

Essential Oxygen Oil for Treatment of Sport-Related Injuries

John B. Leslie¹, Robert B. Raffa², Robert Taylor Jr.^{3,*}, Aaron Tabor⁴, Ernesto Muniz⁵, Srinivas Nalamachu⁶, Joseph V. Pergolizzi Jr.⁷

¹Mayo Medical School – Arizona Campus, Scottsdale, Arizona, USA

¹University of Arizona Health Sciences Center, Tucson, Arizona, USA

²Department of Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, PA, USA

³NEMA Research Inc., Naples, FL, USA

⁴Physicians Laboratories Inc., Kernersville, NC, USA

⁵Kirax Corporation, Bonita Springs, FL, USA

⁶International Clinical Research Institute and Pain Management Institute, Overland Park, KS, USA

⁷Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA, USA

*Corresponding author: robert.taylor.phd@gmail.com

Received January 01, 2013; Revised February 05, 2013; Accepted March 22, 2013

Abstract Sport-related injuries to amateur and professional athletes are responsible for about 10% of emergency department visits and for acute and chronic treatment in a variety of other healthcare settings. Many sport-related injuries involve muscle and joint-tissues such as tendons and ligaments. Clinicians may be understandably reticent to treat such musculoskeletal injuries with systemic analgesics and might opt for topical analgesics for localized rather than systemic pain relief. A novel product, essential oxygen oil (OxyRub™ essential oxygen oil, CreoMed, Naples, FL), has been previously clinically tested in a variety of non-athlete patients. It has been available as an over-the-counter natural massage or comfort oil in Europe for over a decade and has recently become available in the United States. This paper reviews several pilot trials conducted in Europe (and other reports) involving the use of this topical analgesic in top athletes. Competitive athletes are frequently injured, sometimes severely, and typically cope well with pain. Thus, this population is an important one for the evaluation of a topical analgesic product. The essential oxygen oil worked well and was well tolerated.

Keywords: *essential oxygen oil, pain oil, topical analgesic, sports injury*

1. Introduction

In 2001, 29.7 million injured persons were treated in an emergency department [1]. About 10% of the visits resulted from sports-related injuries, particularly in young people (ages 5 to 24 years) [2]. About half of all American school-aged children (roughly 30 million) are involved in some kind of organized athletic activity, and pediatric sports injuries are common [3]. However, sports injuries occur in people of all ages. For example, in a 13-year study of patients ≥ 65 years of age ($n=2,635$), the number of sports injuries in 2008 was double that of sports injuries in the same age population in 1994. The most common injuries were falls (69%), fractures (27%), ligament injuries (19%), and injuries of muscles or tendons (6%) [4]. In adolescents, the most common injuries were torn muscles (35%), knee problems (30%), torn ligaments (19%), and injuries involving the spine (3%) or head (2%) [5]. Competitive and professional athletes are also at risk for injuries, [6,7,8] and are often under pressure to recover quickly and return to competition.

Sedentary lifestyles contribute to an increase in morbidity [9], obesity [10], and mortality [11,12,13]. Growing awareness of these dangers among clinicians, the

media, and the general public has prompted health-conscious individuals to embark on exercise regimens ranging from the sensible to the extreme. The rate of sports injury – even among recreational joggers and walkers – is not unsubstantial, with 17% of such individuals reporting at least one lower-extremity injury in the preceding year [14]. In a survey of physically active American adults ($n=6,313$, ages 20 to 85 years), about a quarter reported a musculoskeletal injury during the preceding year and of those, 80% were related to exercise [15]. Many newly-active populations include: obese patients trying to lose weight, “weekend warriors,” health-conscious middle-aged regular exercisers, children in organized sports, and older individuals in cardiac or other rehab programs. Thus, sports injuries are no longer sustained only by professional athletes, but also by pediatric, geriatric, obese and other patients, some of which have comorbidities.

Topical NSAIDs are an effective treatment for elderly patients managing chronic pain from osteoarthritis [16] and may be useful for acute injury in this setting. They do not appear to be associated with the same adverse events as systemic NSAIDs, but there is little evidence that they improve muscle function following sports injury [17]. Over the counter capsaicin topical products are effective

in treating chronic pain associated with osteoarthritis, but there are no data available supporting the use of such products for acute sports injuries [17]. However, such products are available without a prescription and are widely used as such, presumably with some degree of efficacy. Unfortunately, NSAIDs are also associated with significant adverse effects, particularly in susceptible populations. A novel product, essential oxygen oil (OxyRub™ essential oxygen oil, CreoMed, Naples, FL), has been clinically tested in a variety of non-athlete patients [18,19]. It has been available as an over-the-counter natural massage or comfort oil in Europe for over a decade and has recently become available in the United States.

Although the exact mechanism of action remains unknown, vegetable oils saturated with oxygen through peroxidation (essential oxygen oil) mimic the function of two endogenous enzymes, superoxide dismutase (SOD) and catalase [20]. SOD acts as a scavenger of free radicals; catalase converts hydrogen peroxide in the body to oxygen and water. Together, SOD and catalase combat the toxic action of reactive oxygen species (free radical attack) and hydrogen peroxide. See Figure 1. The oxygen in the essential oxygen oil is transported to the skin by means of a liquid carrier, which works with the skin's natural moisture-binding ingredients to moisturize and soothe the skin, promoting a feeling of comfort. It should be noted that essential oxygen oil feels oily upon contact with the skin, an unusual attribute in topical and transdermal products.

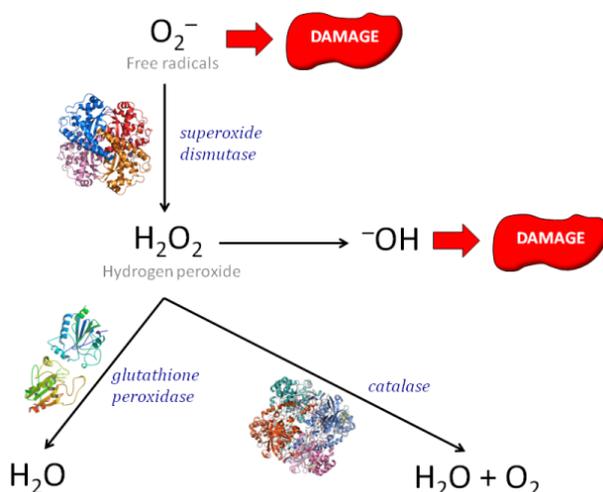


Figure 1. Superoxide dismutase and catalase mechanism of action

2. Materials and Methods

This paper presents the results from several pilot studies that evaluate the role of essential oxygen oil in sports medicine, each of which explored the use of essential oxygen oil as a topical product for injuries sustained by elite athletes. The formulation of the product was the same in all studies. The studies varied in design, patient populations, and endpoints.

3. Results

3.1. Colombes Study: Essential Oxygen Oil in Sports Massage

An open-label comparative study evaluated the standard product used by physiotherapists at an athletic club (Bioes Neutral Cream) and essential oxygen oil. A double-blind study was not possible owing to inherent differences in product texture and appearance. At enrollment, all subjects had been regularly massaged by physiotherapists using the facility's standard product. For a period of one to eight weeks, the physiotherapist continued to massage them regularly, but using only essential oxygen oil. The physiotherapist determined the amount of essential oil to be used. Massages lasted about 30 minutes and were administered by the subject's regular physiotherapist to avoid bias related to massage technique. After both products were used, the athletes and physiotherapists were surveyed about the products' immediate effects, effects the next day or day after, safety, and overall appeal.

3.1.1. Results

Twenty subjects from the Racing Club in Colombes, France enrolled in the study. They were all athletes, four of whom were rugby players. In terms of how well essential oil penetrated the skin, 60% of subjects said it was "good" or "excellent," while 40% said it was "fair." Fifty-five percent of subjects found that essential oil offered a considerable beneficial effect on vascularization, while 40% found it "fair" in this regard and 5% (n=1) said it had no benefits. Relaxation, assessed at the end of the massage, was evaluated to be "good" or "excellent" by 55% of patients. Those who found the product improved vascularization were more likely to report positive results for relaxation, suggesting an association between vascularization and relaxation.

In terms of results the next day and day after, 75% considered their improvement was "good" or "excellent." Ninety percent of subjects noted an improvement in their recovery with essential oxygen oil.

In terms of safety, the product was considered to be "good" or "excellent" by 90% of subjects and physiotherapist. One skin reaction was reported by an athlete, which resolved spontaneously. Although contact irritations with the hands are not unusual, no physiotherapist reported a skin reaction with either product.

3.1.2. Discussion

The most important endpoint of this study in terms of sports medicine is the effect of products on recovery time, both immediate and over the next couple of days. A vast majority of subjects (90%) felt that essential oxygen oil resulted in improved recovery versus the control product. Of this group, 75% judged the improvement to be significant, that is, "good" or "excellent." Ten percent felt there was no difference (n=2); one of these subjects experienced a skin reaction and the other was a high-level athlete who was frequently massaged. The majority of subjects (60%) thought the essential oxygen oil penetrated the skin well. It is possible that the oily quality of this product may make it particularly well suited to massage therapy. Vascularization and relaxation appear to be related in terms of how patients responded. Essential oxygen oil was shown to be more effective and equally

safe when compared to Bioes cream in sports massage of athletes.

3.2. Nimes Study: Hemarthrosis and Hematoma in Athletes

This study had two objectives: to assess the potential value of essential oxygen in sport-related injuries (traumatology) and to evaluate if the use of essential oxygen oil before and after sports-related physical exertion could improve athletic performance.

For sports injuries, the study focused on two frequent types of trauma, namely articular extravasation (hemarthrosis) following knee sprain, and hematoma resulting from impact to a muscle. In the case of hemarthrosis, a compress soaked in essential oxygen oil was applied to the injury in the first days after the injury; the compress was held in place by a loose elastic bandage. Compresses were changed or re-soaked daily and patients were asked to walk with the aid of crutches to avoid use of the injured limb.

For sports performance, the study recorded the number of applications of essential oil, variables regarding time of application (before and after training as well as before and after a competition). Subjects were asked about their impressions of the product and its possible effects on recovery and performance.

3.2.1. Results

A total of 113 high-level athletes involved in a variety of sports enrolled in this study (see Table 1). The mean duration of essential oxygen oil application was four to five days. Subjects were surveyed after using essential oxygen oil. Eighty-nine percent reported that after using essential oxygen oil they were able to resume physical activity earlier following an injury than if they had not used essential oxygen oil. Eighty-one percent found that essential oxygen oil offered rapid resolution of stiffness. In this survey, not all questions were applicable to every athlete, resulting in a relatively high number of non-responses. Fifty-five percent reported reduction in sensitivity to pressure with essential oxygen oil, although 41% did not respond, likely because it was not applicable to them. Negative responses were very low (always <10%) and in some cases zero. See Table 2.

Table 1. Athlete types in the Nimes study

Subject #	Description
10	Weightlifters
2	Skiers
3	Equestrians
14	Swimmers
1	Gymnast
6	Wrestlers
4	Members of French Senior Athletics Team in training at Font-Romeau
13	Athletes from the Sports-Study section at Font-Romeau Secondary School
12	Rugby players
17	Cross-country skiers
4	Professional soccer players
27	Athletes and trainees from the Nimes Olympic Team

The use of essential oxygen oil in this population resulted in a decrease in hematoma within four to five days; in many cases, the hematoma completely resolved in that time. Patellar volume, appearance of yellowish periarticular or pretibial zones, and more rapid and

painless reacquisition of forced-flexion articular mobility were observed.

Table 2. Athletes were surveyed about how essential oxygen oil performed with respect to their injury

Parameter	Positive n (%)	Negative n (%)	Not Specified or Not Applicable n (%)
Pressure sensitivity	62 (55)	5 (4)	46 (41)
Resolution of cramps (if applicable)	32 (28)	0 (0)	81 (72)
More or less rapid resolution of stiffness	92 (81)	0 (0)	21 (19)
Improvement when starting physical activity without warm-up	40 (35)	1 (1)	72 (64)
Earlier resumption of physical activity after injury	101 (89)	4 (4)	8 (7)

3.2.2. Discussion

The study survey included a very high number of non-responses, some of which may be attributed to questions that did not apply to a particular athlete during the study period. Some respondents put a question mark on the form so it is likely some subjects did not understand certain question(s). Since the results were obtained using a written survey, there was no opportunity to follow up individually with the athletes to clarify such omissions. The very low number of negative responses seems to indicate that response to essential oxygen oil was positive, even if athletes left some questions unanswered.

The most important finding in this study was that essential oxygen oil allowed these high-level athletes to resume their sports activities more rapidly after injury. This is an important consideration for competitive, professional, and top athletes who want to quickly get “back to the field.” Furthermore, this study included 113 subjects participating in a variety of sports, suggesting that the rapid recovery associated with essential oxygen oil use applies to a broad spectrum of athletes. This would suggest that essential oxygen oil can be recommended generally to athletes for rapid recovery following sports injury.

3.3. Fontainebleau Study: Essential Oxygen Oil in Sports Massage with Emphasis on Hematoma

The purpose of this study was to evaluate the use of essential oxygen oil in post-competition massage and treatment of hematomas in consecutive high-level athletes participating in various sports. Essential oxygen oil was used in massage therapy in these athletes. In the case of hematoma, essential oxygen oil was applied by compress twice daily (morning and evening). The compress was soaked in essential oxygen oil, placed over the hematoma, covered with a sheet of paper or plastic, and then secured by a bandage. Compresses were used as many days as needed, typically about five days.

3.3.1. Results

A total of 35 athletes were included in the study with a variety of sports-related diagnoses. All patients were treated following their participation in a competitive

sports event. Six patients had hematomas, two of which were considered major.

Hematomas resolved completely after four days of treatment. All hematomas in this study followed the same clinical course with essential oxygen oil compresses:

Day 1: Hematoma (of which many were very deep) became more superficial, observed as bluish traces at the cutaneous level. Functional improvement in terms of muscle contraction and stretching was observed.

Day 2: Hematoma continued to become more superficial with clear functional improvement. Training could be resumed after warm-up.

Day 3: Functional capacity was completely restored. Superficial traces of the hematoma were still visible in some cases.

Days 4-5: All traces of hematoma disappeared.

3.3.2. Discussion

Hematoma, particularly deep and incapacitating hematoma, is a common injury in competitive athletes and was present in 17% of subjects in this study. Hematomas resolved completely over a course of four to five days using essential oil compresses worn all day and night. Functional improvement occurred by day three in tandem with diffusion of the hematoma, which allowed for rapid resumption of athletic activity. Anecdotally, one subject in this study was a boxer who had a hematoma and total functional incapacity at the brachial biceps; after three days of treatment, he not only resumed boxing, he won a final in the Military World Cup competition. Based on results in this study, hematomas can be safely and effectively treated using an essential oxygen oil compress over a course of about five days.

In terms of muscle contracture, results with essential oxygen oil were modest and comparable to results obtained historically using typical ointments and creams. Essential oxygen oil allowed these athletes to resume athletic activity quickly, was well tolerated, and improved function in one day in subjects suffering deep hematoma.

This study had a higher rate of adverse events than other essential oxygen oils reported in this paper, but most were mild skin irritation or erythema, which resolved spontaneously within 24 hours. It is not clear why the rate of adverse events was higher in this study than other studies.

3.4. Kickboxing Study: Pain Relief

Kickboxing, a combination of English boxing and karate, is growing in popularity and is associated with frequent muscular trauma, contusions, and inflammation. Not surprisingly, painful injuries are frequently reported by kickboxers. This study used essential oxygen oil for treating kickboxing injuries in a series of competitive kickboxers.

Injuries appropriate for essential oxygen oil would be treated by applying an oil-soaked compress to the injured area every night and rubbing essential oxygen oil topically into the affected area three times a day. Kickboxers were treated for four days and training schedules were not interrupted.

Following that study, another five injured kickboxers were subjected to the same course of treatment except they were required to stop their training schedule during treatment.

3.4.1. Results

In the first phase of the study, 11 kickboxing patients were enrolled, six of whom had injuries typical for kickboxers: sprain in metatarsal region (n=1), tibial periostitis (n=3), and pain in metatarsal region (n=2). All six injured kickboxers completed the four-day treatment. A modest improvement in pain relief was reported.

In the second phase, 5 kickboxers were treated for tibial periostitis (n=2) and hematomas (n=3). In the two subjects with tibial periostitis complete resolution of painful symptoms occurred after one week of treatment. In the three subjects with hematoma, diffusion of the hematoma was observed after three days. No adverse events were observed.

3.4.2. Discussion

This small observational study showed modest positive results of essential oxygen oil in those kickboxers who continued training, but even in those athletes who interrupted their training schedule; about a week was required to see improvement in tibial periostitis and three days to observe diffusion of hematoma. Essential oxygen oil was safe and somewhat effective in this population. It must be taken into account that kickboxing is a particularly punishing sport and that these injuries were likely deep and severe. The differences between the group of athletes who suspended training activities and those who continued training suggest that essential oxygen oil works better in injured athletes who take time off from training to facilitate the healing process. Anecdotally, one of the kickboxers in the second phase experienced crippling tibial periostitis, but after two days of essential oil treatment and rest, symptoms were reduced to tolerable pain.

3.5. Case Reports

3.5.1. Rugby

A rugby player presented with mild inflammation of the brachial bicep in the bicephalous groove. Essential oxygen oil was applied topically to the area two to three times a day and on two occasions ultrasound therapy was performed. A placebo was applied on day one with an ultrasound. The essential oxygen oil appeared to have potentiating action with ultrasound and resulted in excellent pain relief. The placebo with ultrasound offered minimal pain relief.

3.5.2. Female Athletes

Two women presented with inflammatory tibial periostitis at the anterior surface attributed to the mechanical contraction of the anterior tibial muscle. Inflammation was determined to have resulted from anterior tibial muscle contraction owing to the alternate wearing of high-heeled shoes and sports shoes. The first woman had new-onset tibial periostitis and was treated with essential oxygen oil rubbed into the area topically two or three times a day. Her symptoms resolved completely within 48 hours. The second woman had earlier-onset symptoms and required 10 days to obtain complete resolution of symptoms. No adverse effects were observed.

3.5.3. Tennis Player

A tennis player presented with tendonitis of the plantar aponeuroses which made walking so difficult that he had given up all athletic activities. Essential oxygen oil was used but was not effective. He was prescribed one month of physiotherapy which involved strapping the plantar arches and deep transverse massage of the aponeuroses. This therapy decreased mechanical inflammation but some residual inflammation was still present. He was advised to apply essential oxygen oil topically onto the affected area two or three times a day. After 48 hours, he reported a noticeable and marked decrease in residual pain. After eight days of using essential oxygen oil, the pain was gone.

3.5.4. Three Sportsmen with Articular Pain

Three athletes (one soccer player, one basketball player and one English boxer) presented with residual articular pain following a prior trauma. All were treated with topical applications of essential oxygen oil two or three times a day, rubbed into the painful area. All three reported complete resolution of pain within one week. No adverse effects were observed.

3.5.5. Judo

Four young athletes practicing competitive judo presented with three different painful sports injuries. Two athletes had been treated for a dislocated elbow, one had a repeated right tibial hematoma, and one had a metacarpal-phalangeal thumb sprain. All four athletes reported pain and were treated with essential oxygen oil to be applied topically and rubbed into the painful area two or three times a day. The hematoma patient found that the hematoma was reduced in a few days. All four patients had less pain and reported that the treatment allowed more rapid resumption of athletic activity.

3.5.6. Ballerina

While ballet is not a sport, for the purposes of this article, the authors wish to include a case report involving a professional ballerina as a type of athlete. A ballerina at the Paris Opera presented with an inflamed Achilles tendon and was told to apply a compress saturated with essential oxygen oil to the painful area every night. She was also advised to rub essential oxygen oil into the affected area two to three times a day. Her professional commitments would not allow her to interrupt her performance schedule. In the first few days, pain decreased gradually. A total of two weeks of treatment was required to obtain complete resolution of pain. It is possible that cessation of her ballet activities might have resulted in more rapid resolution of symptoms.

4. Discussion

Competitive and professional athletes compose an interesting patient population in that such subjects are physically fit but are at elevated risk for trauma. Many of the sports-related injuries observed in these short studies are similar to sports injuries of amateur or pediatric athletes or, indeed, in the general ambulatory population. Since competitive athletes are frequently injured, sometimes severely, and typically cope well with pain,

this population is an important one for the evaluation of a topical analgesic product. These small studies and case reports provide strong evidence that essential oxygen oil provides comfort, improves muscle function, and helps diffuse hematomas and promotes their prompt resolution, and enhances recovery. Adverse events were rare and mild, usually resolving spontaneously within 24 hours.

Large-scale randomized clinical trials are cost prohibitive for natural products, so clinicians cannot depend on the type of scientific data generally available for major pharmaceutical products. While there is a paucity or even absence of evidence in the literature for many natural topic products, the availability and loyal use of these products suggest that many patients find value in them [21]. Although many natural products are marketed without such studies, the absence of evidence should not necessarily be seen as the evidence of absence of benefits. For that reason, clinicians interested in the use of such therapeutic options must rely on smaller studies, case reports, and anecdotal evidence to guide therapeutic choices. Patients are better served when evidence is available to a broad range of healthcare professionals involved in the care of patients with sports injuries.

While these studies focused on injuries sustained by professional and elite athletes, the results are applicable to a wide range of acute injuries, including those that occur when formerly sedentary patients seek a more active lifestyle for reasons of health or weight control. Public health demands that the sedentary population be encouraged to exercise more, but even modest levels of exercise are not devoid of risk. Thus, clinicians must be equipped to manage exercise-related injuries safely and effectively and to continue to promote sensible exercise in both healthy and at-risk patients.

5. Limitation

All comparative studies were open label since it was impossible to obscure differences in product texture and appearance between a neutral cream and the essential oxygen oil product. These studies were relatively small and of short duration. Some studies were observational and lacked a control. It is possible that different results might have occurred with larger patient populations or longer-term studies or with a placebo control. The case reports lack the scientific rigor of a randomized clinical trial.

6. Conclusion

Essential oxygen oil is a topical analgesic product which appears to enhance recovery, support muscle health, provide comfort, and promote the diffusion and resolution of hematoma in several small studies and case reports of elite athletes. Essential oxygen oil is a topical natural product, that can be used in a wide range of acute and chronic pain syndromes and works well in the setting of post-performance massage therapy of competitive and professional athletes. The product worked well for a variety of athletes, including skiers, swimmers, and weightlifters, suggesting that it has a role in sports medicine. As increasing numbers of young and older

patients exercise, clinicians will be increasingly called upon to treat sports injuries in pediatric, geriatric, obese, and comorbid patients. With the transition from “couch potato” to “weekend warrior,” healthcare professionals can expect to treat more sprains, hematomas, and sports injuries. The use of systemic analgesics may not be appropriate in all of these cases and is not without risk. Therefore, the use of essential oxygen oil should be considered in amateur and professional athletes or those involved in other demanding physical activities, such as dancers. Essential oxygen oil was well tolerated in all of these studies and its texture makes it particularly suitable for sports massage. Its soothing effect may make it particularly appealing to those new to exercise. The use of essential oxygen oil prior to exercise or exertion might also be considered, as this product may be particularly well suited for preemptive use in order to deliver oxygen to muscles and promote muscle health.

References.

- [1] Vyrostek SB, Annett JL, Ryan GW. Surveillance for fatal and nonfatal injuries--United States, 2001. Morbidity and mortality weekly report Surveillance summaries (Washington, DC: 2002) 2004 Sep 3; 53(7):1-57.
- [2] Burt C, Overpeck M. Emergency visits for sports-related injuries. *Ann Emerg Med* 2001; 37(3):301-6.
- [3] Adirim TA, Cheng TL. Overview of injuries in the young athlete. *Sports medicine (Auckland, NZ)* 2003; 33(1):75-81.
- [4] Kammerlander C, Braitto M, Kates S, Jeske C, Roth T, Blauth M, Dallapozza C. The Epidemiology of Sports-Related Injuries in Older Adults: A Central European Epidemiologic Study. *Aging Clin Exp Res* 2012 Feb 21.
- [5] Habelt S, Hasler CC, Steinbruck K, Majewski M. Sport injuries in adolescents. *Orthop Rev (Pavia)* 2011 Sep 6; 3(2):e18.
- [6] Gerhardt MB, Romero AA, Silvers HJ, Harris DJ, Watanabe D, Mandelbaum BR. The prevalence of radiographic hip abnormalities in elite soccer players. *Am J Sports Med*, 2012 Mar; 40(3):584-8.
- [7] Volpi P, Taioli E. The Health Profile of Professional Soccer Players: Future Opportunities for Injury Prevention. *J Strength Cond Res*, 2012 Feb 15.
- [8] Westin M, Alicsson M, Werner S. Injury profile of competitive alpine skiers: a five-year cohort study. *Knee Surg Sports Traumatol Arthrosc*, 2012 Feb 19.
- [9] Blair SN, Kampert JB, Kohl HW, 3rd, Barlow CE, Macera CA, Paffenbarger RS, Jr., Gibbons LW. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA*, 1996 Jul 17; 276(3): 205-10.
- [10] Martinez-Gonzalez MA, Martinez JA, Hu FB, Gibney MJ, Kearney J. Physical inactivity, sedentary lifestyle and obesity in the European Union. *International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity*, 1999 Nov; 23(11): 1192-201.
- [11] Blair SN, Kohl HW, 3rd, Paffenbarger RS, Jr., Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA*, 1989 Nov 3; 262(17): 2395-401.
- [12] Blair SN, Kohl HW, 3rd, Barlow CE, Paffenbarger RS, Jr., Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *JAMA*, 1995 Apr 12; 273(14): 1093-8.
- [13] Kohl HW, 3rd, Craig CL, Lambert EV, Inoue S, Alkandari JR, Leetongin G, Kahlmeier S, Lancet Physical Activity Series Working G. The pandemic of physical inactivity: global action for public health. *Lancet*, 2012 Jul 21; 380(9838): 294-305.
- [14] Hootman JM, Macera CA, Ainsworth BE, Martin M, Addy CL, Blair SN. Predictors of lower extremity injury among recreationally active adults. *Clin J Sport Med*, 2002 Mar; 12(2):99-106.
- [15] Hootman JM, Macera CA, Ainsworth BE, Addy CL, Martin M, Blair SN. Epidemiology of musculoskeletal injuries among sedentary and physically active adults. *Med Sci Sports Exerc*, 2002 May; 34(5): 838-44.
- [16] Arnstein PM. Evolution of topical NSAIDs in the guidelines for treatment of osteoarthritis in elderly patients. *Drugs Aging*, 2012 Jul 1; 29(7): 523-31.
- [17] Bolin DJ. Transdermal approaches to pain in sports injury management. *Curr Sports Med Rep*, 2003 Dec; 2(6): 303-9.
- [18] Pergolizzi J, Pappagallo M, Raffa R, Gharibo C, Phillips R, Desjonqueres S, Tabor A. Preliminary observations of a novel topical oil with analgesic properties for treatment of acute and chronic pain syndromes. *Pain Prac*, 2010; 10(3): 201-13.
- [19] Taylor R, Jr., Gan TJ, Raffa RB, Gharibo C, Pappagallo M, Sinclair NR, Fleischer C, Tabor A. A Randomized, Double-Blind Comparison Shows the Addition of Oxygenated Glycerol Triesters to Topical Mentholated Cream for the Treatment of Acute Musculoskeletal Pain Demonstrates Incremental Benefit Over Time. *Pain Pract*, 2012 Feb 5.
- [20] Raffa RB, Pergolizzi JV, Jr. Deciphering the mechanism(s) of action of natural products: analgesic peroxide oil as example. *J Clin Pharm Ther*, 2011 Jun; 36(3): 283-98.
- [21] Toland S. Do sports creams rub the pain away? *New York Times*. 2009 May 6.