REVIEW ARTICLE

Pathophysiology of osteoarthritis and Current Treatment

Abdelmoneim A. Ali*, Al-sayed R. Al-Attar, Nahla A. A. Refaat, Aya Samy
Pathology Department, Faculty of Veterinary Medicine, Zagazig University, 44511, Zagazig, Egypt

Abstract

Osteoarthritis (OA) is considered the prevalent arthritis in human and some animals, causing joint pain and disability that reduces quality of life. The exact etiology of OA is unknown till now but there is a variety of predisposing factors for the occurrence of osteoarthritis (OA) such as previous joint injury, genetics, obesity, sex, anatomical abnormalities and excessive load; meanwhile, the predominant factor is ageing. Understanding the pathophysiology of osteoarthritis is a must to provide effective treatment options. Previous researches had studied the pathophysiology of osteoarthritis However several controversies still present. Currently still there is no substantial therapy for OA; treatment options concentrate on the relief of signs. The main goals of therapy are pain relief, improved joint function, and joint stability. New trials of therapies are under study and some of them did promising effects as approaches to regenerative medical therapies such as Platelet Rich Plasma (PRP) and Nanotechnology. The purpose of this study is to provide an overview of pathophysiology information and of the various therapeutic resources suitable for OA.

Keywords:

Introduction

Osteoarthritis (OA) is chronic degenerative lesion of joints which leads to pain and joint deformity [1]. The pathological changes include articular cartilage degradation, and synovitis beside alteration in periarticular tissues, menisci and ligaments degeneration together with thickened subchondral bone due to osteophyte formation [2]. Hip and knee are the most commonly involved joints in OA, but other skeletal joints in hands, feet and spine may be affected [3]. The exact etiology of OA remains unknown, but studies showed that such type of inflammation is closely integrated and complicated process. Some inflammatory mediators, in the development of OA, have crucial roles, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [4]. There are variety of predisposing factors for progression of condition, including trauma, heredity, sex, fattening, joint abnormalities and excessive load; however, the most obvious risk factor is age progress [5]. Some authors classified OA into primary due to unknown cause (idiopathic) and the second traumatic owing to mechanical injury, the latter is the predominant type in animals [6].

The molecular interactions is an important basis in the growing of the disease and more knowledge is important to develop new approaches for prevention and treatment [7].

Pathophysiology of osteoarthritis

In the past, osteoarthritis was considered as a strictly mechanical cartilage degradation condition, but now it is considered to be a difficult illness affecting the entire joint structures, in which activation of matrix metalloproteinases (MMPs) is critically enhances devolvement and progression of the diseases. Articular cartilage, subchondral bone, and synovium can all together be incriminated in disease pathogenesis shown in Figure 1 [5].

*Corresponding author e-mail: (abdelmoneim.ahmedali@yahoo.com), Pathology Department, Faculty of Veterinary Medicine, Zagazig University, 44511, Zagazig, Egypt

Articular cartilage

Hyaline cartilage, which consists predominantly of an extracellular matrix (ECM) with lacunae containing chondrocytes, without blood and lymphatic vessels and nerves is the main structure of articular cartilage. The ECM mainly composed of type II collagen fibers, sulfated-glycosaminoglycan (sGAG), hyaluronic acid, elastin fibers and proteoglycans that including aggrecan; cartilage-specific proteoglycan core protein. The production and degradation of the ECM by renewal of the matrix proteins is induced by chondrocytes [8].

Inability of chondrocytes to keep balance between production and degradation of these ECM constituents leads to development of OA [9].

It is not known what initiates the imbalance between the degradation and the repair of cartilage. Formation of "wear" particles may be allowed by trauma that causes a microfracture or inflammation which may lead to a slight increase in enzymatic activity, then resident macrophages make phagocytosis of these particles [10].

These "wear" particles production devastates the system’s ability to remove them and initiate inflammation, through stimulating the release of degradative enzymes by chondrocyte. Molecules from breakdown of collagen and proteoglycan, also taken up by synovial macrophages, cause release of pro-inflammatory cytokines, like TNFα, IL-1 and IL-6. These cytokines can bind to chondrocyte receptors leading to further release of metalloproteinases and inhibition of type II collagen production, thus increasing cartilage degradation [11].

Subchondral bone

Subchondral bone is the layer of bone which is seen between cartilage (calcified layer) and underlying trabecular bone. There are obvious changes in histology and structure of the
cortical plate and trabecular bone in osteoarthritis than normal one [12, 13].

The osteoblasts as chondrocytes respond to mechanical stimulation by expressing of degradation enzyme and inflammatory cytokines [14]. These factors could act directly on cartilage or changes in the mechanical properties of subchondral bone might have adverse effects on overlying cartilage. Conversely, subchondral bone re-modelling might result from increased loading through loss of cartilage integrity. Subchondral bone is highly innervated and probably contributes to the generation of pain in disease.

**Synovium**

Synovium is a unique connective tissue that covers joints (diarthrodial type), wraps tendons and constitutes bursae and fat pads. It separates the synovial cavity and fluid from adjacent structures in synovial joints. It secretes lubricin and hyaluronic acid which is responsible for the preservation of synovial fluid volume and composition. Additionally, the synovium supply nutrition for chondrocytes together with subchondral bone through the synovial fluid, due to articular cartilage lacks of blood supply and lymphatic drainage [15].

The main characteristic changes of synovium in osteoarthritis are hyperplasia, stromal vascularization and fibrosis [16]. There are several leukocytes which exude from vascular system as a reaction to cytokines [15]. These cells include both macrophages and lymphocytes (t-cell type) which are the most predominant immune cells during osteoarthritis, sometime other cells include mast cells, B cells and plasma cells are also seen by a lesser extent [17, 18].

Synovitis causes recruitment of inflammatory cells including macrophages that secrete pro-angiogenic factors which can induce synovial neovascularization. Also, macrophages can induce other cells, such as fibroblasts and endothelial cells to produce (basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF)) that further promote angiogenesis [19]. Moreover, the inflammatory response is prolonged through increased permeability of blood vessels and up-regulation of adhesion molecules [20].

**Menisci**

A meniscus is a small cartilage found at site of two bones meeting (joint space). Menisci cushion and protect the joint surface and bone ends. The main function of menisci is protecting the surface of joint cavity and absorb the shock [21]. The main characteristic features of meniscle that occur during OA are meniscal degeneration which occur firstly within tissue material then to surface. Meniscal degeneration initiates within the tissue substance rather than surface. It begins with fibrillation and disruption of tissue at inner rim, and then spreads to meniscal articular surfaces [22]. The content of collagen type I gradually decreases from meniscal surface zone to deep osteoarthritic meniscus zones [23].

**Role of Inflammatory mediators in osteoarthritis:**

**Interleukins**

**Interleukin-1 Beta (IL-1β):**

It is controlled by chondrocytes, osteoblasts, synovial membrane cells and mononuclear cells that were infiltrated in the joint during the inflammatory response [17]. IL1β constrains synthesis of main constituents of matrix of articular cartilage, which include (type II collagen and aggrecan). Lastly, IL1β is proved to increase degrading enzymes expression and secretion such as (MMP-1, 3, and 13,) beside aggrecanase ADAMTs [24].

Many researchers stated that, IL-1β within high levels are found in diseased cartilage and also in surrounding tissue such as synovial fluid, synovial membrane, subchondral bone. IL-1β could induce the production of inflammatory mediator as prostaglandin E2 (PGE2) and nitric oxide (NO) in chondrocytes [4].

**Interleukin-6:**

IL-6 is one more cytokine which is elevated in the synovial fluid of osteoarthritic joints. Also, it plays a confounding role in onset and progression of joint osteoarthritis, included with both pro-inflammatory [25] and anti-inflammatory mediators [26].

**Interleukin-17 and 18:**

Interleukin-17 and 18 are also involved in OA. Both promote synthesis of other interleukins, reactive oxygen species (ROS), and enzymes of collagenases [27].
Tumor necrosis factor alpha (TNF-α)

TNF-α has catabolic role in osteoarthritis, also makes down regulation of cartilage matrix constituents, which include (collagen type II and aggrecan) [28]. Moreover, TNF-α encourages synthesis of other cytokines such as IL-1, IL-6 and IL-8. Finally, TNF-α is responsible for pain related to OA, this due to TNF-α interacts with the receptors (TNFR1 and TNFR2) that activate sensory neurons [29].

Moreover, TNF-α and IL-1β induce the production of COX-2, iNOS and PGE2 synthase, thus increasing the quantities of their products [30].

Nitric oxide

An increase in amount of nitric oxide in OA could be attributed to the inducible nitric oxide synthase (iNOS). Consecutively, nitric oxide has a major share in progression of OA by constrains proteoglycan and collagen type II synthesis and stimulates the production of other cytokines [31]. Lastly, nitric oxide stimulates chondrocytes to reduce production of IL-1 receptor antagonist (IL-1Ra), also enhance MMP activity [32].

Adipokines

Increased levels of adipokines either systemically or in synovial fluid is linked with cartilage degeneration and synovial membrane inflammation in OA [33, 34]. Elevated adipokines levels in metabolic syndrome (obesity, hypertension, dyslipidemia, insulin resistance) could be considered risk factors for osteoarthritis induction [35, 36]. Several adipokines have context-dependent immunomodulatory properties, such as adiponectin, leptin, visfatin, resistin, and nefastin-1 [37] and induce osteoarthritis development and progression by prompt synthesis of inflammatory mediators and degrading enzymes [38].

Prostaglandin E2 (PGE2)

PGE2 is an important inflammatory mediator and the production requires two enzymes, prostaglandin E synthase and cyclooxygenase 2 (COX-2). These enzymes are both induced by IL-1β and because of this PGE2 levels increase as a result of higher concentration of IL-1β [39]. PGE2 prevents proteoglycan production, increases A disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS-5) and MMP-13 leading to aggrecan and collagen type II degradation [40].

Reactive oxygen species (ROS)

Reactive oxygen species (ROS) are released by immune cells, such as neutrophils and macrophages, which present in OA. Reactive oxygen species (ROS) including (hydrogen peroxide, superoxide, hydroxyl radicals, and their reactive products). These ROS may cause extensive protein, lipid and DNA damage, if these species are not scavenged [41]

These free radical species are scavenged by antioxidants such as (superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX)). The superoxide dismutase (SOD) enzyme neutralizes O2− by converting it into hydrogen peroxide (H2O2), thus inhibiting the formation of highly aggressive compounds, including peroxynitrite (ONOO−) and hydroxyl radical [42].

When ROS elevated in levels of ROS, it results in an oxidative stress in the cartilage, which in turn lead to chondrocyte apoptosis and articular cartilage degradation [43-44].

Osteoarthritis in different animal species

OA is commonly encountered in human and no one can ignore this problem in animals since encountered in various animal species [45]. The disease was recorded among horse, dogs and cats [46-52]

Equine osteoarthritis

Articular disorders, presented by osteoarthritic pain, represent the greatest single economic loss to the equine industry, and similarly form a major animal quality of life issue [46]. Osteoarthritis in equine veterinary medicine is a significant concern and accounts for up to 60% of all lameness, particularly in race and draft animals [47].

This joint’s disease can occur as a result of multiple predisposing factors such as repeat trauma and synovitis from other pathological lesion, for example, osteochondrosis (OCD) or joint infection [48].

Feline osteoarthritis

OA is relevant and complicated cats’ problem. In older cats, osteoarthritis is a common X-ray finding with prevalence in appendicular joints of up to 90 percent. The
majority of cats are affected with significant long-term pain, which declines mobility and activity [49]. Feline OA is challenging for owners and veterinarians to identify, because signs such as overt lameness are rare. [50]. Some investigators declared that patellar luxation is an important predisposing factor OA in the cats [51].

**Canine osteoarthritis**

It is the predominant form of arthritis in dogs and the most common source of chronic pain in older dogs. It commonly affects large breed dogs, more than small breed dogs. The prevalence of osteoarthritis in dogs over a year old can be as high as 20 percent, with middle-aged and older dogs at higher risk [52]. In dogs, both forms of osteoarthritis (primary and secondary) occur but the secondary type is more common. Canine OA usually develops secondary to hip dysplasia, cranial cruciate ligament rupture, articular fracture, osteochondrosis or other secondary initiating cause [53].

**Diagnosis**

**Clinical signs**

The clinical signs of OA joint include:

(1) **Joint pain:** that ranges according to severity from mild to moderate, also it is characterized by dullness and not continuous at the onset of diseases course.

(2) **Joint swelling:** joint deformity and obvious swelling usually seen in hand joints.

(3) **Bony crepitation:** it is observed during joint movement, this is due to articular cartilage surface is weak and rough.

(4) **Muscle weakness and movement impairment:** it is responsible for uncoordinated joint movement, this due to loss of muscle strength and weakness of the underlying soft tissue [54].

**Biochemical markers**

There are many regulatory molecules that can be used as markers for OA like cytokines, components of ECM (collagen and proteoglycan precursors or degradation products) and enzyme. The levels of these molecules are linked with the metabolism of the tissues [55].

Recently, these biochemical molecules are classified into two main categories. The first are molecules that result from bone and cartilage degradation products such as cartilage oligomeric matrix protein, C-terminal telopeptide of type II collagen, an aggrecan neoepitope and a number of matrix metalloproteinases. The 2nd category include pro-inflammatory and anti-inflammatory agents (for example, interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF)-α, IL-10, IL-13 and IL-4, cytokines) which are involved in pathophysiology of OA through angiogenesis and chemotaxis [56].

**Imaging studies**

**Radiology**

Traditionally, plain film x-ray is used for diagnosis of OA by showing significant imaging features as joint space narrowing, osteophyte formation, subchondral bone sclerosis and cysts development. The most sensitive and reliable x-ray feature is joint space width, which is accepted by FDA to screen the efficacy of disease-modifying medications for osteoarthritis. Scoring systems (Kellgren and Lawrence (KL) and (OARSI) are of lower value than joint width [57].

**Magnetic resonance imaging (MRI)**

MRI provides higher soft tissue contrast in a tomographic presentation. MRI visualize all the structures within a joint, this is considered as advantage that is not found in X-ray or ultrasound. Detection of synovitis by MRI is improved with IV contrast by enabling differentiation from joint effusion [58].

**Pathological evaluation**

Disorganization and severe degeneration of the articular cartilage are the most prominent pathological features of OA. The articular surfaces showed fissures and clefts into the transitional and radial zones together with fibrillation and pannus formation. Apoptotic chondrocytes were common, and the intracellular matrix showed severe reduction in the intensity of Safranin O staining indicating significant loss of proteoglycans [59].

**Management of osteoarthritis**

OA is considered as a progressive degenerative disease, without any regression and restoration of damaged structures. Thus, the primary aim of management is symptom relief unless severe disease requires surgical intervention with joint replacement [60].
Non-pharmacological management

The goal of OA management is to monitor the discomfort caused by these joints and to improve the functionality and quality of life [61].

Loss of body weight is a simple tool to decrease onset of OA in knee joint, thus Individuals with increased weight have higher knee OA rates than non-overweight individuals. People with large body mass index has high load on their knees, which is led to induction or progressive course of knee OA and this is contributed to that fact that force over the knees is 3 to 6 times the body weight [62]. Patients, who cannot do exercises on the land, can substitute it by using aquatic therapies that depend on water, which reduces joint impact. Some individuals can tolerate aquatic treatment and reduce symptom aggravation but occasionally when they restore weight bearing routines, they would experience them again [63].

Pharmacological management

Historically, the predominant and commonly drugs used for medication of OA are cyclooxygenase inhibitors (acetaminophen and NSAIDs), but these drugs are not used for long duration due to their multiple adverse effects such as renal, gastrointestinal, cardiac, and hematological which were reported by many studies [64]. Many studies reported that, topical NSAIDs are safer than systemic NSAIDs, and more effective in controlling OA joint pain [65]. Previous studies have also shown that opioids are similar to NSAIDs in relieving OA pain and the dangers of their use, obviously overshadowing the advantages [66].

Injectable treatment

The promising strategy for therapeutic intervention is intra-articular (IA) administration of biomolecules which target the activity of chondrocyte or synovial inflammation [67]. Therapeutic agents include IA injectable regimens (corticosteroids and hyaluronic acid (HA)) are commonly used and their efficacy therapy has been thoroughly reviewed [68-70]. The anti-inflammatory or immunosuppression effect of the corticosteroids is complex in their mechanism. The anti-inflammatory effect prevents many inflammatory mediators, such as production and secretion of (PG and leukotrienes). The clinical symptoms of anti-inflammatory action can be reflected by decreasing in local edema, erythema, hotness, tenderness and increased viscosity due to an increase in hyaluronic acid (HA) content [71].

Usually, the effect of injection reduces joint pain successfully up to three weeks post injection, while diminishing after longer periods [72]. However, there is no assumption to confirm their effect in improving of joint function. Moreover, there are several studies stated that Long-term IA corticosteroid exposure can have an adverse effect on the articular cartilage and may accelerate its progression [73]. A recent systematic review has established that IA corticosteroid use with higher doses and long treatment times is associated with chondrotoxicity [74].

Visco-supplementation with hyaluronic acid:

Visco-supplementation concept has been applied in abroad scale as knee OA treatment. It depends on synovial fluid substitution with hyaluronic acid. [75].

When OA starts, the concentration of natural HA and its average molecular weight decreases, leading to a decrease in the mechanical properties and motion of the joint.

The IA injection of HA would raise the levels and the viscoelasticity of synovial fluid, which restores joint lubrication, joint safety and shock absorption. HA have anabolic, analgesic, anti-inflammatory effects and chondroprotective mechanisms [76].

Recent research has suggested that IA injection of HA has a less effect on patient outcomes, in relation to its costs [77]. Furthermore, HA injections make improvement of OA joint for short duration, so that, provide for OA management just a temporary solution [78]. Besides, decreasing in drug efficacy may be occurring after the first treatment [79]. It has mild adverse effects, but some complications can occur, because components of soft tissue in the knee are often affected [80].

Regenerative medicine

In recent years, regenerative treatment is used as a new strategy for OA treatment. In fact, the notion uses the application of blood derivatives especially platelet-rich plasma (PRP) in the treatment of knee OA and nanotechnology approaches [81].

Platelet-rich plasma (PRP)
In recent times, platelet-rich plasma (PRP) is used as advanced technique that is able to stimulate repairing of damaged cartilage, this is due to it has α-granule of platelet which stored abundant of growth factors, that many literatures reported their important role in the regulation of articular cartilage [82]. These growth factors include Platelet-derived growth factors (PDGF), transforming growth factor beta (TGF-β), epithelial growth factor (EGF) and vascular endothelial growth factor (VEGF), etc. [83].

The endogenous thrombin and/or intra-articular collagen activate platelets when PRP is injected in the joint [84]. The growth factors are secreted by degranulating the α-granules once they are activated. [85]. Secreting substances include (platelet-derived growth factor (PDGF), interleukin-1 receptor antagonist (IL-1RA), soluble receptor of tumor necrosis factor (TNF-RI), transforming growth factor β (TGFβ), platelet factor 4 (PF4), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), osteocalcin (Oc), osteonectin (On), fibrinogen, vitronectin, fibronectin and thrombospondin-1 (TSP-1).

The majority of abovementioned factors act as anti-catabolic and anti-inflammatory agents. This action can be done through; antagonist effect on IL-1 receptor which in turn inhibits activation of NF_κB gene and cytokines which involved in apoptosis and the inflammation process [86].

Furthermore, chondrocyte safety occurs through the ability of soluble tumor necrosis factor receptors that bind to TNF-alpha, thus preventing its interaction with cellular receptors and its pro-inflammatory activation. TGFβ-1 activity is done through inhibiting cartilage degradation, controlling and improving gene expression of metalloproteinase inhibitor tissue (TIMP-1). Also, there are other factors like IGF-1, PDGF and TGFβ -1 which enhance cartilage stability via controlling regulation of chondrocytes and subchondral bone metabolic functions. Studies reported that growth factors of platelets induce synovial fibroblasts to synthesize hyaluronic acid [87].

**Nanotechnology Approaches**

Nano-medicine is a recently concept that provide a combination between nanotechnology with biomedical and pharmaceutical sciences, which aims to developed or emerging a new drugs and imaging agents with higher efficacy, moreover, they also can improve safety and toxicological profile [88].

Nano medicines shown many advantages that make it a best choice in treatment of OA. Firstly, it’s ability to transport material for a long period efficiently through tiny capillaries and lymphatics. Secondary, higher binding capacity to biomolecules, and lastly higher accumulation in target tissues, reduced oxidative stress, and inflammatory process beside immune responses in target tissues [89].

Curcumin can be helpful in treatment and prophylactic regimen in OA problems, however, update researches proved that there are some drawbacks that include poor bioavailability owed to its low absorption, quick metabolism, and rapid systemic elimination.

Nanotechnology has proved the key to overcome this problem of curcumin through drug delivery (curcumin loading on appropriate nanoparticles). Moreover, there are numerous nanoparticles suited for curcumin encapsulation in various diseases to boost their therapeutic effects [90].

Curcumin is the best herbal agent which has been extracted from roots of Curcuma longa (Turmeric) on the past, the traditional Chinese and Ayurvedic medicine used it for a long duration as an anti-inflammatory treatment. Also, more studies reported that curcumin has many advantages that help in treatment of OA such as anti-inflammatory and antioxidant ability [91].

Furthermore, many clinical trials revealed that curcumin could reduce the pain and improve the functionality of the osteoarthritic joint [92]. The anti-inflammatory properties of curcumin act through reduction in the synthesis of some inflammatory mediators [93] also, stimulate inhibition of IL-1β that make induction of extracellular matrix degradation [94] and chondrocyte apoptosis [95].

Additionally, intra-articular injections of nanostructures of HA conjugates [97] have shown beneficial features, including good biocompatibility, sustained drug release,
cartilage protection, reduction of inflammatory cytokines such as IL-1β and TNF-α, and maintenance of epiphysis thickness. Nano crystal-polymer particles have been designed as potential drug delivery carriers for OA treatment. Nano crystals (NPPs) of kartogenin (KGN) demonstrated high drug loading and prolonged drug release. In vivo, the KGN-NPPs show higher bioactivity compared to KGN in solution and sustained intra-articular persistence without any irritation [98].

Furthermore, Avidin nanocarriers are appropriate for intra-cartilage delivery of dexamethasone (DEX). In cartilage explants in vitro, a single dose of Avidin-DEX significantly inhibits the cytokine-induced loss of sulfated-glycosaminoglycan (sGAG), as well as decreasing and even suppressing IL-1α-induced cell death and enhancing sGAG synthesis levels [99]. As a novel strategy in the treatment of OA, KGN-conjugated chitosan nano-microparticles can promote cartilage regeneration. These carriers demonstrate excellent properties in terms of prolonged release (7 weeks), strong stimulatory effects on the expression of chondrogenic markers in vitro, long retention time in the knee joint after intra-articular injection, and inhibitory effects on cartilage degeneration in vivo. KGN-conjugated polyurethane NPs (PN-KGN) have demonstrated great potential for OA treatment [100, 101].

Mesenchymal Stem Cell Therapy for OA

The regenerative potential of cellular therapy is currently used to meet the medical needs of various degenerative conditions such as OA. Cellular therapy has been extensively invested in exploring a new pattern for the treatment of many degenerative conditions including degenerative disc disease (DDD) and osteoarthritis of the joints. The disease-modifying potential of cellular therapy such as the use of adult stem cells for regeneration of the damaged tissues has provided an exciting promise to chronic degenerative conditions. Currently, there are clinical trials exploring the safety and efficacy of adult stem cells, e.g., pluripotent stem cells, umbilical cord-derived stem cells, placental stem cells, and mesenchymal stem cells, to treat OA. Of these, mesenchymal stem cells have been a leading choice for many medical researchers around the world [102]. In the clinical studies, MSCs are isolated from the patient either from the bone marrow or from adipose tissues, purified, and administered as intra-articular injection in the affected joint under ultrasound guidance. MSCs are described to exert their therapeutic effects by homing to the injured site when injected locally to the joint for a short period of time and then disappearing and are believed to be secreting a countless growth factors and cytokines to initiate the repair process[103].

Conclusion:
Knee osteoarthritis does not have a clear pathophysiology or a single most efficient intervention to treat the symptoms and degeneration associated with it. Physical activity and lifestyle modification are important and may delay the need for surgical intervention. Regenerative medicine (PRP), Nano medicine and stem cell therapy are the main choices of medical treatment in clinical studies.

Conflict of interest statement
The authors report no conflicts of interest in this work.

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