J Surg Med. 2019;3(5):371-376.
DOI: 10.28982/josam.560609

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Protective effects of krill oil on ischemic reperfusion injury in experimental model of priapism

Kril yağının deneysel priapizm modelinde iskemik reperfüzyon hasarı üzerine koruyucu etkileri

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Abstract

Aim: The aim of the study is to evaluate the effects of krill oil on priapism induced ischemia-reperfusion injury in priapism rat model.

Methods: Total of 24 rats were randomly divided into three groups with eight rats in each group. Group 1 was determined as the control group. Experimental priapism model was constructed in rats in Groups 2 and 3 for 1 hour and then priapism was terminated for 30 minutes to evaluate ischemia-reperfusion injury. The rats in Groups 1 and 2 were given tap water and standard chow pellets. Group 3: The same feeding procedure was applied to the experimental animals but supplemented with krill oil for one month. At the end of the experiment penectomy were performed, and blood samples were withdrawn from inferior vena cava of the rats to determine the levels of protein carbonyl (PC), malondialdehyde (MDA), nitric oxide (NO), glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) in systemic circulation, and cavernosal tissues.

Results: Biochemical examination of penile tissues showed that MDA and PC levels in Group 3 were significantly lower than group 2, while GSH-Px activities were significantly increased (P=0.001, P=0.005, P=0.003, respectively). Serum analysis results showed that MDA and NO levels in Group 3 were significantly lower than Group 2 and SOD activities significantly increased (P=0.011, P=0.001, P=0.009, respectively).

Conclusion: In this study, protective effect of krill oil against priapism induced ischemia-reperfusion injury in cavernosal tissue was observed based on biochemical evidence.

Keywords: Krill oil, Ischemia, Reperfusion, Priapism

Öz

Amaç: Mevcut çalışmanın amacı ratlara uyarlanmış priapizm modelinde krill yağının priapizm kaynaklı iskemi-reperfüzyon hasarı üzerindeki etkilerinin değerlendirilmesidir.

Yöntemler: Toplam 24 adet rat her bir grupta 8 rat bulunacak şekilde randomize edildi. Grup 1 kontrol grubu olarak belirlendi. Deneysel priapizm modeli Grup 2 ve 3'teki ratlara 1 saat süreyle uygulandı ve ardından iskemi-reperfüzyon hasarını değerlendirmek için priapizm 30 dakika süre ile sonlandırıldı. Grup 1 ve 2 deki ratlara standart yem ve musluk suyu verildi. Grup 3: Aynı beslenme prosedürü deney hayvanlarına uygulandı, ancak bir ay boyunca krill yağı ile takviye edildi. Deney sonunda süperoksit dismutaz (SOD), glutatyon peroksidaz (GSH-Px), malondialdehid (MDA), nitrik oksit (NO), protein karbonil (PC) düzeylerinin belirlenmesi amacı ile tüm ratlara penektomi uygulanarak vena kava inferiordan kan örneği alındı.

Bulgular: Penil dokuların biyokimyasal değerlendirmesinde Grup 3'teki MDA ve PC seviyeleri Grup 2'e göre anlamlı derecede düşük gözlemlenirken GSH-Px aktiviteleri anlamlı düzeyde yüksek olarak izlendi (sırasıyla P=0.001, P=0.005, P=0.003). Serum analiz sonuçları ise Grup 3'teki MDA ve NO seviyelerini Grup 2'e göre anlamlı derecede düşük olduğunu gösterirken SOD aktivitesini anlamlı düzeyde yüksek olduğunu ortaya koydu (sırasıyla P=0.011, P=0.001, P=0.009).

Sonuç: Bu çalışmada krill yağının; kavernosal dokuda gelişen priapizm ile indüklenen iskemi-reperfüzyon hasarına karşı koruyucu etkinliği biyokimyasal kanıtlara dayanılarak gözlenmiştir.

Anahtar kelimeler: Krill yağı, İskemi, Reperfüzyon, Priapzm

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Ethics Committee Approval: Ethics committee approval was received from local ethic committee (HAYDEK 2015-26).
Etik Kurul Onayı: Çalışma için lokal etik kuruldan etik kurul onayı alınmıştır (HAYDEK 2015-26).

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 5/8/2019
Yayın Tarihi: 08.05.2019

How to cite / Atıf için: Kölükçü E, Uluocak N, Unsal V. Protective effects of krill oil on ischemic reperfusion injury in experimental model of priapism. J Surg Med. 2019;3(5):371-376.

Introduction

Priapism is defined as an ongoing erection lasting longer than 4 hours without sexual stimulation [1]. This term is derived from the Greek god Priapus [2,3]. According to the pathophysiology of priapism, which has an important place in urological emergency practices, is considered in three groups as stuttering (recurrent or intermittent), nonischemic (high-flow or arterial) and ischemic (low-flow or venous-occlusive) priapism. Nonischemic priapism which is not accompanied with findings of ischemia penile tissue, and stuttering priapism, which is characterized by painful erection periods constitute only 5% of all patients with priapism [1]. It is estimated that the annual incidence of ischemic priapism, also known as a compartment syndrome, is between 0.3 and 1.5 per 100,000 men, which constitutes 95% of cases diagnosed with priapism [4].

In ischemic priapism tissue blood supply becomes deficient and stasis occurs in the corpus cavernosum. This circulatory disorder occurring in the cavernous tissues results in the development of an acidic, anoxic, hypercarbia and glucopenic environment [4,5]. Ischemic priapism is one of the most important urological emergencies affecting the sexual life of couples in the short and long term. Application of treatment algorithms without wasting time is very critical in preventing tissue damage. Otherwise, cavernosal smooth muscle necrosis, corporal fibrosis and erectile dysfunction develop in patients with ischemic priapism [6]. The first administration involves aspiration and installation of the most common phenylephrine, α-adrenergic agonists, during an attempt to increase smooth muscle tone. Although there is no universally accepted treatment algorithm, surgical approaches are considered in patients who did not respond to treatment or seek medical help at a very late stage of the disease [7].

With the termination of ischemic priapism, the tissues are reperfused, but a very complex chain of reactions, called ischemia-reperfusion injury becomes manifest. Reperfusion carries a vital importance for ischemic tissues. However, this situation leads to a number of metabolic effects that, paradoxically, only lead to more serious consequences than ischemia-induced damage. In tissues that are deprived of high energy during ischemic period; alteration in electrolyte content results in a decrease in antioxidant enzyme level, increase in the production of proinflammatory cytokines and leukocyte adhesion molecules, and leads to the formation of a vulnerable environment against damage that may occur during reperfusion period [8]. In fact, with reperfusion of ischemic tissue, molecular oxygen enters into cells and initiates chain reactions where rapidly emerging reactive oxygen species play a main modulatory role in the induction of ischemia-reperfusion injury which damages important molecules as membrane lipids, genetic material, intracellular structural and functional proteins [9]. When we look at previous studies, it has been observed that many pharmacological agents have been investigated in order to protect the tissues from ischemia-reperfusion injury or to minimize the damage.

Krill oil is obtained from the Antarctic krill (Euphausia superba) which is a rich source of long-chain fatty acids [10]. Krill oil contains high concentrations of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA); there are many important functions such as preservation of membrane structures, modulating of an inflammatory response, and regulation of fetal development [10,11]. In addition, Krill oil also contains very effective antioxidants such as astaxanthin, vitamins E and A [12]. Thanks to all of these features, krill oil has been investigated in many different fields ranging from cardiovascular diseases to central nervous system disorders.

In this study, we aimed to determine the effect of krill oil against priapism induced ischemia-reperfusion injury in cavernosal tissue was observed based on biochemical evidence. To the best of our knowledge this is the first experimental study investigating the effects of krill oil on rat priapism model.

Materials and methods

Animals

A total of twenty-four 10 week-old-male Wistar-Albino rats weighing between 220 and 450 g were used in our study. The protocol of the experimental study were performed in compliance with the provision of 1986 Strasbourg Universal Declaration on Animal Welfare and approved by the local ethical committee (HAYDEK 2015-26). The rats were maintained in standard solid cages as three rats for each cage under 12 hours of light and dark cycle and, at a constant temperature of 22 ° C.

Experimental design

All surgical procedures were performed under an appropriate depth of anesthesia. To this end an anesthetic agent xylazine hydrochloride with sedative and muscle relaxation effects (Rompun 2%, Bayer, Turkey) was administered through the intraperitoneal route at a dose of 10mg/kg. Also ketamine hydrochloride with dissociative anesthetic effectiveness was also given via intraperitoneal route a dose of 50-60 mg/kg (Alfamine 10%, Ege Vet, Turkey). Priapism in experimental animals was performed according to the method described by Sanli et al [13]. Vacuum the erection was performed with the tip of the 5 cc syringes. Then 2 mm wide constriction bands prepared from 16 Fr Foley catheters were tied around the base of the rat's penis to sustain erection. Total of 24 rats were randomly divided into three groups with eight rats in each group. Group 1 was assigned as the control group. The rats only penectomy was performed and 3 cc blood samples were withdrawn form inferior vena cava to determine the baseline levels of protein carbonyl (PC), malondialdehid (MDA), nitric oxide (NO), glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) in systemic circulation, and cavernosal tissues. Group 2: Priapism was induced in compliance with the above-indicated priapism model. At the end of the first hour priapism was terminated and penile reperfusion was applied for 30 minutes [13,14]. Then penectomy were performed, and 3 cc blood samples were withdrawn from inferior vena cava of the rats to study the same parameters. The rats in these two groups were given tap water and standard chow pellets. Group 3: The same feeding procedure was applied to the experimental animals but supplemented with krill oil for one month. Krill oil (SuperbaTM Krill Oil, Aker Biomarine, Norway) was given to experimental rats at a dose of 0.5 ml-100g/kg [15]. In this group, the same ischemia-reperfusion model was applied to the second group. Penile and

blood samples were analyzed using the same procedure as in the other groups (Figure 1).

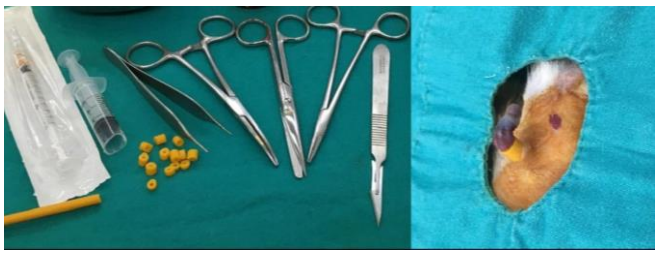

Figure 1: Priapism induced in rat model

Biochemical evaluations

Measurement of MDA levels

The reaction of the lipid peroxidation product MDA with thiobarbituric acid (TBA) yields a pink color at a wavelength of 532 nm during spectrophotometry [16].

Determination of SOD activity

Experimental principle is that the superoxide present in the xanthine/xanthine oxidase system is a byproduct of the reduction of nitro blue tetrazolium (NBT). This complex gives maximum absorbance at 560 nm in the spectrophotometer [17].

Determination of GSH-Px activity

The method is based on the measurement of GSH-Px activity and the reduction of absorbance at 340 nm due to the removal of NADPH present in the medium. In the experimental environment, there were reduced glutathione, sodium azide, glutathione reductase, NADPH and H2O2 as the last substrate [18].

Determination of PC levels

Based on the principle that the groups would react with 2.4-dinitrophenylhydrazine to form 2.4 dinitrophenylhydrazone, levels of PC group were measured spectrophotometrically at 370 nm [19].

Determination of NO levels

The determination of nitrite/nitrate, the stable end product of NO radicals, is often used as a measure of NO production. The total NO concentration is generally determined as the sum of nitrite and nitrate concentrations. The amounts of nitrite and nitrate were determined by spectrophotometric analysis at 540 nm with the Griess reaction [20,21].

Statistical analysis

The calculations were made by statistical software (IBM SPSS Statistics 21, SPSS inc., an IBM Co., Somers, NY). Data were shown as means±standard deviation, and Kruskal-Wallis test was used for analysis. If statistically significant results were obtained, then the Mann-Whitney U test was employed for comparisons of differences between the two independent groups. $P<0.05$ was accepted as the level of statistically significant.

Results

The results of biochemical analysis in penile tissues are presented in Table 1. Experimental animals were compared, and higher MDA, PC and NO values found in Group 2 relative to Group 1 without any statistically significant intergroup difference ($P>0.05$). The mean MDA and PC values in Group 3 were measured as 42.41 (8.4) nmol/g wet tissue and 2.15 (0.56) nmol/µg protein respectively. Although both values were considered to be low compared to Group 2 ($P=0.001$, $P=0.005$ respectively). On the other hand, no statistically significant correlation was found between Groups 2 and 3 when NO levels were evaluated in penile tissue samples ($P=0.12$). When the antioxidant enzyme activities of the experimental animals in Group 3 were investigated, SOD and GSH-Px values were measured as U/mg protein 0.15 (0.03) U/mg and 18.69 (7.22) U/mg protein respectively. GSH-Px value significantly increased relative to the other Groups 1 and 2 ($P=0.01$, $P=0.003$ respectively). No statistically significant correlation was found between the other two groups in terms of SOD values ($P= 0.14$).

Results of serum biochemical analysis are presented in Table 2. Accordingly, the mean NO value in the experimental animals in Group 3 was 71.14 (12.53) µmol/L which was significantly lower than Group 2 ($P=0.001$). The mean SOD and GSH-Px values in Group 3 were measured as 11.75 (1.24) U/ml and 760.87 (333.9) U/L respectively. Although both values were higher when compared with the other two groups, only SOD values were found to be statistically significantly higher ($P=0.009$). On the other hand, the mean MDA and PC values of the experimental animals in Group 3 were 1.65 (0.43) nmol/g and 712.1 (103.69) nmol/m, respectively. Although both values were considered to be low compared to Group 2, only mean MDA value was statistically significantly lower in Group 3 ($P=0.011$). On the other hand, no statistically significant relationship was found between the control group and the ischemia-reperfusion group in both serum and tissue biochemical examinations. This condition is thought to be related to the short duration of ischemia-reperfusion injury.

Table 1: Biochemical analysis results and comparisons in penile tissues of all groups

Groups (n:8)	SOD (U/mg protein)	GSH-Px (U/mg protein)	MDA (nmol/g wet tissue)	PC (nmol/µg protein)	NO (µmol/g wet tissue)
Group 1	0.11 (0.03)	7.15 (2.19)	53.49 (6.59)	3.87 (0.59)	3.17 (0.85)
Group 2	0.16 (0.03) [a]	6.75 (2.01)	69.42 (11.88)	4.21 (1.1)	3.62 (0.42)
Group 3	0.15 (0.03)	18.69 (7.22) [b]	42.41 (8.4) [c]	2.15 (0.56) [d]	5.61 (3.12) [e]

SOD: Superoxide dismutase, GSH-Px: Glutathione peroxidase MDA: Malonyldialdehyde, PC: Protein carbonyl, NO: Nitric oxide

The paired comparison of biomarkers in tissue between the study groups

a) In comparison between Group 1, and Group 2 $P=0.044$.
b) In comparison between Group 1, and Group 3 $P=0.01$ and between Group 2, and Group 3 $P=0.003$.
c) In comparison between Group 2, and Group 3 $P=0.001$.
d) In comparison between Group 1, and Group 3 $P=0.007$, and Group 2 and Group 3 $P=0.005$.
e) In comparison between Group 1, and Group 3 $P=0.037$.
A statistically significant difference was not found between other groups.

Table 2: The biochemical analysis results of all groups in serum and comparisons between the groups

Groups N: 8	SOD (U/ml)	GSH-Px (U/L)	MDA (µmol/l)	PC (nmol/ml)	NO (µmol/L)
Group-1	8.34 (1.34)	563.26 (153.99)	2.85 (0.74)	1098.37 (147.9)	325.83 (99.06)
Group-2	8.37 (1.09)	451.01 (97.11)	3.05 (0.94)	1058.28 (454.6)	432.74 (37.39)
Group-3	11.75 (1.24) [a]	760.87 (333.9)	1.65 (0.43) [b]	712.1 (103.69) [c]	71.14 (12.53) [d]

SOD: Superoxide dismutase, GSH-Px: Glutathione peroxidase MDA: Malonyldialdehyde, PC: Protein carbonyl, NO: Nitric oxide

The paired comparison of biomarkers in serum between the study groups

a) In comparison between Group 1, and Group 3 $P=0.007$ and between Group 2 and Group 3 $P=0.009$.
b) In comparison between Group 1, and Group 3 $P=0.02$, and between Group 2 and Group 3 $P=0.011$.
c) In comparison between Groups 1, and Group 3 $P=0.018$.
d) In comparison between Groups 2, and Group 3 $P=0.001$.
A statistically significant difference was not found between other groups.

Discussion

Ischemic priapism is a pathological condition requiring urgent intervention characterized by prolonged, painful and rigid erection. When evaluated clinically, the corpus cavernosum is completely rigid and painful, while the corpus spongiosum and glans penis are affected mildly or not at all [4]. Penile smooth muscle plays an effective role in both formation of tumescence,

and detumescence. The smooth muscles relax during erection which is the functional and active state of the penis. In case of detumescence this process is reversed. In dysregulation of penile smooth muscle functions, the tendency for relaxation increases which predisposes to ischemic priapism [1,4]. In only 40% of the diagnosed patients' history of etiologic factors such as hematological disorder, malignancy, neurological disease, or antihypertensive, psychotropic, vasoactive drug use have been detected [7].

Histopathological evaluations using electron microscopy to reveal histological changes in ischemic priapism; have shown that the destructive changes in the cavernosal smooth muscle manifest themselves as interstitial edema after 12 hours. At the end of the 48th hour, thrombus is evident in sinusoidal cavities and its presence in fibroblast-like cells indicates that smooth muscle necrosis is taking its effect [22]. Fibrosis that develops in smooth muscle directly plays a role in the emergence of erectile dysfunction, which is common in priapism patients. Patients presenting with a sustained erection without detumescence interval for longer than 4 hours should be treated immediately. Early intervention in ischemic priapism has a critical importance for functional recovery. Permanent erectile dysfunction may develop in 90% of the cases with priapism that persists for more than 24 hours [6]. On the other hand, it is evident that the majority of patients with priapism is very reluctant to resort to healthcare services because of predominantly felt embarrassment, and shame [23]. In parallel with the prolonged priapism period, an intense fibrosis occurs in the corpus cavernosum. It is known that this situation complicates implantation of penile prosthesis to be performed in the future [4]. Implantation of penile prosthesis is recommended for patients presenting with priapism for more than 36 hours according to current urology guidelines [14,23]. On the other hand untreated or prolonged priapism may present with severe clinical conditions, such as penile gangrene [24].

Ischemia-reperfusion injury is a common clinical entity that may develop as a consequence of many conditions including cerebrovascular accident, hemorrhagic shock, medical or surgical interventions as thrombolytic therapy, coronary angioplasty, and transplantation [9]. Similarly, ischemic reperfusion injury is seen with the treatment of compartment syndrome in ischemic priapism. With the reperfusion of the tissue, paradoxically, ischemia-reperfusion injury depending on the degree of the ischemic injury leads to severe tissue damage [5]. Ischemia is the state in which oxygen (O2) and other substances cannot reach the tissues adequately as a result of impairment of tissue perfusion. Along with hypoxia that occurs after ischemia, the energy level in the cell decreases. The increase in glycolytic rate and ATP consumption directly reduces the cytosolic pH due to the liberation of hydrogen (H+) from the damaged lysosomes. This results in an increase in cytosolic sodium (Na+) and calcium (Ca+2) concentrations and inhibit the activation of the sodium-potassium ATPase (Na-K ATPase) pump. Increase in cytosolic Ca+2 concentration activates hydrolases such as proteases and phospholipases. Hydrolases further enhance the destructive process. Increased intracellular Na+ causes an increase in osmotic pressure and contributes to the degradation of the plasma membrane [25]. Antioxidant enzyme formation decreases and the number of leukocyte adhesion molecules of proinflammatory cytokines increase with the changing ion concentration during the ischemic period. This condition makes the tissue more sensitive to damage during reperfusion period [26,27]. Though a small amount of free radicals are produced during ischemia following reoxygenization, in the reperfusion phase, much greater amounts of free radicals are produced and increase the severity of destructive changes. Following ischemia, inflammatory response begins with reperfusion. This inflammatory process involves endothelial cells, macrophages, neutrophils, platelets, lymphocytes, parenchymal cells as well as non-cellular complement system, blood clotting cascade, free radicals, NO, proinflammatory and anti-inflammatory cytokines, elements, mediators and thus the microvascular perfusion is disrupted [5,8,26,28].

Irreversible cellular damage occurs due to the destructive effects of oxidative stress which leads to an increase in MDA, one of the end products of lipid peroxidation [16]. In a study, Evliyaoglu et al. [29] reported that MDA levels increased in all experimental animals in which priapism were induced compared to the control group. Similar results have been obtained in many studies using ischemia reperfusion model [30]. In our study, MDA levels increased in both penile tissues and serum samples in rats with ischemia-reperfusion injury. But this was not statistically significant. On the other hand, protein metabolism is very adversely affected, as lipids, and also the level of a protein oxidation product, PC increases in ischemia-reperfusion injury [31]. In our study, though not statistically significant, increased tissue PC levels in rats with ischemia-reperfusion injury were detected. NO, is synthesized in smooth muscle, endothelial cells and many other cells as a result of the oxidation of guanidino nitrogen of the amino acid L-arginine via nitric oxide synthase. In low concentrations, decreased concentrations of NO plays a role in important physiological functions, but in cases where tissues are exposed to unaccustomed conditions as oxidative stress, concentrations of NO climb to higher levels and rapidly react with superoxide radicals leading to rapid the formation of peroxinitrite [20,21,32]. In a study, Ozkan et al. [33] reported that NO levels increased in all experimental animals in which intestinal ischemia-reperfusion was induced compared to the control group. In our study, though not statistically significant, NO levels in the penile tissue and serum samples of rats exposed to ischemia-reperfusion injury increased compared to the control group. The superoxide radicals produced in destructive conditions are reduced by an antioxidant enzyme, SOD to hydrogen peroxide. This reduced hydrogen peroxide is converted into water and oxygen by another antioxidant enzyme called GSH-Px [34]. In our study, positive changes were detected that antioxidant enzyme in Group 3 than in Group 2.

Krill in Norwegian means fry fish. It is a shrimp-like, red-crusted small sea creature that lives in the cold waters of the Antarctic Ocean. These creatures do not consume heavy metals and pollutants as opposed to other fish [35,36]. Krill oil is an important phospholipid which differs from other oil types with its omega-3 and astaxanthin content. Of the long-chain fatty acids found in krill oil, a large part of the omega-3 fatty acid is in the form of phospholipid such as phosphatidylcholine and

phosphatidylethanolamine. Omega-3 bound to phospholipids is soluble in water. Thanks to its phospholipid binding, omega-3 in krill oil is easily absorbed and used by the human body. Because of its bioavailability, krill oil is shown as a top source of omega-3 [37]. Omega-3 fatty acids compete to arachidonic acid which is an omega-6 fatty acid. Arachidonic acid is converted into prostaglandin H2 (PGH2) via some enzymatic pathways. PGH2 is converted to thromboxane A2, a pro-inflammatory lipid through thromboxane synthase. When the arachidonic acid is replaced by omega-3 fatty acids, this inflammatory effect decreases. For this reason, omega-3 fatty acids are called anti-inflammatory compounds. Omega 3 fatty acids are metabolized in the human body with EPA and DHA. In these molecules, there is evidence that they have many different positive effects on blood lipid profile, central nervous system, and regulation of immune reaction steps [11,36,38]. Krill oil also contains a very powerful natural antioxidant called Astaxanthin, which gives it its red color. Literature information has been analyzed about astaxanthin in previous years, many useful biologic effects of astaxanthin including suppression of carcinogenesis in some cancer types as bladder and colon cancer, prevention of cardiovascular diseases, protection against free radicals, reinforcement, and modulation of immunologic system may be seen [39-44].

In recent years, the protective effects of krill oil on human body have been the subject of many researches. For example in their multicenter study, Bunea et al. [45] evaluated krill oil in 120 patients with hyperlipidemia, and showed that krill oil contributed very favorably to the lipid profiles by reducing total cholesterol, LDL, and triglyceride levels and increasing HDL levels. In an experimental study, Ierna et al. [46] reported that enriching the diet with krill oil exerted very beneficial effects on the clinical and histopathological findings of inflammatory arthritis. Similarly, Deutsch [47] revealed that krill oil significantly inhibited inflammation and alleviated symptoms of arthritis in a short-term treatment. Çiftçi and Gevrek [48] evaluated effectiveness of krill oil in a rat model where they induced ischemia-reperfusion injury in skeletal muscle. In this study, they concluded that krill oil provided a strong protection against ischemia-reperfusion injury based on their both histological and biochemical evaluations. Gamoh [49] observed the effects of krill-derived phospholipids on adult rat memory, and found that lipid peroxidation was suppressed in plasma and brain tissues in the krill-derived phospholipids group. Similarly, in an animal experimental study, Mellouk et al. [50] detected that krill oil decreased oxidative stress.

Study limitations

Establishment of the study on biochemical basis and no histopathological examination of penile tissue samples.

Conclusion

We can say that priapism induced oxidative damage, adverse effects at penile tissue. This leads to sexual dysfunction that may affect patients presenting with priapism their lifetimes. Based on our literature review, our study was the first study to show the effectiveness of krill oil in the experimental priapism model and also it indicated that ischemic priapism plays an important role in the alleviation of ischemia reperfusion injury. However, we think that our study results should be supported with further prospective more randomized and controlled studies.

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The National Library of Medicine (NLM) citation style guide is used in this paper.
Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: htt*P*=//www.nlm.nih.gov/citingmedicine