMI have been investigated in some clinical trials. Clinical trials conducted with patients with NAFLD, MetS, or both, revealed that 12 and 8 weeks of supplementation with 60 to 100 mg/day of CoQ10 had no significant effects on the anthropometric indices of these patients [17,22,38]. Other studies conducted in diabetic patients showed different results. Hosseinzadeh-Attar et al. (2015) reported that 12 weeks of supplementation with 200 mg/day of CoQ10 significantly decreased the weight and BMI of patients with type 2 diabetes [39] and Fallah et al. (2018), after 12 weeks of supplementation with 120 mg/day, did not notice any changes in weight or BMI [23]. A large meta-analysis of randomized controlled trials showed that there is no beneficial effect of CoQ10 supplementation on body weight and BMI [36].

Contrary to weight and BMI, we noticed a mean decrease of 2 cm in the analysis of waist circumference for the group supplemented with CoQ10 ($p = 0.03$), while no change was observed in the placebo group. Some authors found results similar to ours, in which they noted a slight decrease in mean waist circumference after supplementation with CoQ10 [39,40]. A possible explanation for the effect of CoQ10 on obesity measure by waist circumference would be its inhibitory power in the differentiation of adipocytes. It is postulated that this action occurs by inhibiting the AMPK-mediated PPARa pathway, meaning that CoQ10 can increase AMPK phosphorylation through increased Ca^{2+}/calmodulin-dependent protein kinase activity. In addition, it may happen by decreasing the gene expression of enzymes responsible for the synthesis of endogenous lipids and increasing the gene expression of proteins responsible for greater energy expenditure, such as uncoupling protein-1 (UCP1) and carnitine palmitoyltransferase 1 [41].

In this study, despite being insignificant, we noticed in the analysis obtained by MRI that there was a 13% reduction in the mean percentage of liver fat fraction in the CoQ10-supplemented group, whereas no change was found in the placebo group (Figure 1). Our study can be considered a pioneer in the evaluation of percentage of hepatic fat fraction after supplementation with CoQ10 through NMR, and there are no other studies as a parameter of comparison for this analysis. Few studies have evaluated the effects of CoQ10 on hepatic steatosis [42]. In animal models, CoQ10 supplementation prevented progression to cirrhosis in NAFLD rats through downregulation of oxidative stress markers [43]. Farsi et al. administered 100 mg/day of CoQ10 for 12 weeks and concluded that it was sufficient to promote a decrease in NAFLD grade in patients evaluated by ultrasound [17]. Mohammadshahi et al. [44], with a design similar to that of Farsi et al. [17], did not find beneficial effects of CoQ10 supplementation in patients with NAFLD. The literature reports that the main limitation of the use of CoQ10 in hepatic steatosis is the need of high doses (>100 mg/day) and modified formulations to have some increased bioavailability, since CoQ10 itself has a low oral bioavailability [45]. We emphasize that we found a trend in our results. We believe that more clinical trials are needed in order for significant changes to be proven.

Regarding the analysis of abdominal fat obtained by MRI, we noticed that the volume of visceral fat was significantly reduced by about 21% in the group supplemented by CoQ10, whereas in the placebo group it remained stable. Although not statistically significant, there was a tendency to improve subcutaneous fat and total abdominal area only in the CoQ10-supplemented group. As abdominal adipose tissue is composed of subcutaneous and visceral (intra-abdominal) fat, this differentiation is important in terms of the particularities of each type of fat in the metabolic function. Visceral fat accumulation is associated with increased cardiovascular risk, MetS (hypertension, dyslipidemia, type 2 diabetes), and insulin resistance [46]. The predominance of abdominal obesity may be caused by the increasing size of adipocytes. It is worth noting that visceral fat is metabolically more active and more sensitive to lipolysis induced by catecholamines, an aspect that is related to greater expression of β1, β2, and β3 adrenergic receptors and inhibition of α2 adrenoreceptors, a system that is activated in adipocytes. This cascade of events leads to greater mobilization of FA to the hepatic system, with a consequent reduction in hepatic insulin clearance by degradation and inhibition of its binding, which triggers systemic hyperinsulinemia [47]. We did not find any clinical trial in the literature in CoQ10-supplemented individuals who evaluated the volume of visceral and subcutaneous fat through MRI. Finally, we infer that the decrease in abdominal circumference is in line with the decrease in visceral fat volume assessed by MRI, and that these may be as a result of CoQ10.

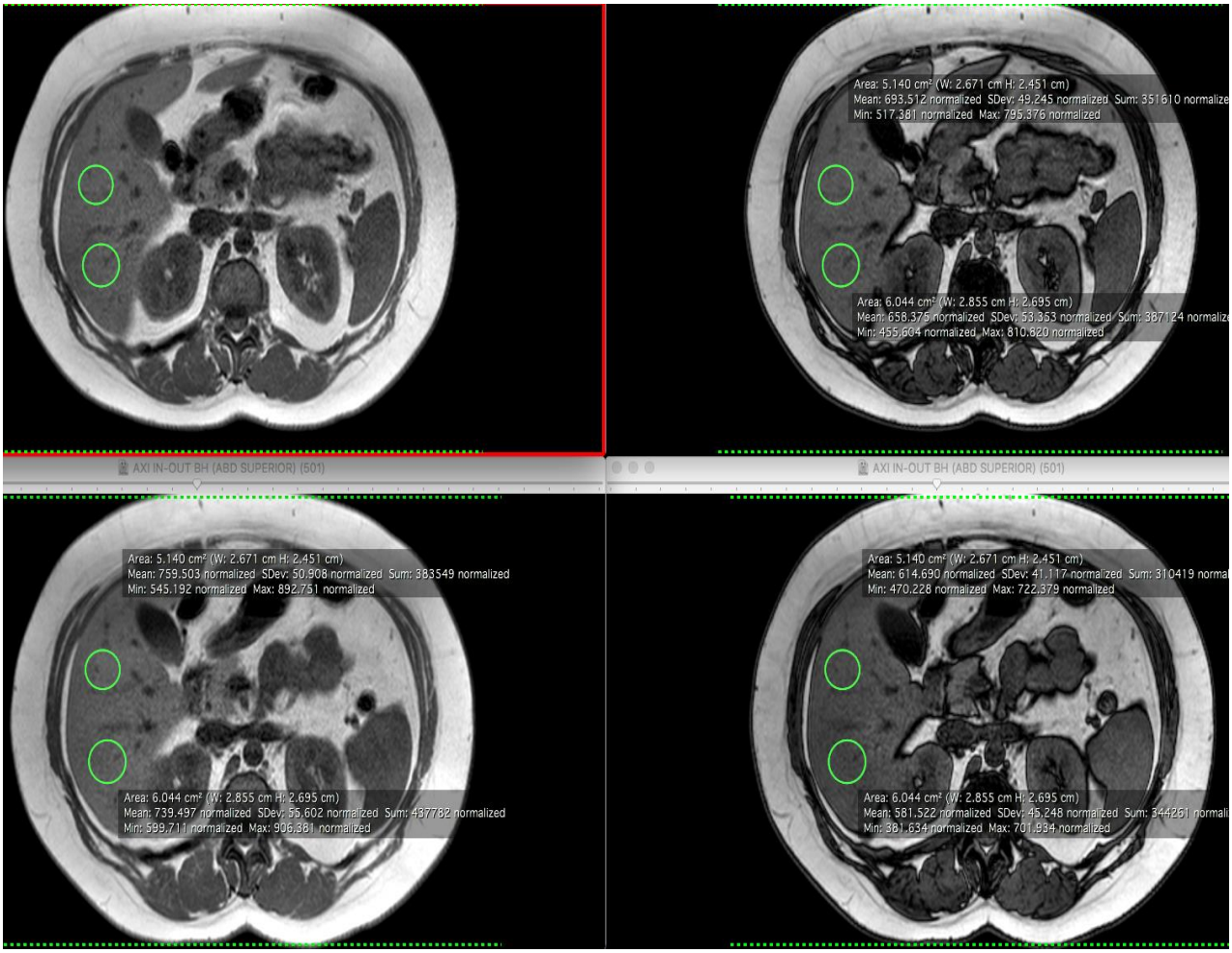

Figure 1. NMR image of a volunteer for reference of cut point position. Images of patient with steatosis demonstrating signal intensity, in-phase (**left**) and out-of-phase (**right**), before (**top**) and after (**bottom**) CoQ10 supplementation.

To interpret our results, some limitations are needed to be considered. We consider that our results can be attributed to the size of the sample studied. We believe that the loss of continuity of some patients influenced the final result. Furthermore, the present study was a relatively short-term intervention.

5. Conclusions

In conclusion, with a randomized placebo-controlled design and a low-dosage, commonly used, this study found interesting results obtained only in the group supplemented with CoQ10, such as some decrease in both visceral fat volume and abdominal circumference, and an increase in HDL-cholesterol. It also showed no statistically significant changes in the percentage of liver fat fraction, triglycerides, blood pressure, or blood glucose. These findings suggest that, although the literature provides evidence that supplementation with CoQ10 at this dose can be effective, 200 mg/day for 12 weeks may still not be sufficient to recommend its supplementation in women with MetS and NAFLD. We reiterate that there is still no established dose of supplementation or duration. We believe that long-term interventions can result in greater changes and in the need of carrying out more clinical trials to demonstrate the effects and enable the implementation of CoQ10 in clinical practice.

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