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Effects of the Avocado Oil Supplementation on Oxidative and Insulin Resistance Parameters in a Double-Blind and Randomized Clinical Trial in Metabolic Syndrome Patients

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Abstract

Background: Metabolic Syndrome (MetS) is a group of comorbidities that increase the risk of developing cardiovascular diseases and appears to be associated with chronic low-grade inflammation and oxidative stress. On the other hand, avocado oil has shown a positive effect in improving oxidative stress, but there is a lack of translation studies focusing on MetS patients. Thus, the present study aimed to evaluate the effects of avocado oil supplementation on oxidative parameters and insulin resistance in obese patients with metabolic syndrome.

Methods: Thirty-three obesity adults, of both genders, diagnosed with MetS, were included and separated into two groups: Control group (n=17) and avocado oil group (n=16). The subjects consumed 10 mL of soybean oil or avocado oil for 3 months and were instructed to maintain their regular medications and normal lifestyle. Anthropometric, insulin resistance markers (fasting blood glucose, fasting blood insulin, glycated hemoglobin A1c and homeostatic model assessment), lipid profile (triglycerides, low-density lipoprotein, high-density lipoprotein and total cholesterol) and oxidative stress parameters were assessed both before and after supplementation.

Results: The mean and standard deviation of all parameters were evaluated. There were no significant differences observed between the pre and post intervention measurements in both the control and avocado oil groups. However, when comparing the post-supplementation measurements between the control and avocado oil groups, higher levels of triglycerides were observed in the avocado oil group.

Conclusion: The dose and duration of avocado oil supplementation used in this study did not affect oxidative stress and insulin resistance parameters in obese individuals with MetS.

Keywords: Obesity; Metabolic syndrome; Oxidative stress; Insulin resistance; Avocado oil supplementation

Introduction

Metabolic Syndrome (MetS), a complex of interconnected risk factors for cardiovascular disease and diabetes, consists of central obesity (increased waist circumference), hyperglycemia, dyslipidemia (elevated triglyceride levels, reduced high-density lipoprotein levels) and elevated blood pressure [1]. These pathological conditions are strongly associated with insulin resistance. Over the past few decades, significant progress has been made in understanding obesity-induced insulin resistance, particularly regarding the underlying mechanisms. Among these mechanisms, low-grade chronic inflammation is currently the most widely accepted. This inflammatory state is characterized by elevated levels of inflammatory cytokines, including TNF-α and IL-1β, as well as increased macrophage infiltration in peripheral tissues [2]. However, there has been considerable interest in the role of oxidative stress in inducing insulin resistance. Upon activation, many immune cells generate free radicals and conversely, the production of reactive oxygen species promotes an inflammatory state.

Oxidative stress, resulting from an imbalance between pro-oxidant and endogenous antioxidant systems, serves as a significant pathological foundation of MetS [3-7]. It has been suggested that oxidative stress is closely associated with the clinical manifestations of MetS, with elevated levels of nitric oxide and hydrogen peroxide observed in obesity, insulin resistance, dyslipidemia and systemic arterial hypertension [8]. A recent study revealed an increased activity of the NAPDH oxidase complex in macrophages, immune cells, adipocytes,

endothelial cells, Vascular Smooth Muscle Cells (VSMCs) and renal epithelial cells in patients with MetS, implicating its involvement in both the initiation and progression of MetS [9].

Despite recent advances in knowledge, pharmacological therapy for MetS has not made significant progress and further research is needed for the approval of certain treatments. In light of this, researchers have turned their attention to testing therapies based on specific nutrients and bioactive compounds known as nutraceuticals. One such nutraceutical that has garnered interest is Hass avocado (*Persea americana*) due to its potential beneficial effects. Avocados are a rich source of monounsaturated fat, dietary fiber and various important phytochemicals, including lutein, vitamin E, niacin and folate, which contribute to a healthy diet [10,11]. Previously, we demonstrated that supplementation with avocado oil yields molecular-level benefits in mice with a history of obesity, even without causing changes in body weight and adiposity [12]. Avocado oil supplementation also led to reduced serum triglyceride levels, minimized oxidative damage to proteins in all tissues, improved antioxidant enzyme activity and reduced inflammation in both epididymal adipose and skeletal muscle tissues. However, therapeutic intervention using avocado oil in MetS patients has not been tested thus far. Therefore, the aim of this study was to evaluate the effects of avocado oil supplementation on insulin resistance and oxidative parameters in patients with metabolic syndrome.

Methods and Materials

Subjects

Thirty-three obese adults (BMI>30 kgm^2), diagnosed with metabolic syndrome for at least one year, both genders, were included in this double-blinded, randomized placebo-controlled trial and assigned to either the control (soybean oil) or the avocado oil group [13]. The inclusion criteria were as follows: Age between 30 to 65 years; written informed consent to take part in the study; no evidence of active coronary artery disease; presence of three or more MetS criteria. The exclusion criteria used in order to eliminate factors which might influence the biochemical parameters were as follows: Glycemia>300 mg/dL; triglyceridemia>1000 mg/dL, evidence of metabolic and hemodynamic dysfunction; exacerbated weight loss in the last 3 months (voluntary or involuntary); cigarette smoking or alcohol and drug abusing. All subjects reported that they were not taking food supplements or any diabetes medication starting in the last 3 months.

Research participants were evaluated over five visits, carried out on different days. The first two visits, subjects were submitted to an anthropometric and nutritional evaluation, blood collection and delivery of soybean or avocado oil. At the end of the 12-week intervention period, the patients underwent the same initial tests (nutritional assessment, anthropometry and blood collection). Subjects were asked to maintain their usual lifestyle, including their regular diet, associated with the intervention proposed. All individuals were informed about the aim of the research, the possibility of refusal of the participation and provided written informed consent. The study was approved by the local ethics committee (number 3.685.349) and conformed to the standards set by the declaration of Helsinki **(Figure 1)**.

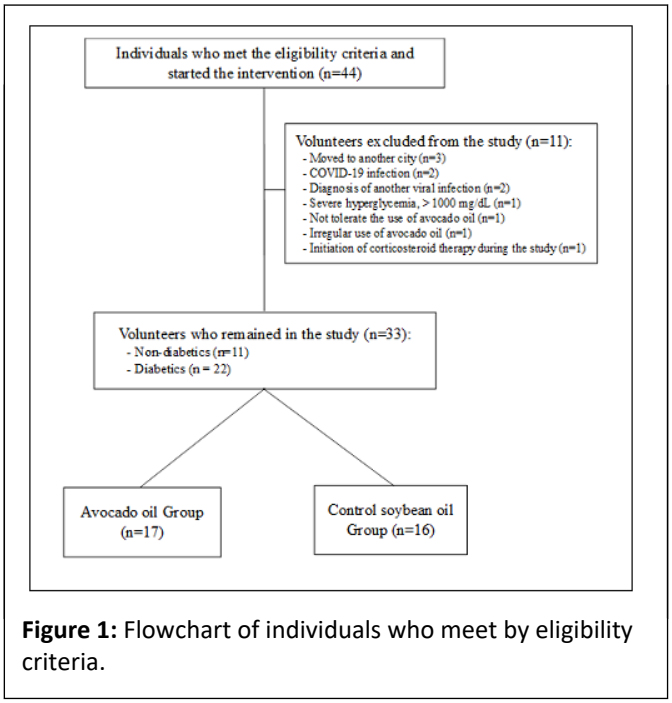

Figure 1: Flowchart of individuals who meet by eligibility criteria.

Supplementation procedure

The participants were randomly assigned to two groups: (1) The control group receiving soybean oil (n=17); and (2) the avocado oil group (n=16), receiving avocado oil vials at a daily dose of 10 mL, without any restrictions on timing or food intake, for a duration of sixty days. The placebo group consumed an equal number of vials containing soybean oil, matching those provided to the avocado oil group. Participants were instructed to continue taking their medications at the prescribed doses throughout the period of avocado oil supplementation.

Measurements

Anthropometric measurements: Each participant's height and weight were recorded to calculate Body Mass Index (BMI). Height was measured to the nearest 0.1 cm whilst barefoot using a stadiometer. Body weight was measured to the nearest 0.1 kg with participants wearing light clothing. Waist circumference was measured using a metric tape to the nearest 1 mm.

Biochemical analysis: All clinical data were obtained after an overnight fast. All subjects reported to the laboratory and had venous blood drawn for the determination of fasting blood glucose; fasting insulin; glycated hemoglobin; total cholesterol; HDL-C; LDL-C (calculated of according Friedewald formula) and triglycerides. The blood samples were collected to determine the aforementioned markers before the study protocols and after the diet intervention. Immediately after collection, the blood samples were centrifuged. Part of the serum was immediately used for analysis and another part was immediately frozen in 80°C freezer for later analysis. The Homeostatic Model

Assessment of Insulin Resistance (HOMA-IR) was calculated according to the method described by Wallace, et al.,

Intracellular determination of ROS and nitric oxide: The production of hydroperoxides was determined by the intracellular formation of 2',7'Dichlorofluorescein (DCFHDA) from the oxidation of 2',7'Dichlorodihydrofluorescein Diacetate (DCFHDA) by ROS according to the method previously described by Hempel, et al., with some modifications [14]. The production of Nitric Oxide (NO) was evaluated spectrophotometrically through the stable metabolite nitrite. The nitrite content was calculated based on a standard curve from 0 nM to 100 nM performed with the metabolite sodium nitrite ($NaNO_2$). The results were calculated in µmol Nitrite/mg protein [15].

Antioxidant defenses (GSH): Glutathione (GSH) levels were determined as described by Hissin and Hilf, with some adaptations [16]. GSH was measured in the palatal mucosa homogenate after protein precipitation with 1 mL of 10% trichloroacetic acid. An 800 mM phosphate buffer, pH 7.4 and 500 µm DTNB was added to part of the sample. Absorbance was read at 412 nm after 10 min. A standard curve of reduced glutathione was utilized to calculate the GSH levels in the samples.

Statistical analysis

All analyses were performed using the SPSS statistical software package and the results were expressed as mean and Standard Deviation (SD). Normality of data variances were tested using the Shapiro-Wilk. The difference in variables between the pre and post intervention periods was assessed using the t-test for paired samples (parametric variables). Differences were considered significant at $p<0.05$.

Results

Forty-four subjects, with an average age of 53.4 ± 10.4 in the control soybean group and 50.1 ± 11.1 in the avocado oil group, started the intervention. However, 11 participants were withdrawn from the study due to various reasons: Three relocated to another city, two contracted COVID-19, two had a different viral infection unrelated to COVID-19, one had severe hypertriglyceridemia (above 1000 mg/dL), one had intolerance to the oil, one did not comply with regular oil usage and another started corticosteroid treatment during the intervention period. Among the remaining 33 participants, 22 were diabetic, with seven using NPH insulin. The other participants were on medications such as metformin, sulfonylureas, DPP-4 inhibitors, or SGL-T2 inhibitors alone or in combination for more than three months prior to the intervention. According to the FFQ, there were no significant differences in energy consumption changes between the control and treatment groups before and after the intervention (data presented in another paper by the group) [17]. The mean and standard deviation of the anthropometric, insulin resistance, lipid profile and oxidative stress markers are described in **Table 1**. There were no significant differences observed in the evaluated parameters between the pre and post intervention moments in both the control soybean and avocado oil groups, except for triglycerides, which were higher in the post-intervention avocado oil group.

Table 1: Mean and standard deviation of antropometric, insulin resistance, lipemic parameters and oxidative stress markers of the metabolic syndrome patients submitted to soybean or avocado oil supplementation and p-value of difference between pre and post intervention.

Measurements	Control soybean oil group					Avocado oil group					
	Pre		Post		p-value[a]	Pre		Post		p-value[a]	p-value[b]
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		
Anthropometric parameters											
Body weight (kg)	99.52	17.64	99.96	17.72	0.942	103.55	17.72	104	16.79	0.94	0.506
BMI (kg/m2)	38.94	6.91	39.14	7.03	0.935	38.46	7.03	38.63	6.12	0.94	0.827
WC (cm)	120.29	14.32	120.8	14.24	0.914	117.81	14.24	119.2	12.45	0.75	0.728
Insulin resistance parameters											
FBG (mg/dL)	114.41	30.87	132.5	28.5	0.085	136.06	28.5	141.3	42.88	0.71	0.488
FBI (mU/L)	17.91	12.03	20.82	11.87	0.482	18.01	11.87	17.33	9.85	0.85	0.365
HbA1c (%)	6.18	0.77	6.00	0.79	0.504	6.55	0.79	6.26	1.47	0.56	0.516

HOMA-IR	4.75	2.64	6.71	3.56	0.077	5.93	3.29	5.86	3.59	0.95	0.501
Lipemic parameters											
Triglycerides (mg/dL)	145.23	68.79	140.4	52.02	0.819	140.41	52.02	189.1	81.55	0.77	0.048*
LDL (mg/dL)	109.52	42.79	109.1	37.51	0.976	109.11	37.51	116	33.74	0.77	0.584
HDL (mg/dL)	47.05	9.9	47.35	9.27	0.929	47.35	9.27	43.37	8.83	0.87	0.217
CT (mg/dL)	185.64	52.67	184.6	46.06	0.95	184.58	46.06	197.2	33.27	0.92	0.377
Oxidants stress markers											
NO	0.255	0.14	0.264	0.144	0.843	0.324	0.172	0.34	0.131	0.57	0.128
GSH	0.01	0.003	0.011	0.001	0.839	0.011	0.002	0.011	0.002	0.43	0.282
DCF	0.083	0.026	0.077	0.024	0.537	0.084	0.024	0.079	0.021	0.57	0.857

Discussion

Considering the high prevalence and complexity of MetS, its management necessitates a multidisciplinary approach, emphasizing lifestyle modifications that include healthy eating and regular physical exercise. The significance of the fatty acid profile, particularly MUFA, in the control of MetS, motivated our investigation into the potential impact of daily consumption of 10 ml of MUFA-rich avocado oil over a three-month period on oxidative and insulin resistance parameters in obesity individuals with MetS [18]. Our hypothesis was that this intervention would positively affect the evaluated parameters.

In this study, we did not observe any significant changes in the evaluated oxidative and IR parameters in the avocado oil group. However, interestingly, the data showed that the control soybean group experienced a clinical deterioration in HOMA-IR, with a notable 86.5% increase in HOMA-IR values after the intervention. In contrast, such deterioration was not observed in the avocado group, which further highlights the safety and importance of incorporating Monounsaturated Fatty Acids (MUFA) into the diet. This finding aligns with a randomized controlled study by Khan, et al., where they investigated the effects of consuming one whole avocado per day for three months in overweight and obesity individuals and found no significant effects on glycemia and insulinemia [19]. Longer intervention periods are needed in order to determine whether this supplementation could have a more significant impact on these parameters.

Growing evidence suggests the involvement of OS in MetS and its associated clinical complications [8]. In a study using diabetic rats induced by Streptozotocin (STZ) and treated with avocado oil (1 mL/250 g/day for 3 months), Ortiz-Avila, et al., demonstrated reduced levels of Reactive Oxygen Species (ROS) and lipid peroxidation, along with an improvement in the ratio of reduced to oxidized glutathione and brain mitochondrial function [20]. Other studies analyzed the effects of treatment with avocado oil (4 mL/kg for 3 months) on hepatic mitochondria in STZ rats. They observed that the oil reduced the effects of OS caused by diabetes on liver mitochondria without improving glycemic control [21]. However, randomized clinical trials evaluating ROS levels in MetS patients following avocado oil supplementation have not been described. In the present study, OS was evaluated by measuring serum levels of nitric oxide, dichlorofluorescein and reduced glutathione. No significant differences in these markers were observed between the groups before and after the intervention.

The Lipgene study, a European multicenter dietary intervention study, investigated the effects of fat quality and quantity on risk factors associated with MetS, comparing high-MUFA-fat, high-saturated-fat and low-fat diets over 12 weeks. The authors found no differences in OS and fasting inflammatory markers [22]. However, a subgroup of the same study, including 75 participants with MetS, found improvement in OS plasma parameters in the postprandial period [23]. In our study, we evaluated OS parameters only in the fasting period.

We did not observe significant differences regarding weight, BMI or waist circumference after using avocado oil, neither when comparing pre and post, nor when compared to the control group. The longitudinal study NHANES evaluated, in 55,000 individuals, the habitual consumption of avocado. The results showed less weight gain and a reduced risk of overweight and obesity in individuals who used this fruit [11]. The aforementioned studies by Ortiz-Avila, et al., (2015a) and Ortiz-Avila, et al., (2015b) who observed beneficial effects on OS and improvement in the lipid profile found no change in the body weight of mice [20,21]. In humans, significant weight loss was only described when fruit intake (one avocado per day) was associated with a hypocaloric diet [24]. It is noteworthy that the intake of SFAs and total fat cannot be neglected, as their high consumption can promote changes in metabolic parameters, regardless of the amount of MUFAs and PUFAs ingested [25]. This evidence highlights the complexity involved in the

relationship between OS, inflammation and diet. The single addition of MUFA-rich food to the usual diet without other lifestyle interventions does not appear to be sufficient to improve the inflammatory status in individuals with overweight under free-living conditions [26].

Another noteworthy point is that the participants in our study were obese and many of them already had type 2 diabetes (DM2) with likely pancreatic dysfunction, as indicated by a third of the participants using regular insulin. This aspect makes it more challenging to improve the metabolic status of these patients, which may have contributed to the absence of significant changes after only a 3-month intervention. Additionally, the relatively short duration of the study and the measurement of fasting serum parameters represent potential limitations. Furthermore, the study had a small number of participants and a highly heterogeneous sample, which may have impacted the results. Another factor that might have influenced the lack of response to avocado oil supplementation is the absence of lifestyle changes, as there was no specific guidance provided regarding diet and physical activity.

Conclusion

In the present study, the use of avocado oil did not alter oxidative and IR parameters in obesity individuals with MetS. Although our findings do not support our hypothesis, additional research is needed to better characterize the effects of daily consumption of avocado oil in obesity patients with MetS, especially paying attention to dose, time and inclusion criteria.

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