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ORIGINAL ARTICLE

Effect of Argan Oil on Liver in Patients Suffering from Metabolic Syndrome

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ABSTRACT

Background: Hepatic steatosis is widely considered as the hepatic manifestation of metabolic syndrome. The effect of argan oil consumption on the possible hepatic complications of metabolic syndrome has been evaluated in this study.

Methods: Twenty-nine patients with metabolic syndrome were selected among 70 hypertensive patients recruited in the Cardiology Department of University Hospital of Casablanca, Morocco. The patients were randomly divided into 2 groups. Group one consumed argan oil (25 mL) every day for 3 weeks and the control group who did not receive the oil. The dietary intake was analyzed before, during and after the interventions. Plasma triglycerides, apolipoprotein A1 (ApoA1) and apolipoprotein B100 (ApoB100) were determined before and after interventional study. Also, plasma α-2 macroglobulin was measured as a marker of the risk of chronic liver diseases in these patients.

Results: An improvement in lipids levels was observed in the group consumed argan oil by a significant decline in triglyceride levels ($P<0.001$) from 246±112 mg/dL to 126±56 mg/dL and increase in the ApoA1 level from 0.59±0.25 g/L to 0.69±0.28 g/L, but was not significant. After consuming argan oil, ApoB100 decreased from 0.82±0.29 g/L to 0.76±0.26 g/L, but was not significant. The serum concentration of α-2 macroglobulin improved after argan consumption too.

Conclusion: Argan oil could prevent the liver complications associated with metabolic syndrome by improving plasma lipids and apolipoproteins and α-2 macroglobulin.

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Introduction

Hepatic steatosis is the hepatic manifestation of metabolic syndrome, including diseases related to type 2 diabetes, resistance to insulin, truncular obesity (1), hyperlipidemia, hypertriglyceridemia and high blood pressure (2). Non-Alcoholic Fatty Liver Disease (NAFLD) or hepatic steatosis is a condition defined as excessive accumulation of fat in the liver as triglycerides and more than 5% of hepatocytes are affected at histological level (3).

Although simple steatosis found in NAFLD is not associated in the short term with increased morbidity or mortality. However, its progression to Non-Alcoholic Steato-Hepatitis (NASH) is rapid. The latter rises the risk of developing fibrosis and further cirrhosis, liver failure or hepatocellular carcinoma (1, 4, 5). The prevalence of NAFLD in the general population was shown to be between 5.4% and 24% (6, 7), while, it is between 20 and 30% in Europe (of which 10-20% would suffer from NASH) (8, 9) and between 30 and 45% in the United States (8) (of which 5% would have NASH) (10). This prevalence is much higher in obese subjects with 65-75% of hepatic steatosis (8).

Indeed, in black Africa, 37.20% of patients with metabolic syndrome have developed steatosis (6). NAFLD is also a risk factor for cardiovascular mortality (11, 12), so it is important to manage it at the asymptomatic stage, which is reversible (8). Until now, there is no specific treatment for steatosis. Food habits modification remains the only recourse within the framework of primary prevention (13). This fact brings us back to launch a nutritional intervention study based on argan oil (14, 15) to investigate the effect of argan oil on hepatic complications of the metabolic syndrome.

Indeed, argan oil is recognized for centuries for its many virtues as culinary and cosmetic oil. So it would be very interesting to know about its chemical composition. Argan oil is extracted from the fruit of a tree endemic to the south-west of Morocco, called Argan tree or *Argania spinoza*. The triglyceridic fraction of argan oil is composed of about 33.7% of polyunsaturated fatty acids, 44.8% of monounsaturated fatty acids and 80% unsaturated fatty acids. The unsaponifiable fraction is rich in antioxidants, mainly polyphenols, sterols, and tocopherols (14, 15). The recent data, from our laboratory, have demonstrated the positive effect of argan oil on lipid markers in metabolic syndrome patients (16). In this study, we investigated its protective effects against hepatic complications in metabolic syndrome patients.

Materials and Methods

This study was undertaken on 29 patients suffering from metabolic syndrome. The sampling was a random sampling method based on tables of random values. From the patients consulting the Cardiology Department of the Ibn Rochd University Hospital of Casablanca, Morocco, hypertensive patients were randomized during a period of one month and managed to reach a total number of 70 hypertensive patients. Among them, 43 patients were enrolled according to well-defined inclusion and exclusion criteria. However, only 29 patients were eligible to complete the study, because 14 patients left the study due to personal reasons. The enrolled patients were informed about the objectives of the study and they agreed to participate in this study protocol by a signed informed consent letter approved by the Institutional Review Boards of Ibn Rochd Hospital Center (Casablanca) according to ethical standards defined by regional committee on human experimentation and based on Helsinki Declaration of 1975, that was revised in 2000.

All patients underwent a complete clinical examination using an electrocardiogram and a Doppler echography. Then the anthropometric data were determined for all patients. The weight of each patient was measured using a weighing scale which was properly tarred before each use (the unit as kg), the size was measured with a fixed measuring rod graded in cm, the waist and hip measurements were conducted by a tape measure graded in cm. The body mass index (BMI) was determined using WHO formula of BMI (kg/m^2)=weight (kg)/size^2(m^2).

A food record was completed by a nutritionist enrolling the nutritional data of each patient before the nutritional intervention of argan oil. The questionnaire made it possible to record the data on eating habits as well as a food anamnesis. The gathering of information was carried out after 24-hour reminder and by determining the food history. The latter estimated the usual intake over a defined period. It was based on a detailed examination of the usual daily diet. Thus the total energy intake of each patient was calculated with the Nutrilog software.

The 1st step was to define the study population and in the 2nd step, the clinical and nutritional criteria of the two groups of patients (Argan group and Control group) were studied based on a univariate analysis comparing the results between the period before nutritional intervention and after nutritional intervention of argan oil, knowing that the 2 groups were not different clinically and nutritionally. In the 3rd step, the judgment criteria evaluated the effect of the consumption of argan oil and the biological markers were compared between the two periods before and after nutritional intervention of argan oil.

The patients met the criteria for the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III): ATPIII metabolic syndrome (17). The inclusion criteria were waist circumference more than 102(M)/88(F) cm, plasma triglyceride ≥150 mg/dL, plasma high density lipoproteins (HDL) cholesterol <50 mg/dL in women, and <40 mg/dL in men, presence of high blood pressure (≥130/85 mm Hg), plasma glucose ≥110 mg/dL or confirmed diagnosis of type 2 diabetes.

The exclusion criteria were presence of liver and kidney diseases, HIV, regular smoking, hormonal treatment in the previous six months, and treatment with statins, oral antidiabetics and insulin.

The enrolled 29 patients were randomly divided into 2 groups. Group one (17 patients) received argan oil (25 mL) every day for 3 weeks and the control group (12 patients) who did not consume the oil. Before the nutritional intervention, a clinical fact sheet was developed containing information on cardiovascular risk factors (dyslipidemia, diabetes, obesity, smoking) of patients and possible antecedents.

A diet was followed for all patients during the nutritional intervention. This diet was calculated using NUTRILOG software based on WHO recommendations defined as normoglucidic, normoprotidic and normolipidic intake consisted of proteins intake at a rate of 1 to 1.2 g/kg/day, i.e. 12 to 15% of daily energy intake, proteins of marine and plant origin, lipid intake at a rate of 1 g/kg/day, i.e. 30 to 35% of daily energy intake [with significant contribution in monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs)], and carbohydrates intake at a rate of 3 to 5 g/kg/day, i.e. 50-55% of daily energy intake with reduction in carbohydrates with high glycemia index.

The control group followed the dietary recommendations suggested in the study design. For the argan oil group, a substitution of lipid ratio by 2 table spoons (25 mL) of argan oil was followed during the 3 weeks of intervention period. Argan oil was provided from Arganoil Company packaged as 250 mL bottles. A first blood sample was taken before the nutritional intervention for all participants. At the end of nutritional intervention, a second blood sample was prepared 12 hours following fasting. Blood sample was collected in EDTA and dry tubes and then centrifuged at a speed of 4000 rpm for 15 minutes. The serum obtained from dry tubes and the plasma obtained from EDTA tubes were distributed in Eppendorfs tubes before being stored at -20°C for subsequent use.

Serum concentrations of α-2 macroglobulin, triglycerides (TG), Apolipoprotein B100 (ApoB100), and apolipoprotein A1 (ApoA1) were determined using non-hemolyzed serum samples. Triglyceride was determined by spectrophotometry. The α-2 macroglobulin, ApoA1, and ApoB100 were quantitatively measured using Roche/Hitachi Cobas C systems by *in vitro* immunoturbidimetric tests, based on antigen-antibody complex and agglutination was assessed by turbidimetry. STATA software was used in statistical analysis to compare the paired samples by student's t test and the difference was considered significant, when the p value was less than 0.05.

Results

Among both argan and control groups, the mean age of patients was 61.28±11.73 years old. The gender ratio of men to women was 6:23. Patients in the control group had an average waist circumference of 92.33±4.62 cm for men and 106.33±13.88 cm for women, while patients in the argan oil group had an average waist circumference of 98±10.82 cm for men and 103.71±11.44 cm for women. These waist circumference values were high in women according to ATP III in both groups (Table 1). Mean waist circumference for the argan oil group was 102.7±11.22 cm and 102.83±13.56 cm for the control group (P=0.352). The W/H ratio was about 1 in both groups. The distribution of adiposity was android; therefore, the risk of developing hepatic steatosis was high for these patients.

Patients included in this study had high blood pressure with or without antihypertensive medications. About 59% of argan oil group were on monotherapy (Furosemide) in comparison to 75% for the control group following a low-salt diet.

Table 1: Anthropometric data of the two groups (Argan and control) of patients suffering from metabolic syndrome (18).

Variable	Argan group	Control group	P value
Age (years)	63.76±10.49	57.75±12.93	0.662
Weight (kg)	71.98±13.23	76.68±14.58	0.838
Size (m)	1.60±0.07	1.60±5.88	0.615
BMI (kg/m²)	28.19±5.37	29.47±5.88	0.691
WS (cm) men	98±10.82	92.33±4.62	0.676
WS (cm) Women	103.71±11.44	106.33±13.88	0.707
HC (cm) Men	97.66±3.34	94.66±3.34	0.667
HC Women (cm)	103.50±22.50	110.55±14.45	0.343
Medium Waist (cm)	102.70 ±11.22	102.83 ±13.56	0.352
Medium hip Circumference (cm)	102.70 ±11.90	106.58 ±12.56	0.799
Ratio Waist/hip Circumference (cm)	1±0.92	0.97±1.08	0.42

BMI: Body mass index, WS: Waist size in centimeter, HC: Hip Circumference in centimeter

Table 2: Clinical data of the two groups (Argan and control) of patients suffering from metabolic syndrome. Values are expressed as a percentage.

Clinical data	Argan group (%)	Control group (%)
Hypertension	100	100
Diabetes	0	0
Dyslipidemia	47	17
Obesity	41	50
Coronary inheritence	18	25
Smoking	0	0
Physical activity	0	0
Treatment monotherapy	58,82	75
Compliance	94	100
Self-measurement	47	42
Secondary hypertension	0	0
Complications	0	0

Table 3: Distribution of total daily energy intake of the group consuming argan oil and the control group expressed in percentage.

Distribution of the total daily energy intake (%)		Control group	Argan group	P value
Before nutritional intervention	Carbohydrates	58.25±10.16	49.39±7.76	0.404
	Lipids	25.07±10.65	36.13±9.16	0.689
	Proteins	12.97±1.67	11.28±2.94	0.075
After nutritional intervention	Carbohydrates	48.30±6.66	48.25±7.30	0.06
	Lipids	19.22±2.7	19.40±5.2	0.078
	Proteins	28.42±8.3	28.32±6.6	0.09

Good compliance was observed in all patients (stable blood pressure of 140/90 mmHg). In all cases, the hypertension was essential and did not result from any cardiac, renal, thyroid or hormonal vascular causes. All patients had a metabolic syndrome without apparent complications. They did not smoke, but were sedentary and did not engage in any physical activity. Dyslipidemia was present among 47% of the argan oil group and 17% of the control group (Table 2).

Type 2 diabetes was present in both argan oil and control groups with proportions of 65% and 25%, respectively. Doppler ultrasound did not detect any fatty deposits in the liver or venous thrombosis in patients of both groups, and 18% of the argan oil group and 25% of the control group had a coronary heredity and were likely to develop atherosclerosis in a long run. The presence of hypertension (in all patients), dyslipidemia (32% of patients) and fasting hyperglycemia (45% of patients) demonstrated their susceptibility to develop fatty liver disease and the risk of steatohepatitis or even cirrhosis or fatal hepatocarcinoma.

Before the nutritional intervention, the total daily energy intake (TEA) of carbohydrates, lipids and proteins for argan oil group was 49%, 36% and 11%, respectively; while it was 58%, 25% and 13% for the control group, respectively. The distribution of dietary intake showed that the argan group had a normoglucidic (50 to 55% of TEA), normolipidic (30-40% of TEA) and normoprotidic diet (12-16% of the TEA). Totally, 65% of this population was diabetic without following a low sugar diet. The control group had a slightly hyperglucidic (50% were obese), hypolipidic (17% had dyslipidemia) and normoproteic food distribution (Table 3).

After the nutritional intervention, we noted a decrease in total daily energy intake of lipids and carbohydrates with an increase in proteins in both groups. Three weeks following nutritional intervention, the argan oil group revealed a very significant decrease in triglyceride levels from 246±112 g/L to 126±56 mg/dL (P<0,001), while for the control group, a non-significant increase in triglyceridemia levels from 89±30 mg/dL to 100±30 mg/dL was shown (Table 4).

α-2 macroglobulin as a biomarker for chronic liver disease varied according to gender. In men it was between 150 and 350 mg/dL and between 175 and 420 mg/dL in women. The serum concentration of α-2 macroglobulin for patients consuming argan oil decreased from 223±83 mg/dL to 200±71 mg/dL. For the control group, α-2 macroglobulin increased from 208±51 mg/dL to 267±65 mg/dL. Indeed, all patients in the study had a normal serum concentration of α-2 macroglobulin. However, an

Table 4: Biological parameters before and after the nutritional intervention with argan oil.

Variable	Argan group			Control group		
	Before nutritional intervention	After nutritional intervention	P value	Before nutritional intervention	After nutritional intervention	P value
Triglyceridemia (mg/dL)	246±112	126±56	<0.001	89±30	100±30	0.01
ApoA1 (g/L)	0.59±0.25	0.69±0.28	0.11	0.78±0.28	0.73±0.25	0.18
ApoB100 (g/L)	0.82±0.29	0.76±0.26	0.32	0.74±0.26	0.86±0.32	0.24
α-2 macroglobulin (mg/dL)	223±83	200±71	0.29	208±51	267±65	0.18

improvement was observed for the group consuming argan oil (Table 4).

After three weeks of nutritional intervention, we noted a non-significant increase (P>0.05) in serum concentrations of apoA1 for the argan group from 0.59±0.25 g/L to 0.69±0.28 g/L; while in the control group, a slight decrease from 0.78±0.28 to 0.73±0.25 g/L was observed (Table 4). After three weeks of nutritional intervention, we realized a non-significant decrease in serum ApoB100 from 0.82±0.28 to 0.76±0.26 g/L (P>0.05); while in control group, a slight increase from 0.74±0.26 to 0.86±0.32 g/L was observed (Table 4). The argan group showed a non-significant decrease of ApoB100/ApoA1 ratio from 1.65±1.14 to 1.27±0.66 g/L.

Discussion

NAFLD is still the most common chronic liver disease (CLD) in the world, and its prevalence increases with the epidemic trend of obesity and diabetes (19). Hepatic chronic diseases can lead to a rise in insulin resistance and among at-risk groups resulting in the development of diabetes. Diabetes is particularly accompanied with obesity and dyslipidemia and contributes to development of hepatic steatosis, as well as, to non-alcoholic steatohepatitis, which can progress to cirrhosis that can be complicated by hepatocellular carcinoma (19).

NASH is linked to an influx of free fatty acids from adipose to the hepatic tissue, where they are stored. Actually, the foundation of NASH treatment has been based on lifestyle and dietary measures, including a low-calorie diet (low in fast and slow absorption carbohydrates) and physical activity. A loss of 8 to 10% in initial weight is essential to improve liver function and reduce cardiovascular risks as the leading cause of death in these patients (12).

Indeed, any improvement in inflammation and the oxidative process will be in favor of a decrease in liver toxicity and therefore a better health condition (20).

This has been demonstrated by the work carried out on a murine model. Argan oil, by its anti-inflammatory effect, down-regulated the genes coding pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) and increased the expression of anti-inflammatory genes coding interleukin-10 (IL-10) and interleukin-4 (IL-4) according to the (IL-10/LXR) and (IL-4/PPAR) mechanisms (20). Similarly, we have reported in a previous finding the plasma lipids improved after 3 weeks of argan oil consumption in patients suffering from metabolic syndrome. Indeed, the consumption of argan oil allowed a significant increase in plasma ApoA1 concentrations, and by the same way significantly improved HDL-cholesterol concentration (P=0.01) and decreased plasma ApoB100 (16).

The same results were found in a study in patients with dyslipidemia which demonstrated the hypolipemic and antioxidant effect of argan oil (21, 22). This decrease in the ApoB100/ApoA1 ratio is in favor of cardiovascular risk reduction (23, 24). However, this ratio increased from 1.05±0.57 to 1.29±0.58 g/L in the control group. Also, Batta et al. during a study on 47 Moroccan dyslipidemic patients under hemodialysis during 5 weeks nutrition with argan oil, an improvement in the blood lipid profile noted. Patients experienced a significant decrease in LDL-C and ApoB100, and an increase in HDL-C and ApoA1 (25).

Another nutritional intervention on humans has shown a significant improvement in the lipid and apoproteic balance by argan oil (26). Based on the composition of argan oil to be rich in polyunsaturated fatty acids, activates the nuclear receptors peroxisome proliferator activating receptors alpha (PPARα). This stimulation increases the synthesis of HDL and ApoA1. In this way, the reverse transport of cholesterol is promoted. Argan oil can stimulate PPARα and Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) signaling, and help to stimulate the oxidation of fatty acids via the impact of PGC-1α as a coactivator of HNF-4α that preserves gluconeogenesis (27).

Furthermore, both spinasterol and schottenol in the argan oil can modulate the gene expression of two nuclear receptors of liver X receptor LXRα and LXRß, and the target genes of ABCA1 and ABCG1. Nonetheless, only schottenol revealed a differential activation vis-à-vis the nuclear receptor LXRß. So spinasterol and schottenol can be considered as new LXR agonists, that can have protective roles by the modulation of cholesterol metabolism (28). Via the mechanism of cholesterol efflux, nascent HDL or free ApoA1 recover unesterified cholesterol from peripheral tissues and further form HDL discoidal, composed of ApoA1, phospholipids and unesterified cholesterol (Preß-2 HDL) (26).

The carrier ABCA1 plays a prominent role in this mechanism of cholesterol efflux to nascent HDL or ApoA1. In this study, argan oil significantly reduced triglyceridemia ($P<0.001$) in comparison to the control group. In fact, similar results were found previously in healthy Moroccan volunteers who consumed argan oil showing a decrease in triglycerides by 17.5% only in the group consuming argan oil in comparison to the group consuming olive oil (26) revealing that this improvement in dyslipidemia is linked to the normalization of the fats in the liver. In addition, serum concentrations of ApoB100 decreased in patients consuming argan oil when compared to the control group with a slight increase. Indeed, this decline is in favor of not only a reduction of cardiovascular risks (26, 29), but also a decrease in inflammation and insulin resistance as shown in another study which mentioned that high levels of ApoB are an early sign of insulin resistance in obese postmenopausal women (30).

The mechanism responsible for this decrease is probably due to the role played by LDL receptor in the secretion of ApoB100 (31). Moreover, the plasma α-2 macroglobulin which is a biomarker for chronic liver diseases has been measured in plasma of all patients included in the study and the results showed normal concentrations in both groups. However, we noted a slight decrease in the levels of α-2 macroglobulin for the argan oil group in comparison to the control group that remained within the standards (32, 33).

Therefore, all these patients suffered from metabolic syndrome in absence of any apparent complications. Indeed, this slight improvement proves once again that argan oil has a probable effect on the liver by preventing not only the storage of fatty acids in the form of triglycerides in liver cells, but also the evolution towards more severe pathologies that are invaded by a state of inflammation and fibrosis. Its mechanism of action probably involves the activation of PPARα nuclear receptors by the high PUFA content of argan oil. However, several studies indicated that the α-2 macroglobulin gene is regulated by a PPAR agonist α (32, 33).

In fact, α-2 macroglobulin is a significantly upregulated protein in diabetic patients and is considered as bio-marker of diabetes (34). Therefore, any decrease in the level of this protein is in favor of improvement of diabetes and possible insulin resistance. Otherwise, as shown in a previous study, argan oil induced a decrease in plasma lipoperoxides, and an increase in α-tocopherol in the consumers of argan oil (35, 36). These results suggest the plasma level of argan oil consumers to be more protected against the oxidation process due to the high level of minor compounds, such as polyphenols and tocopherols, which are powerful antioxidants in argan oil (35).

Moreover, it was documented that argan oil can affect and decrease the oxidative damages caused by H_2O_2 on the liver and therefore, could reduce the pathogenesis induced by oxidative stress on liver tissue (37). In fact, vitamin E can significantly improve liver function and histologic changes in patients with NAFLD/NASH (38). In addition, in a study carried out on 151 postmenopausal Moroccan women, the serum level of vitamin E increased in the group of argan oil consumers (39) leading to an improved liver function. Taken together, these results support the benefits of antioxidant supplementation in patients with NAFLD (40).

Conclusion

Our findings can be of interest in nutritional management of NAFLD, while argan oil can be part of a dietary recommendation to prevent hepatic complications in patients suffering from metabolic syndrome.

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Conflict of Interest

None declared.

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