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Original Research Article

Systematic Review of the Effects of Alpha Lipoic Acid and Ubiquinone / Coenzyme-Q_{10} Preparations in the Treatment of Avascular Necrosis of the Femoral Head

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Abstract

Osteonecrosis cannot be only described with the presence of a specific disease, but is characterized with modifications of bone remodeling activity, weakening of bone structure, and disruption of bone microarchitecture. Osteonecrosis is a common disease that develops due to some conditions, ultimately leading to an impairment of blood supply to the bone tissue. In this systematic review, the aim was to evaluate the effects of alpha lipoic acid and Coenzyme-Q_{10} (CoQ_{10}) / ubiquinone, known to have an antioxidant effect, in the treatment of osteonecrosis. A comprehensive and systematic literature search of numerous electronic databases was performed. Keywords used to retrieve studies broadly associated with the topic of interest were related to antioxidant and avascular necrosis of the femoral head. Data related to the studies that met the research criteria were recorded. Results were reported with descriptive statistical methodology. Of the 530870 publications, full texts of 4 studies that investigated the effects of antioxidants in the treatment of avascular necrosis of the femoral head were examined. However, none of these articles were level –I clinical trials. Given the researches performed before, it is concluded that the benefits of antioxidant drugs in the treatment of osteonecrosis may be revealed after performing further randomized, placebo-controlled, double-blinded, clinically designed studies including multiple races.

Keywords: Alpha lipoic acid, antioxidant, avascular necrosis of the femoral head, Coenzyme-Q_{10}, osteonecrosis, osteonecrosis femoral head, trauma, ubiquinone

INTRODUCTION

As is well known, osteonecrosis is defined as the cell death originating from the impaired blood supply in bone components such as hematopoietic bone marrow and mineralized bone tissue. Osteonecrosis most frequently affects the femoral head. However, it may be seen in the femoral distal, humeral head, the small bones of the hands and feet or jaw (Chughtai et al., 2017; Kang et al., 2018). It is also one of the common causes of hip arthralgia (Scheret al., 2010).

The main purpose of the treatment of osteonecrosis is to reduce the load on joints and to provide some pain relief. Vasoactive pharmacological agents, such as Naftidrofuryl oxalate (Vietto et al., 2018) and dihydroergotamine (Lynch et al., 2010) can be used for initial treatment of disease to reduce bone marrow pressure. Some studies have suggested that low molecular weight heparin may be beneficial in patients with thrombophilia and impaired fibrinolysis (Cao et al., 2017; Glueck et al., 2005).

In addition, the electromagnetic field and extracorpo-

real shock waves are believed to be beneficial in managing osteonecrosis as the conservative treatment options (Yu et al., 2018). It is also reported that bisphosphonates (Axelsson et al., 2017; Yu et al., 2018) or prostaglandin analogues are also useful in the treatment of osteonecrosis (Pountos and Giannoudis, 2018).

There are three main surgical approaches for the treatment of avascular necrosis of the femoral head that cannot be managed by the medical and conservative treatment options: non-operative treatment, surgical procedures performed to preserve the femoral head, and surgical procedures performed to replace or remove the femoral head surface. Total hip replacement surgery aims to relieve hip pain and improve function by using instruments in both the femoral head and the acetabulum. Surgical procedures such as, hemiarthroplasty, which is performed to increase the circulation in the femoral head by decreasing the intramedullary pressure on the femoral head and neck, total hip replacement, core decompression, and osteotomy are also preferred for the treatment of in patients with osteonecrosis (Mont et al., 1996; Shigemura et al., 2018)

Despite all these treatment options, osteonecrosis may not be treated successfully. Tolerance may sometimes develop to analgesics (Yilmaz and Ulugol, 2009), a pharmacological treatment modality, thereby diseases cannot be treated with pharmacological options or invasive techniques. Although there are innovative medical treatment options, progress in pharmacotherapy has been limited (Furlan et al., 2017).

This may result in a significant decrease in the qualityof patients' life and place an economic burden on healthcare systems.

Therefore, researchers continue to focus on novel drug discovery. Of these drug researches, the ones on preparations such as lipoic acid (Lu andLi, 2012) and ubiquinone / coenzyme-Q_{10} (CoQ_{10}) (Kalyan et al., 2014; Komurcu et al, 2014), which play a significant role in mitochondrial dehydrogenase reactions, have gained momentum.

Lipoate, or its reduced form, dihydrolipoate, reacts with reactive oxygen species such as superoxide radicals, hydroxyl radicals, hypochlorous acid, peroxyl radicals, and singlet oxygen. It also protects membranes by interacting with vitamin C and glutathione, which may also recycle vitamin E. Lipoic acid administration has been believed to be beneficial in some oxidative stress models such as ischemia-reperfusion injury, diabetes, cataract formation, HIV activation, neurodegeneration, and radiation injury. In addition, lipoate can function as a redox regulator of proteins such as myoglobin, prolactin, thioredoxin and NF-kappa B transcription factor (Packer et al., 1995).

The cells and tissues in these organisms inhibit radical reactions and products. Antioxidants are defined as substances that prevent the progression of autoxidation/peroxidation by reacting rapidly with radicals. Prevention of any first radical product, which is formed in some way, to attack biomolecules and cellular structures is a part of the antioxidant defense system (Byung 1994).

Ubiquinone, also known as CoQ_{10}, is a natural, fat-soluble, vitamin-like antioxidant substance. Ubiquinone, an auxiliary cofactor in the intercellular electron transport chain, has become one of the most popular nutritional supplements in recent years. The effectiveness of ubiquinone and alpha lipoic acid in the treatment of osteonecrosis is being investigated.

In this systematic review, the aim was to evaluate, in the light of literature, the efficacy of alpha lipoic acid and CoQ_{10} / ubiquinone, known to have an antioxidant effect, in the treatment of osteonecrosis. Thus, it was aimed to make a guideline for future studies on the recovery of functions lost after osteonecrosis.

MATERIALS AND METHODS

A comprehensive and systematic literature search of numerous electronic databases, including Embase, Ovid, PubMed, was performed. Keywords used to retrieve studies broadly associated with the topic of interest were as follows: "alpha lipoic acid / α-lipoic acid", "antioxidant", "coenzyme-Q_{10}", "ubiquinone" and/or "osteonecrosis" or "osteonecrosis femoral head" or "avascular necrosis femoral head"

The headings and abstracts of all studies on the use of antioxidants in the treatment of post-osteonecrosis injuries were reviewed. The full texts of the appropriate studies were retrieved according to the headings and abstracts, then inclusion and exclusion of these studies were decided after a comprehensive review (Akgun et al., 2018; Akyuva et al., 2018; Karaarslan N[a], 2018; Karaarslan N[b], Karaarslan N[c], 2018; 2018; Topuk et al., 2017).

Letters to the editor, bibliography, review, and meta-analysis were excluded from the study. *Critical appraisal checklists* were used to assess and analyze the quality of the selected studies**.** At the stage of summarizing the obtained data, the findings which were synthesized in a clear and understandable manner were listed through tables. The present study was conducted on the basis of the guidelines of the *Preferred Reporting Items for Systematic Reviews and Meta□analysis* (PRISMA guidelines) (Akgun et al., 2018; Akyuva et al., 2018; Karaarslan N[a], 2018; Karaarslan N[b], Karaarslan N[c], 2018; 2018; Topuk et al., 2017).

The screening process of the studies that did not meet the inclusion criteria, thereby remain out of the systematic review was presented in Figure-1.

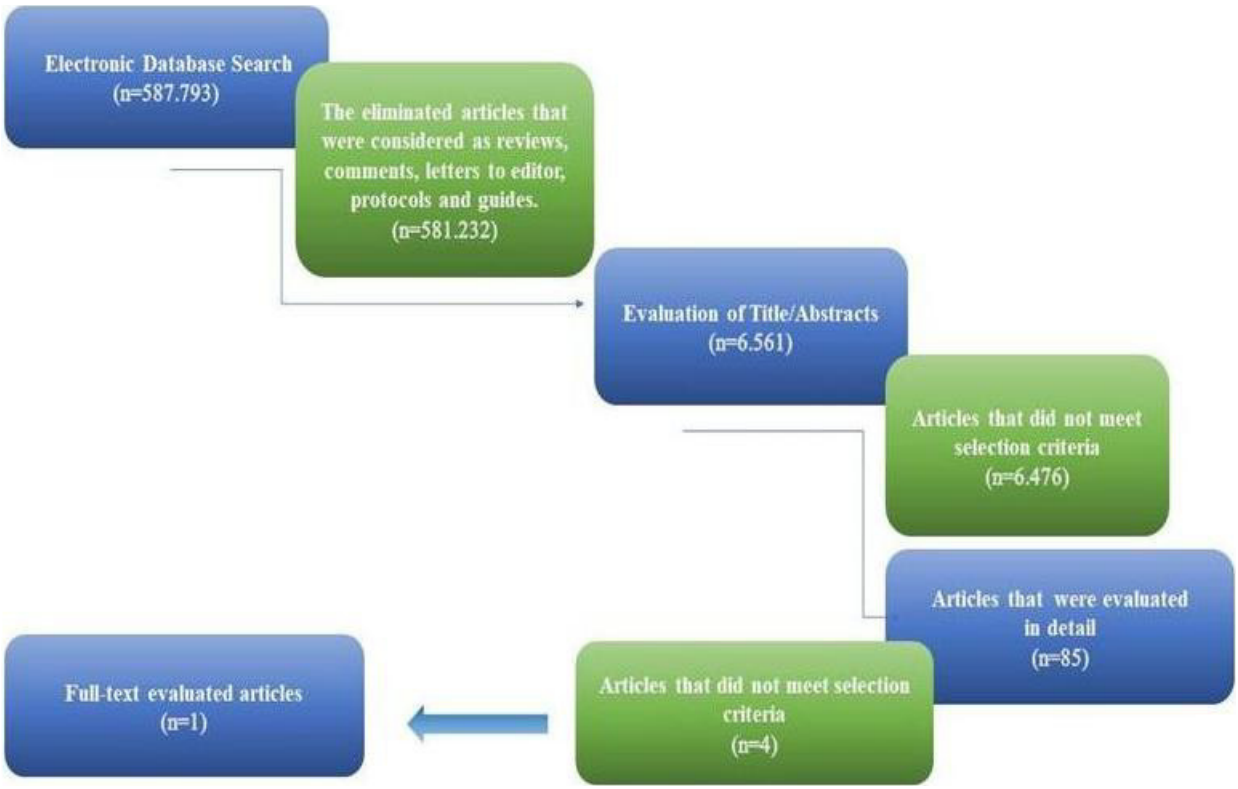

Figure 1. Screening process and excluded studies

RESULTS

A total of 4 publications were retrieved using the keywords “osteonecrosis” and/or “ubiquinone” or “Coenzyme-Q_{10}” or “alpha lipoic acid”. Of these studies, one (Kalyan et al., 2014) had not a clinical design, and three (Lu and Li, 2012; Komurcu et al., 2014; Wang et al., 2016) had a clinical design (Lu andLi, 2012; Komurcu et al., 2014; Kalyan et al., 2014; Wang et al., 2016).

DISCUSSION

The femoral head blood flow is extremely sensitive and can be easily impaired, and this can occur through two main mechanisms: intravascular obstruction and extravascular compression.

Some studies have denoted that osteocyte necrosis of the femoral head occurs after approximately a few hours of anorexia (Wang et al., 2015) and that the necrotic area is surrounded by fibrous tissue (Sissonset al., 1992). The aim is to preserve the existing anatomical structure in the treatment of avascular necrosis of the femoral head, a very serious medical condition. Therefore, factors such as age, general condition, concomitant diseases, stage of the disease, and the location and size of the segment affected should be considered.

Along with surgical procedures performed to remove the load applied to the hip, the use of vasodilator, anticoagulant, lipid-lowering drugs and systemic alendronate have provided promising results in the treatment of avascular necrosis of the femoral head. However, its treatment has been reported not to be fully achieved. Thus, the efficacy of pharmaceutical preparations, which have antioxidant effects, in osteonecrosis treatment was started to be investigated.

In the present study, the aim was to evaluate, in the light of literature, the efficacy of alpha lipoic acid, CoQ_{10} / ubiquinone in the treatment of osteonecrosis.

As is well known, alpha-lipoic acid is a natural substance found in some foods and synthesized in the human body. Lipoic acid which prevents free radical damage is unique among antioxidants due to its solubility both oil and water.In humans, lipoic acid is a part of various 2-oxo-acid dehydrogenases involved in energy production. There are two forms of lipoic acid; α-lipoic acid and the reduced form dihydrolipoic acid. Dihydrolipoic acid is biologically more active. Lipoic acid is synthesized in mitochondria from octanoic acid and a sulfur source. More than %93 of dihydrolipoic acid is absorbed by the intestine when taken orally, and it goes through 20% to 30% of its first- pass metabolism in the liver. The primary metabolic pathway of α-Lipoic acid in humans is S-methylation β-oxidation. Lipoic acid is an acyl carrier and is responsible for carrying two electrons. It is involved in α-ketoglutarate dehydrogenase and

pyruvate dehydrogenase enzyme complex. Lipoic acid acts as a coenzyme in oxidative decarboxylation of pyruvate. Lipoic acid has been shown to regenerate vitamin E and vitamin C, which prevents free radical damage (Caoet al., 2018; Tibullo et al., 2017).

Lipoic acid acts as a coenzyme in oxidative decarboxylation of pyruvate. Pyruvate first loses the carboxyl group and binds to the enzyme-bound thiamine pyrophosphate in the form of its hydroxyethyl derivative. The electrons and acetyl group are then transferred to the lipoic acid bound to the dihydrolipoyl transacetylase enzyme, and thereby 6-acetyl dihydro-lipoic acid is formed. It then transfers the acetyl group on lipoic acid to coenzyme A. Thus, a reduced dihydrolipoic acid is formed. The oxidation of lipoic acid is catalyzed by the dihydrolipoyl. Lipoic acid is linked to the ε-amino group of a lysine residue of the enzyme dihydrolipoyldehydrogenase via an amide bond. This linkage is achieved by the ATP-dependent synthetase, and the elimination is achieved by a hydrolase (Gonidakis et al., 2010; Shen et al., 2007).

Lipoic acid binds acyl groups and transfers them from one part of the enzyme complex to another. During this process, lipoic acid is reduced to dihydrolipoic acid, which subsequently reoxidized by lipoamide dehydrogenase with NADH formation. Hence, lipoic acid and dihydrolipoic acid can act as a redox couple and carry electrons from the substrate of the dehydrogenase to NAD + (Huanget al., 2017).

In human cells, R-LA is present as abound form of lipoillis in mitochondrial proteins that play a significant role in oxidative metabolism. Researchers have recently demonstrated that lipoic acid regenerates vitamin E and vitamin C, which prevents free radical damage. Vitamin E is one of the main components of the antioxidant cycle. This vitamin works to stop reactivation of high free radicals in adipose tissue and membranes (Busse et al., 1992).

Oxidation reactions and radicals cannot be completely eliminated due to the formation of a small amount of hydroperoxide in each step of the chain breaking reactions and inability to wipe off the products in the environment. In cases where oxidants increase or antioxidants are inadequate, cellular metabolism deterioration due to the oxidative stress causes molecular destruction and tissue damage. Antioxidant defense mechanism functions by performing the followings: a) preventing the production of radical metabolites and wiping off of the produced radicals b) repairing cell destruction, c) terminating chain reactions that produce secondary radicals d) increasing the endogenous antioxidant capacity (Gutteridge, 1995).

A-lipoic acid, which is the only antioxidant that is soluble in oil and water, can be called the universal antioxidant. Alpha lipoic acid has two enantiomers as R-α lipoic acid and S-α-lipoic acid. These two forms have the same number of atoms, but have a different arrangement of atoms. Both the R and S forms are isomers. The R-enantiomer is 28 times faster than the S-enantiomer. Researchers in Europe and U.S.A work with synthetic lipoic acid because of the extreme difficulty of isolating natural lipoic acid. Synthetic lipoic acid is made of the mixture of the same amount of these two enantiomers (Bast and Haenen, 2002; Streeper et al., 1997). Lu. et al. (2012) investigated in vivo effects of lipoic acid in preventing steroid-induced osteonecrosis and the possible pathway in a rabbit model. They divided sixty rabbits into two groups. They treated the rabbits in group A with a lipoic acid aqueous solution, intraperitoneally injected, at 36 mg/kg of body weight per day for 4 weeks, and treated those in group B with physiologic saline. The rabbits were then treated with 20 mg/kg of methylprednisolone acetate at 2 weeks after treatment initiation. They examined the femora for the presence of osteonecrosis. They also analyzed the plasma levels of total cholesterol, low-density lipoprotein, high-density lipoprotein, glutathione, endothelin, and malondialdehyde at 2 weeks after administration of methylprednisolone acetate. They observed that the occurrence of osteonecrosis was significantly higher in Group B (73.1%) than in Group A (20.8%) and that the glutathione level was higher in Group A than in Group B after the lipoic acid injection. They also denoted that the plasma malondialdehyde and endothelin levels were lower in Group A than in Group B at 2 weeks after the methylprednisolone acetate administration. They concluded that lipoic acid might halt the development of steroid-induced osteonecrosis in rabbits and that inhibited oxidative stress and amendment of vascular endothelial dysfunction was a possible mechanism for this effect (Lu and Li, 2012).

Komurcu et al. (2014) investigated the role of CoQ10 in the prevention of steroid-induced osteonecrosis of the femoral head in rats. They treated 20 Sprague-Dawley rats with 20 mg/kg of methylprednisolone acetate to induce osteonecrosis. They divided animals into two groups; Group 1 was given no prophylaxis, then group 2 was given CoQ_{10}. They performed a hematological examination before steroid injection and at 4 weeks after a steroid injection and examined femoral heads histologically to evaluate osteonecrosis. They observed that changes in glutathione and malondialdehyde concentrations were less significant in the CoQ_{10} group, and that the incidence of histologic changes consistent with early osteonecrosis was lower in the CoQ_{10} group than the control group. They concluded that CoQ_{10} might be useful as a preventing agent in steroid-induced osteonecrosis of the femoral head (Komurcu et al., 2014).

Kalyan et al. (2014) investigated the CoQ_{10} and antioxidant status in relation to nitrogen-bisphosphonate (N-BP), which is the most widely used drug for bone fragility disorders, and long-term or high-dose use of which is correlated with unusual serious side effects such as osteonecrosis of the jaw, musculoskeletal pain, and a

typical fractures of long bones, exposure in women with postmenopausal osteoporosis. They included 71 postmenopausal women with osteoporosis and no other malignancy in a cross-sectional study. 17 patients were treatment-naive, 27 were on oral N-BP, and 27 were on i.v. N-BP. They observed that vitamin E γ-tocopherol levels (µmol/mL) were significantly reduced in N-BP users, and that length of time (days) of N-BP exposure, but not age, was inversely associated with the CoQ_{10}/cholesterol ratio. They also expressed that the degree of N-BP exposure appeared to be associated with the compromised CoQ_{10} status and vitamin E γ-tocopherol levels in postmenopausal women with osteoporosis. They concluded that this phenomenon might be correlated with certain adverse N-BP-associated effects (Kalyan et al., 2014).

Wang et al. (2016) examined pharmaceutical approaches for the treatment of steroid-induced bone infarction of the femoral head. They denoted that during the first year of steroid usage, osteocyte necrosis and blood vessel blockage might occur, which later might produce steroid-induced bone infarction (SIBI) leading to painful movement of the patient. They proposed the basic approach which includes the use of many pharmacologically active compounds involving bisphosphonates, hyperbaric oxygen, CoQ_{10}, erythro-poietin, antihyperlipidemic, anticoagulants, antioxidants, and tissue repair protein. They expressed that there was no pharmaceutical agent that might completely treat this disease due to the many factors responsible for SIBI development and that further studies were needed for the search of a novel agent in the treatment of SIBI (Wang et al., 2016).

CONCLUSION

It can be inferred in the light of the clinical studies that alpha lipoic acid, and CoQ_{10} / ubiquinone, which have an antioxidant effect, can give positive results when used for the treatment of avascular necrosis femoral head in patients with osteonecrosis.

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