REDUCTION OF THE SIDE EFFECTS OF THE STATIN TREATMENT BY ADMINISTRATING KRILL OIL IN TEATING DYSPLEDEMIA

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Abstract

Dyslipidemia is a condition characterized by altered fat metabolism evidenced by modified values of cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides. The goal of the treatment of dyslipidemia is to lower levels of cholesterol, LDL-cholesterol, triglycerides and to increase HDL-cholesterol, reducing thus the risk of cardiovascular diseases. Due to their effects on the brain, heart, kidneys and other vital organs and extremities, cardiovascular diseases combined with atherosclerosis represent the number one cause of morbidity and mortality. Numerous randomized clinical trials have shown that decrease of the serum cholesterol slows or reverses the progression of coronary diseases. To reduce cholesterol values, drugs called statins, or the alternative that uses natural products based on omega-3 fatty acids known for their protective effects on the body, are administered.

Key words: dyslipidemia, LDL-cholesterol, HDL-cholesterol, statins, krill oil, omega-3 fatty acids

INTRODUCTION

The goal of the treatment of dyslipidemia is to reduce levels of cholesterol, LDL-cholesterol, triglycerides and increase HDL-cholesterol reducing thus the risk of cardiovascular diseases.

Dyslipidemia can be treated pharmacologically – with drugs - by administrating statins. Statins are HMG-CoA reductase inhibitors, acting upon the enzyme that lies at the origin of the synthesis of cholesterol in the liver. Cholesterol is actually an indispensable part of the human body, and our body produces it both in the liver as precursor of the bile acids and in the brain. (Taylor F, Ward K, Moore TH et al. 2011, Bengtson et al., 2014, Bungău S. Et al., 2015). Findings of an extensive clinical trial have established that favourable changes of dyslipidemia lead to clear improvements in the coronary system (Friedewald, 2013, Bunea R. et al., 2004, Graf B. A. et al., 2010).

Statins are well tolerated, but have side effects such as increased transaminases (MHRA Drug Safety Update. Statins, 2012) muscle injury, insomnia, fatigue (Bunea R., 2013, Li D.M. Zhou et al., 2013), headaches,

digestive disorders (Bays H., 2005), polyneuropathy, sexual dysfunction (Silva M. A, 2006), increased risk of diabetes (MHRA Drug Safety Update Statins, 2012) that appear especially after using high doses (40-80 mg) (Harding A., 2007), effects that are generally reversible after discontinuation of treatment.

Typically, cholesterol must not exceed 200-230 milligrams per 100 millilitres of blood (Rizzo M., 2007).

The balance of polyunsaturated essential fatty acids (omega-3, omega-6, omega-9) in the body is important for maintaining healthy cell membranes and hormonal control. The exact mechanism by which omega-3 fatty acids favourably modify cardiovascular diseases and related disorders is not yet fully confirmed (Holub B.J., 2002, Schuchardt J. P et al., 2011).

Krill oil is extracted from Antarctic krill, Euphausia superba, a crustacean zooplankton rich in phospholipids with a long chain of polyunsaturated omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Hu FB, 2002). Krill oil also contains various strong antioxidants, including vitamins A and E, as well as astaxanthin, a novel flavonoid similar to 6,8-Di-C-glucosilluteolin but with two or more molecules of glucose and an aglycone (Bunea R., 2013, Vicaş S. I. et al., 2014).

Krill oil has a unique bio molecular profile of natural phospholipids rich in omega-3 fatty acids and various antioxidants significantly different from the usual profile of fish oils (Holub B.J., 2002, Sadzuka Y. et al., 2012). The association between phospholipids and the long chain of omega-3 fatty acids facilitates the easy passage of fatty acids molecules through the intestinal wall, the increase of bioavailability and, ultimately, an improvement in the absorption of omega-3 and intake of omega-6 (Hu F. B., 2002).

Unlike the fish oil that has been widely researched, krill oil is not present in too many studies. Researchers have declared that more studies on human subjects are needed, but krill oil has been proven safe and effective for our body so far (Bunea R., 2013, Ţiţ D. M. et al., 2014).

MATERIAL AND METHOD

In order to assess the side effects of statins used to treat dyslipidemia we have run a comparative, randomized, open-label, non-interventional study on a trial group composed of 157 patients with dyslipidemia, of which 89 have been treated with statins and 68 with krill oil for a year. Krill oil was administrated under the form of soft capsules containing 500 mg. of 100% krill oil, a capsule per day. The lipid profile was performed at baseline and at 12 months. To interpret the results, we have used the “effect size” (ES) statistical computing system based on various types of clinical

research or long-term observational studies. ES is a method of standardizing the magnitude of the change of a variable after a determined period of time.

The formula to calculate ES is:

$$\mathbf{ES = (m_1 - m_2) / s_1}$$

where: ES – effect size, m_1 – average value of the initial score, m_2 – average value of the initial score after a determined period of time, s_1 – value of the standard deviation of the initial score.

The interpretation is:

- $< 0.2 \Rightarrow$ unimportant change;
- $0.2 – 0.49 \Rightarrow$ small change;
- $0.5 – 0.8 \Rightarrow$ moderate change;
- 0.8 or $> \Rightarrow$ major change.

The characteristics of the study groups are presented in the tables 1-4.

Table 1.

Distribution of the study groups according to age

Age	Statin		Krill oil	
	No.	%	No.	%
<30 years	2	2.25	3	4.41
31-40 years	7	7.87	8	11.76
41-50 years	11	12.36	12	17.65
51-60 years	31	34.83	17	25.00
>60 years	38	42.70	28	41.18
Total	89	100.00	68	100.00

Table 2.

Distribution of the study groups according to origin

Origin	Statin		Krill oil	
	No.	%	No	%
Urban	66	74.16	48	70.59
Rural	23	25.84	20	29.41
Total	89	100.00	68	100.00

Table 3.

Distribution of the study groups according to sex

Sex	Statin		Krill oil	
	No.	%	No	%
Women	42	47.19	36	52.94
Men	47	52.81	32	47.06
Total	89	100	68	100.00

Table 4.

Characteristics of the study groups

Characteristics	**Statin**	**Krill oil**	**p**
Women/Men	47.19%/52.81%	52.94%/47.06%	0.249
Urban/Rural	74.16%/25.84%	70.59%/29.41%	0.433
Average age	55.79±8.12 years	53.68±8.83 years	0.672

RESULTS AND DISSCUSIONS

The results obtained in medical tests at baseline and at 12 months have revealed a reduction in total cholesterol, LDL cholesterol and triglycerides, respectively an increase in HDL-cholesterol both in the group of patients treated with statins and in the group of patients receiving krill oil. The values are listed in the table 5, 6 and are presented in the graphics 1-5.

Table 5.

Values of standard deviation

Parameter	**Statin**			**Krill oil**		
	Baseline	**At 12 months**	**ES**	**Baseline**	**At 12 months**	**ES**
Total Cholesterol (mg/dL)	330.5±24.2	292.3±22.6	1.58	321.8±26.5	296.3±27.1	0.96
HDL-cholesterol (mg/dL)	37.12±4.66	39.07±5.28	0.42	38.23±4.78	41.33±6.32	0.65
LDL-cholesterol (mg/dL)	151.2±15.2	139.5±13.0	0.77	153.6±17.7	139.7±14.8	0.79
Triglycerides (mg/dL)	229.8±21.6	179.2±16.5	2.34	221.6±20.9	181.3±17.2	1.93

Total cholesterol values have decreased in both groups, the effect size being very good. In the group using statins the effect size is 1.6 times higher than in the group using krill oil (ES = 1.58 vs. ES = 0.96) (fig. 1).

HDL cholesterol values have increased in both groups, the effect size being small in the group using statins (ES = 0.42) and moderate in the group using krill oil (ES = 0.65) (fig. 2).

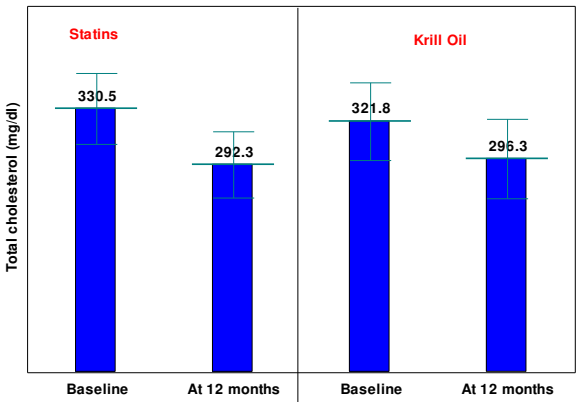

Fig. 1. The evolution of the average values of cholesterol

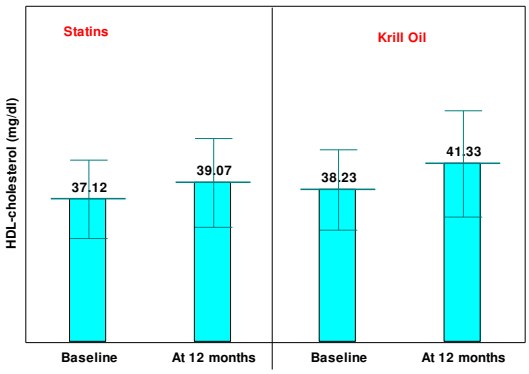

Fig. 2. The evolution of the average values of HDL-cholesterol

LDL cholesterol values have decreased in both groups, the effect size was moderate, almost equal (ES= 0.77 vs. ES= 0.79) (fig. 3).

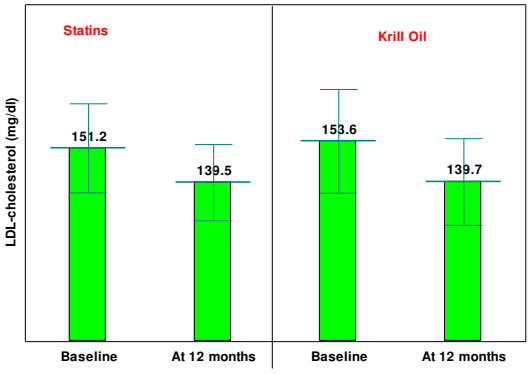

Fig. 3. The evolution of the average values of LDL-cholesterol

Triglycerides have decreased in both groups, the effect size being very good. In the group using statin, the effect size is 1.2 times higher than in the group using krill oil (ES = 2.34 vs. ES = 1.93) (fig. 4).

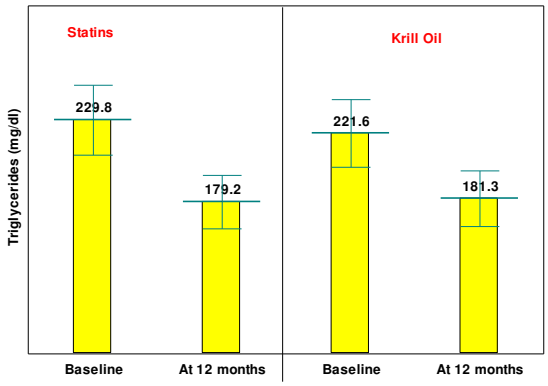

Fig. 4. The evolution of the average values of triglycerides

Table 6.

Incidence of the side effects

Symptoms	Statin		Krill oil		p
	No.	**%**	**No.**	**%**	
Insomnia	4	4.49	2	2.94	0.047
Fatigability	7	7.87	3	4.41	0.021
Headaches	20	22.47	9	13.24	0.006
Myalgia	3	3.37	1	1.47	0.011
Total	**22**	**24.72**	**11**	**16.18**	**0.020**

As it is shown in table 6, the incidence of side effects at 12 months of treatment is significantly higher than in the group using statins than in the group using with krill oil (24.72% vs. 16.18%) (p = 0.020).

The most common side effects were headache (22.47% vs. 13.24%) (p = 0.006) and fatigue (7.87% vs. 4.41%) (p = 0.021) (fig. 5).

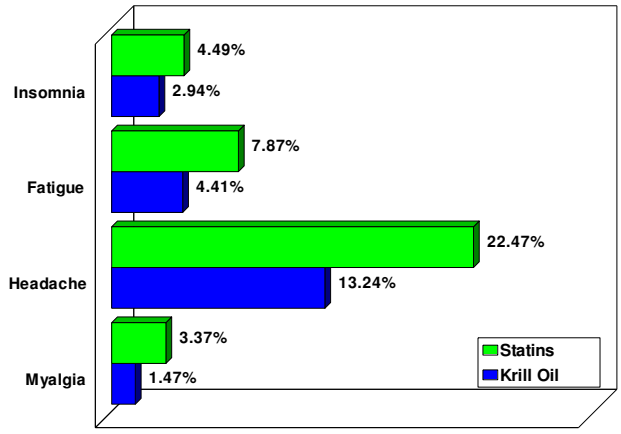

Fig. 5. Incidence of the side effects at 12 months post treatment

CONCLUSIONS

The use of statins in treating dyslipidemia has proven safe and efficient. One can notice their beneficial effects on reducing the level of cholesterol and triglycerides in the subjects of the study group that were treated with statin.

The use of krill oil, little known as an alternative to reduce total cholesterol, LDL-cholesterol and triglycerides, respectively to increase HDL-cholesterol, presents medical importance.

REFERENCES

1. Bays H., 2005 Statin Safety: An Overview and Assessment of the Data –Am J Cardio. 2006; 97[suppl]:6C-26C
2. Bengtson Nash S.M., Schlabach M. and Nichols, P.D., 2014, A nutritional-toxicological assessment of antarctic krill oil versus fish oil dietary supplements. Nutrients, 6: 3382-3402
3. Bungău S., Bungău C, Țiț D. M., Studies about last stage of product lifecycle management for a pharmaceutical product, Journal of Environmental Protection and Ecology, 2015, Vol. 16, No. 1, pp. 56-62
4. Bunea R., El Farrah K. and Deutsch L., 2004, Evaluation of the effects of Neptune Krill Oil on the clinical course of hyperlipidemia. Alternative Medicine Review, 9: 420-428.
5. Friedewald-Estimated Versus Directly Measured Low - Density Lipoprotein Cholesterol and Treatment Implications, 2013, J Am Coll Cardiol.;62(8):732-739. doi:10.1016/j.jacc.2013.01.079
6. Graf BA, Duchateau GS, Patterson AB, Mitchell ES, van Bruggen P, Koek JH, Melville S, Verkade HJ, 2010, Age dependent incorporation of 14C-DHA into rat brain and body tissues after dosing various 14C-DHA-esters. Prostaglandins Leukot Essent Fatty Acids, 83:89–96
7. Harding Anne, 2007, Docs often write off patient side effect concern, Reuters

8. Holub BJ., 2002, Clinical nutrition: 4. Omega-3 fatty acids in cardiovascular care. CMAJ;166:608-615
9. Hu FB Bronner L, Willett WC, et al., 2002, Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. JAMA, 287:1815-1821.
10. Li D.M., Zhou D.Y., Zhu B.W., Chi Y.L., Sun L.M., Dong X.P., Qin L., Qiao W.Z. and Murata Y., 2013, Effects of krill oil intake on plasma cholesterol and glucose levels in rats fed a high-cholesterol diet. Journalof the Scienceof Foodand Agriculture doi: 10.1002/jsfa.6072
11. MHRA, 2012, Drug Safety Update. Statins: risk of hiperglycaemia and diabetes
12. Rizzo M., Rini GB, Berneis K. – Effects of statins, fibrates, rosuvastatin, andezetimibe beyond cholesterol: the modulation of LDL size and subclasses in highriskpatients, Advances in Therapy, 2007, vol. 24, No. 3, 575-582
13. Ruxandra Bunea, Khassan El Farrah, Luisa Deutsch**,** 2013, Evaluarea Efectelor Neptune Krill Oil în Cercetarea Clinică a Reducerii Colesterolului
14. Schuchardt JP, Schneider I, Meyer H, Neubronner J, von Schacky C, Hahn A, 2011, Incorporation of EPA and DHA into plasma phospholipids in response to different omega-3 fatty acid formulations–a comparative bioavailability study of fish oil vs. krill oil. Lipids Health Dis, 10:145
15. Sadzuka Y, Sugiyama I, Miyashita M, Ueda T, Kikuchi S, Oshiro E, Yano A, Yamada H., 2012, Beneficial effects by intake of Euphausiacea pacifica on high-fat diet-induced obesity. Biol Pharm Bull, 35:568–572
16. Silva MA, Swanson AC, Gandhi PJ, Tataronis GR, 2006, Statin-related adverse events: a meta-analysis, ClinTher, 28 (1): 26–35.
17. Taylor F, Ward K, Moore TH et al., 2011, Statins for the primary prevention of cardiovascular disease, In Taylor, Fiona. Cochrane Database Syst Rev (1): CD004816. doi:10.1002/14651858.CD004816.pub4 PMID 21249663
18. The SEARCH Collaborative Group, SLCO1B1, 2008, Variants and Statin-Induced Myopathy - A Genomewide Study, NEJM, 359 (8): 789–799.
19. Bungău S., Copolovici D., Copolovici L., 2015, Instrumental Analitical Methods/Metode instrumentale de analiză, Ed. Italian Academic Publishing
20. Vicas S. I., Teusdea A., Muresan M., Sabau M., Marian E., Tunde J., Gitea D., Borza I., Vicas L., 2014, Preliminary study regarding to the total polyphenols and antioxidant capacity of yellow maize corncobs Analele Universităţii din Oradea, Fascicula Protectia Mediului, Vol. 23, Ed. Univ. din Oradea, 179-184