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Krill Oil Associated with Caloric Restriction Ameliorates Parameters of Metabolic Syndrome and Hepatic Enzyme Outcome in Postmenopausal Women: A Retrospective Study

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ABSTRACT

Metabolic syndrome (MetS) is a pathological condition in which more risk factors for cardiovascular events coexist. The prevalence of MetS increases with age and with menopause onset. Polyunsaturated fatty acids (PUFAs) of the ω-3 series have been demonstrated to positively affected MetS features. In this study, we evaluated if krill oil (KO), a source of ω-3 PUFAs in the form of phospholipids, could favorably affect plasma lipids, glycemia and anthropometric parameters in MetS postmenopausal women.

We retrospectively evaluated the long-term effect of KO (225 mg) associated with a calorie restricted diet on anthropometric parameters, fasting blood glucose and lipid level in 18 postmenopausal women (mean age 55.8 ± 7.1 years) diagnosed for MetS(KO group, KG). We used anthropometric and biochemical parameters of 20 female (mean age 53.4 ± 6.5 years) affected by MetS and assigned to a calorie restricted regime as control (control group, CG).

At 6 and 12 months of treatment KG showed a significant improvement of anthropometric parameters, plasma cholesterol, triacylglycerol, and glucose level with respect to controls. In addition, KG revealed a great improvement of liver outcomes.

This retrospective study indicates that KO supplementation, associate to a calorie restricted regime, could be a useful suggestion for postmenopausal management of MetS.

Introduction

Metabolic syndrome (MetS) is a group of morbid conditions occurring together and it is closely linked to increased cardiovascular risks [1]. The most known and applied definition in clinical practice is that of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [2]. It split up the presence of three variables simultaneously present between the following: abdominal obesity, hypertension, hypertriglyceridemia, low HDL cholesterol, and blood glucose >100 mg/dL (also including diabetes).

The prevalence of MetS increases with age in both men and women. It is estimated that almost 20-30% of the middle-aged population is affected by this syndrome [3] and this percentage varies from 8 to 24% in males [4,5] and from 7 to 46% in females [6,7]. Many cross-sectional studies have shown a MetS increased risk in postmenopausal women [8-10], principally caused by the loss in female sex hormones which represents the main cause of increased cardiovascular diseases (CVD) [11]. Moreover, some studies report menopausal status as an independent predictor of MetS among women [11]. However, it must be considered that, as reported in a recent meta-analysis, among the individual components of MetS which can increase the CVD risk in elderly obese, increased blood glucose and HDL levels were the main component to be significantly associated with an increased mortality [12].

An important dietary component which may induce beneficial effects in MetS, and related CVD, is the fish rich in ω-3 long-chain polyunsaturated fatty acids (ω-3 PUFAs), mainly in the form of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA).

Several studies have suggested that fish or dietary ω-3 PUFAs intake may have beneficial effects on the incidence of MetS and on its individual components [13-15]. Interestingly, the major effects of ω-3 PUFAs on body weight and metabolic complications associated with MetS were reported when ω-3 PUFAs were combined with energy-restricted diets [16-19].

Consumption of fish and fish oil, rich in ω-3 PUFAs, has been associated with reduced CVD in both cohort studies and randomized clinical trials [20]. Furthermore, recently a meta-analysis of randomized controlled trials reports a relationship between EPA+DHA supplementation and reduced coronary heart disease among participants with elevated cardiovascular risks [21]. Moreover, ω-3 PUFAs have been demonstrated to induce benefit on glucose homeostasis in animal models of obesity and metabolic syndrome [22,23]. The beneficial effect of EPA and DHA has been mainly associated with the reduction in plasma lipids, in particular, TAG level, and an amelioration of cardiac arrhythmia and inflammation [20].

Both EPA and DHA are enriched in krill and fish, though ω-3 PUFAs found in krill oil (KO) and fish oil differ in their structural form as EPA and DHA in fish oil are in the form of triglycerides, whereas in KO the majority EPA and DHA are esterified into phospholipids [24,25]. Moreover, KO contains several lipid-soluble antioxidants among which of particular significance is the presence of the astaxanthin [26]. It has been reported, both in rodents [27-29] and humans [30-32] that ω-3 PUFAs in phospholipid form are more absorbed and bioavailable and KO seems to increase plasma levels of EPA and DHA more efficiently when compared to fish oil [27-32].

KO has been showed to improve blood lipid levels and reduced hepatic steatosis and glycemia in obese mice [33,34]. Recent studies have demonstrated that KO has a positive effect on different parameters of metabolic syndrome [33,35]. Moreover, it has been reported that KO, even at lower doses, is more effective than FO for the reduction of glucose, TAG, and LDL levels in hyperlipidemic patients [36]. In addition, the presence of astaxanthin, not only ensure stability to KO but also exerts anti-inflammatory and hypolipidemic effects in human and animals [37-39].

Given the above, the primary aim of our study was to retrospectively evaluate the long-term effect of a low-dose of KO (38 mg/day EPA + DHA 2:1), associated to a calorie restricted regime, on anthropometric (BMI and waist circìunference)and biochemical (glycemia, total cholesterol, HDL cholesterol and triacylglycerols)parameters in postmenopausal MetS women. This was done by comparing patients assigned to an energy-restricted diet, including ω-3 PUFAs, with other assigned to an energy-restricted diet. For both groups, energy-restricted diets were similar in composition with regard to total fat, protein and carbohydrate content.

Materials and Methods

From the database of the civil hospital U.O. Internal Medicine and long-term care of Grottaglie (Italy) we selected 38 women who MetS have been diagnosed

using two different criteria furnished by the International Diabetes Federation (IDF) and NCEPATPIII.

Although the cut-off values for waist circumference by IDF definition were lower than those defined by NCEP-ATPIII abdominal obesity was the common component of all studied population (100% for both definitions). It was followed by low serum high-density lipoprotein cholesterol (85% in both groups and for both definitions). 75% of the subjects in both groups had a fasting glucose level ≥ 100 mg/dL (median values 110 mg/dL and 120 mg/dL for control and krill oil group respectively) and 100% of patients in both groups had triacylglycerol levels ≥ 150 mg/dL (median values 219 and 212 mg/dL for control and krill oil group respectively).

Selected patients not used hormone therapy and had an intact uterus. The exclusion criteria were CVD (except hypertension); thyroid, renal, hepatic, gastrointestinal, oncologic diseases, or acute infection and utilization of lipid-lowering drugs, estrogens replacement therapy, drugs for hyperglycemia, and intake of fish oil or antioxidant supplements. Selected subjects did not undertake any specific physical activity regimen.

All the selected patients were assigned to a low-calorie diet in which 57% of energy was provided from low glycemic index carbohydrates, 14% from protein and 29% from fat (mainly from extra virgin olive oil and nuts). Moreover, only eighteen of these patients were also recommended to take at breakfast one capsule/day of KO whose composition is reported in Table 1.

Table 1: Krill oil composition

Krill oil for capsule 225 mg.	
EPA	24.7 mg
DHA	13.5 mg
αδιχα χινελονιΛ–	2.7 mg
Stearidonic acid	0.7 mg
Vitamin A	600 µg
Astaxanthin	84 µg

The composition of krill oil/capsule. We reported the amount of EPA and DHA esterified as phospholipids.

For all the subjects considered the basal metabolic rate was calculated by applying Harris-Benedict (HB) equations [40] with a correction factor due to the overweight status of the subjects [20]. The weight that was used in the HB equation was calculated as follow: (actual weight-ideal body weight) × 0.25) + ideal body weight. Ideal weight was calculated following formula: 50 + (0.75 × (height-150)). Total energy expenditure was calculated taking into account the physical activity level of patients. Subjects were instructed to follow a diet energy-restricted by about 30% of the estimated energy expenditure (approximately 1.200-1.800 calories/day). Both control and KO supplemented groups were seen three times per month. Follow-up at month 6 and 12 were considered in the presented study. No side effects induced by supplement were reported.

The study was approved by the Ethics Committee of ASL/Brindisi (Prot. N° 47312) and conducted in compliance with the Declaration of Helsinki, and the subjects gave informed consent to the treatment of their data.

All data were inserted into a database created by trained personnel. Data were computed with Excel (Microsoft 7). The comparison was made using one-way repeated measures ANOVA. Further comparisons were made by using paired-sample t-test. SPSS/PC computer program (SPSS, Chicago, IL, USA) was used to performing all statistical analyses. Statistical significance was set at $p \leq 0.05$. Data are presented as mean ± SD.

Results

1. Body mass index and waist circumference

The volunteers enrolled in the study came from different towns of southern Apulia. Results from 38 female aged 49-64 years (mean 54.6 ± 5.5) were analysed. Anthropometric and biochemical parameters at baseline are reported in Table 2. Weight loss was significant in both groups (22 ± 4.4 Kg for CG and 23 ± 4.9 Kg for KG, $p<0.005$). No significant difference was referred between groups. Regarding BMI, repeated measures ANOVA revealed a significant time effect ($F=17,930$; $p<0.001$) and the paired sample t-test showed significant decrease in BMI between the sixth month and

baseline (t = 7.39, p<0.05), between the sixth and the twelfth month (t = 25.27, p<0.05) and between the twelfth month and baseline (t = 11.78, p<0.05) in KG. Instead, a significant difference in the CG was only measured between the sixth and the twelfth month (t = 9.52, p <0.05) (Figure 1A).

Table 2: Characteristics of the two groups at baselinea

	CG	KG
Age (year)	53.4 ± 6.5	55.8 ± 7.1
Menopausal age (year)	50.0 ± 3.5	51.0 ± 4.4
Body weight (Kg)	110.7 ± 27	107.0 ± 14.2
WC (cm)	117.3 ± 11.3	118.4 ± 10.7
BMI (Kg/m2)	39.0 ± 9.5	37.7 ± 5.0
Cholesterol (mg/dL)	189.9 ± 16.8	210.3 ± 27.2
HDL	39.9 ± 7.5	37.0 ± 10.3
Triacylglycerols (mg/dL)	214.9 ± 47.5	215.9 ± 41.6
Glucose (mg/dL)	110.6 ± 12.5	119.1 ± 16.6
AST (U/L)	34.6 ± 12.5	37.3 ± 8.9
ALT (U/L)	58.7 ± 11.3	57.5 ± 14.6
GGT (U/L)	110.6 ± 15.3	118.6 ± 49.9

[a]Values are given as mean ± SD. Abbreviations: CG: Control Group; KG: Krill Oil Group; BMI: Body Mass Index; HDL: High-Density Lipoprotein; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; GGT: γ-Glutamyltranspeptidase

Repeated measures for Waist Circumference (WC) showed a significant effect of time (F=31,687; p<0.001) but not diet or diet x time effects. No significant difference was referred between groups. Both groups showed a significant decrease in WC values through time (Figure 1B).

2. Plasma glucose and lipid levels

KG presents a significant decrease in fasting blood glucose level (-27.7% p<0.005). The median of glycaemia at follow-up was 95 mg/dL (88-110 mg/dL) for control and 87 mg/dL (70-111 mg/dL) in KG. A significant correlation between WC and glycemia in KG was also found (R^2=0.2345, p<0.05). Moreover, repeated measures ANOVA showed a significant time effect (F=13.375; p<0.005) and paired sample t-tests underlined a significant reduction (p<0.005) already at 6 months in the group supplemented with KO and both groups showed a significant reduction in blood glucose at the last follow-up (p<0.05 for CG and p<0.001 for KG) (Figure 1C). Interestingly, the average value of blood glucose dropped in the normal range at the end of both nutritional interventions.

Just like glycemia, total plasma cholesterol level dropped below the normal threshold in both groups at the end of the experimental period. Repeated measures ANOVA revealed a significant time (F=13.9; P<0.001) and diet x time effect (F=3.4; p<0.05). The paired sample t-test shows a significant effect between baseline and the sixth (t=3.27; p<0.05) and the twelfth (t=5.65; p<0.005) month and between month 6 and 12 (t=3.24; p<0.05) in the KG. In the CG a significant effect was only measured between month 6 and 12 (t=4.01; p<0.05) (Figure 1D).

As regard for HDL-cholesterol, repeated measures ANOVA showed a significant time effect (F = 148.612; p<0.005) and time x diet effect (F = 8.627; p<0.05). Thus, the dietary intervention had an important effect HDL increase over the time. Paired sample t-tests disclosed an increase in HDL in both KG and CG through the time (p<0.05 and p<0.005 respectively) (Figure 1E). In KG, plasma TAG underwent a significant decrease (-18.9%, p<0.05) compared to pre-treatment values (Figure 1F). Repeated measures ANOVA showed a significant effect of time (F=20,233; p<0.001). Paired sample t-tests disclosed a significant effect on plasma TAG in both group at the last follow-up, but with a greater effect when ω-3 PUFAs were included in the diet (p<0.001). However, in the KG a significant effect on TAG plasma level was already measured at 6 months of dietary supplementation (p<0.05) (Figure 1F). The alteration in plasma lipids results in a significant reduction in the TAG/HDL ratio at the last follow-up in both CG (p<0.05) and KG (p<0.001) groups (Figure 1G).

3. Hepatic enzymes

Serum liver enzyme abnormalities were defined as ALT or AST of > 40 U/L and GGT≥ 25 U/L [41]. Repeated measures ANOVA showed a significant time effect both for ALT (F=12.99; p<0.005) and AST (F=7.75; p<0.01) values. Paired sample t-tests revealed a significant effect on AST in the group supplemented with KO (p<0.05) (Table 3). A significant correlation was measured between body weight loss and AST for both groups (R^2=0.2574; p<0.05 in CG; R^2 =0.2393; p<0.05 in KG). As for ALT, KG group showed a significant decrease at both 6 and 12 months, whereas

the control one had a significant effect only at the last follow-up (Table 3). GGT values at 12 months were reduced by about 46% and 21% in KG and CG respectively and repeated measures ANOVA indicated a significant time ($F=106.7$; $p<0.0001$) and diet x time ($F=5.55$; $p<0.05$) effects. Paired sample t-tests disclosed a significant decrease in GGT values in both groups. Moreover, a significant difference ($p<0.05$) was measured between the groups at the last follow-up (Table 3).

Table 3: Liver enzyme outcomes

	Baseline		Month 6		Month 12	
	CG	KG	CG	KG	CG	KG
AST (U/L)	34.6 ± 12.5	37.3 ± 8.9	30.9 ± 11.2	26.9 ± 8.7*	25.7 ± 10.9	23.3 ± 7.1**
ALT (U/L)	58.7 ± 11.3	57.5 ± 14.6	46.4 ± 10.2	42.3 ± 10.1*	44.3 ± 10.0*	41.1 ± 9.9*
GGT (U/L)	110.6 ± 15.3	118.6 ± 49.9	98.9 ± 13.1	69.9 ± 40.4**	87.3 ± 9.1***a	63.5 ± 6.7***b

Abbreviations: CG: Control Group; KG: Krill Oil Group
Asterisks represent significant differences with respect to the baseline. Values are given as mean ± S.D. AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: γ-glutamyltranspeptidase. *p<0.05; **p<0.005; ***p<0.0005. Letters represent significant differences between groups.

Discussion

Several studies have indicated that ω-3 PUFAs may be useful in reducing obesity [16]. The main mechanisms underlying this effect might include suppression of appetite, improvements of nutrient delivery to skeletal muscle for their oxidation, and increased expression of genes correlated to fat oxidation and energy expenditure. Although the effect of ω-3 PUFAs supplementation has been shown to reduce obesity in rodents, evidence in humans is limited. Interestingly, the major slimming effect of ω-3 PUFAs in humans was recorded when combined with energy-restricted diets or exercise [16,17]. Moreover, caloric restriction and ω-3 PUFAs supplementation have been reported to protect from some of the metabolic complications associated with MetS [16,17].

The present study shows that a long-term intake of a low-dosage of ω-3 PUFAs in the form of phospholipids, as those found in KO, beneficially affected several parameters linked to CVD-risk in postmenopausal women with MetS.

Studies comparing the effect of KO with that of fish oil demonstrated a higher bioavailability of ω-3 PUFAs and a higher therapeutic effect [42]. Moreover, it has been reported that KO can modulate the expression of genes in the intestine and the liver different from those modulated by fish oil [43]. In particular, KO is capable of up-regulating the activity of the mitochondrial respiratory chain and downregulating the activity of pathways involved in lipid and cholesterol synthesis and hepatic glucose production, while fish oil did not modulate the same metabolic pathways regulated by krill oil [43].

With this work, we have highlighted that KO more than a calorie-restricted diet alone significantly decreased BMI and WC (Figure 1).

Central obesity, main diagnostic criteria for the MetS, is considered to predispose individuals to insulin resistance. WC, the best anthropometric indicator of central obesity, is closely associated with insulin resistance [44]. It has been estimated that the prevalence of MetS is directly related to the amount of abdominal fat which tends to accumulate in women after menopause [11].

Although many animal studies report an effect of ω-3 PUFAs in reducing body fat, the impact of these fatty acids on body composition in humans is less certain. A study conducted on healthy adults (BMI 20-40 kg/m^2) reported an inverse relationship between plasma ω-3 PUFAs level, BMI, and WC suggesting a role for ω-3 PUFAs in protecting against obesity [45].

Our observations, together with others [45,46], suggest that KO supplementation may play an important role in inducing fat mass loss when supplemented concomitantly with a structured weight-loss program. The outcome of the present study is the usage of a very low dosage of ω-3 PUFAs from KO.

Moreover, our results are biologically plausible because several mechanisms underlying the association between ω-3 PUFAs and obesity have been shown [47,48].

On the light of the cardiometabolic risks associated to abdominal fat accumulation and considering that a

moderate weight loss may contribute to several health advantages [49,50], our results point out a very interesting effect on overweight woman affected by MetS.

It has been reported that 4 weeks KO supplementation to rats fed on a high-fat diet lead to a significant reduction in fasting plasma glucose level [33,51].

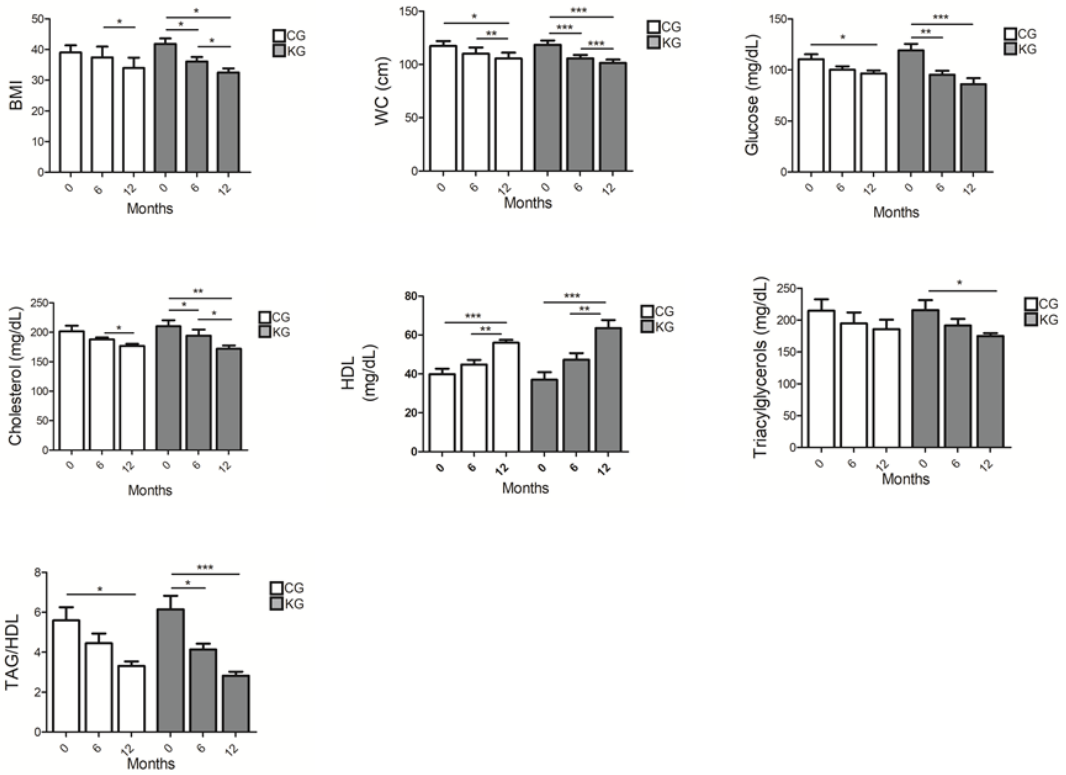

Figure 1. Anthropometric and biochemicalcharacteristics of control group (CG) and krill oil group (KG) at baseline and after 6 and 12 months. Values are the means ± SD. The comparison was made using one-way repeated measures ANOVA. Further comparisons were made by using paired-sample t-test (*p<0.05; **p<0.01; ***p<0.001).

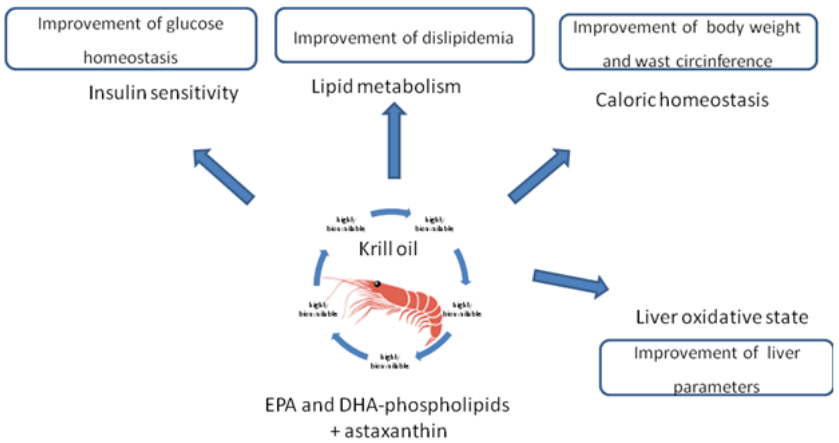

Figure 2: Schematic representation of krill oil as regulator of metabolic pathways.
In the krill oil, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are esterified to phospholipids instead of triacylglycerols as they are in the fish oil. This chemical characteristic makes EPA and DHA more bioavailable. By regulating glucose and lipid metabolism, the krill oil can improve glycemia, dyslipidemia and reset body weight homeostasis. Moreover, thanks to the presence of astaxanthin, the krill oil owns antioxidant properties that, at least in part, might be responsible for improving in the liver functions.

EPA and DHA present in KO may be responsible for the glucose-lowering effects mainly by improving insulin sensitivity [52]. In addition to PUFAs, two other components of KO, phospholipids, and astaxanthin, also showed glucose-lowering effects and increased insulin sensitivity in spontaneously hypertensive rats [53]. This last data may justify the greater effect of a low dosage of KO on glycemia with respect to the control group. Moreover, the decrease in blood glucose level in KG (Figure 1C) was positively correlated with the reduction in WC in this group. Thus, we may speculate that weight loss in KG patients could be, at least in part, responsible for glycemia improvement in this group. Interestingly, data describe KO as effective, more than fish oil, in the reduction of glucose level in hyperlipidemic patients [47].

Studies demonstrated that the risk of MetS in women at menopause is mainly related to increases in testosterone and this latter has been correlated to central adiposity, increased TAG, and decreased HDL levels [11]. Patients in the present study at baseline suffered from all the indicated diseases.

Some studies on humans and animals indicated that phospholipid-fatty acids had better bioavailability than TAG-fatty acids [29,32]. The better bioavailability may also contribute to the better physiological functions of phospholipid n-3 PUFAs.

A very recent meta-analysis of randomized trials demonstrated that KO supplementation significantly reduces plasma concentrations of LDL and TAG and significantly increases HDL concentration in hyperlipidemic patients but it results without effect in normolipidemic patients [21].

We found that both blood cholesterol and triglyceride levels were lowered by caloric restriction with a greater effect when KO was included. Moreover, a significant improvement of TAG/HDL ratio, a useful marker of CHD [54], was measured at 1-year follow-up in KG (Figure 1G). A reduced level of total cholesterol and TAG, as well as increased levels of HDL, are related to improved cardiovascular health [55]. Thus, the magnitude of increased HDL, in combination with a reduction in total cholesterol and TAG, seems to indicate that KO may be very effective in dyslipidemic patients.

ALT level is considered a specific marker of liver damage [56]. Therefore, our results showing more important changes in ALT than in AST concentrations suggest a transient injury to the liver (Table 3).

A significant improvement in liver enzymes was measured at the last follow-up in both groups with KG showing the largest changes. Accordingly, a recent randomized study demonstrated a reduction in serum ALT and AST after 1-year of a diet supplemented with ω-3 PUFAs in non-alcoholic fatty liver disease patients [57].

Central obesity is strongly correlated with serum GGT levels [58] and increased level of GGT is predictive of lobular inflammation and fibrosis [59,60]. Our results demonstrated a hugely decreases in GGT level at follow-up in KG. In the light of this result, we can speculate an improvement in liver cholestasis [61]. Our results have therapeutic implications. A weight-reducing nutritional regimen associated with KO improves, more than a hypocaloric diet, liver histology.

To note that, although not yet fully defined in humans, astaxanthin is considered a candidate supplements for liver protection because of its antioxidant activity and other functions. Animal studies have reported the effects of astaxanthin treatment on liver damage [62]. Thus, we consider that astaxanthin, at least in part, will be responsible for improving liver parameters measured in our patients.

As a whole, the present work demonstrated that a low dosage of KO, more than a hypocaloric regime alone, can ameliorate MetS features such as type II diabetes, dyslipidemia, and excessive visceral fat depots. Moreover, the antioxidant effect of astaxanthin present in the KO could contribute to good liver enzyme outcomes of MetS patients (Figure 2).

Conclusion

This is the first report about a prolonged KO supplementation performed in postmenopausal women with MetS and results are backed up by biological plausibility. Moreover, we used a very low ω-3 PUFAs

dosage from KO. As far as we know there is no evidence about the optimal amount of treatment for MetS, as this is the first study performed in postmenopausal women affected by MetS, we cannot exclude that a higher intake could have reached even better results.

Nonetheless, although the present study had a limitation in the number of participants, the beneficial metabolic effects, good acceptability, and ease of implementation shown for the diet suggest this type of regime as a promising tool for dietary preventive action against CVD in postmenopausal women.

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