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Role of Glucosamine in the treatment of Osteoarthritis

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Abstract

Osteoarthritis (OA) is a chronic, degenerative joint disease that is characterized by increased loss of cartilage, remodelling of the periarticular bone, and inflammation of the synovial membrane. The primary pathophysiologic process responsible for osteoarthritis is believed to be progressive deterioration of articular cartilage. It can affect any joint, most commonly affected joints includes joints in hands, knees, hips and spine. Glucosamine is the most frequently used alternative worldwide in the treatment of osteoarthritis, due to their chondroprotective properties and their long effects. Glucosamine (2-amino-2-deoxy-D-glucose) is an aminomonosacchride, a primary constituent of cartilage proteoglycans. It is the basic building block required for the biosynthesis of glycosaminoglycans. It enhances cartilage specific matrix components and prevents collagen degeneration in chondrocytes, suppresses the free radical generation and IL-1 induced inflammatory mediator activation . Studies suggest that use of glucosamine on osteoarthritis provide pain relief, reduced tenderness and improved joint function. This objective of this article is to provide information about osteoarthritis and the role of glucosamine in treating osteoarthritis.

Keywords: Chondrocytes**,** Loss of cartilage, Extracellualr matrix degradation, Glucosamine, Glycosaminoglycan, Proteoglycans.

Introduction

Osteoarthritis (OA), also known as degenerative joint disease, is the most common joint disease that affects humans in which cartilage or bone is damaged. It is a chronic, degenerative disease characterized by progressive cartilage deterioration, subchondral bone remodelling, loss of joint space, marginal osteophytosis, and loss of joint function (Jorge U Carmona, 2009 ; Xiuling Ji, 2019).

Osteoarthritis involves all tissues of the diarthrodial joints including the bone, cartilage, and supporting elements. It can affect any joint, the most commonly affected joints includes joints in hands, knees, hips and spine.

The prevalence of osteoarthritis is increasing due to population ageing and an increase in related factors such as obesity. An estimated range of 10% to15% of all adults aged over 60 have some degree of OA, with prevalence higher among women than men. (Fransen M et al., 2011)

Etiology

The exact cause of osteoarthritis is not known. The interaction of several factors may cause osteoarthritis. Events which changes the function and properties of the chondrocytes has the potential to cause osteoarthritis.

Factors which has the potential to cause osteoarthritis are

- Age (above 50 years)
- High bone mineral density
- History of immobilization
- Obesity
- Prolonged occupational or sports stress
- Trauma
- Gender and ethnicity
- Genetics and family history
- Diet (Hinton R et al., 2002 ; Haq I et al.,2003)

Types of osteoarthritis

There are two main types of osteoarthritis:

a) Primary: It is the most common, generalized type occurs when cartilage failure due to unknown cause and it primarily affects the knees, hips, fingers, thumbs, spine and the great (big) toes.

b) Secondary: It occurs with a pre-existing joint abnormality, including injury or trauma, such as repetitive or sports-related; inflammatory arthritis, such as rheumatoid, psoriatic, or gout; infectious arthritis; genetic joint disorders, such as Ehlers-Danlos (also known as hypermobility or "double-jointed; congenital joint disorders; or metabolic joint disorders (Gui xing qiu, 2010)

Articular cartilage (composition and structure)

The articular cartilage comprises of chondrocytes, which are highly specialized cells and an extracellular matrix consisting of proteoglycans (PGs), collagens (types II, IX, XI), water, non-collagenous matrix proteins and lipids.

Interaction between proteoglycans and collagen provides unique structural and physiological properties for cartilage to function in weight bearing and joint motion (Scarpellini M et al., 2008)

The proteoglycan molecules consist of numerous long-chain glycosaminoglycans linked to a core protein. These glycosaminoglycans are repeating disaccharide units, composed of a hexuronic acid and a hexosamine.

Glucosamine is the hexosamine constituent of keratan sulfate, the glycosaminoglycan found in hyaline cartilage along with chondroitin-4 sulfate and chondroitan-6 sulfate. These proteoglycan molecules are further linked together on one hyaluronic acid filament forming a large aggregate proteoglycan macromolecule (Owens S et al., 2004; Ng HY et al., 2017)

Healthy cartilage maintains a dynamic equilibrium between processes that produce and processes that degrade the matrix components (Dodge GR and Jimenez SA, 2003)

Pathogenesis of osteoarthritis

The pathogenesis of osteoarthritis involves a combination of cellular, mechanical and biochemical process. The interaction of all these processes leads to changes in the function, composition and properties of articular cartilage. (Man GS and Mologhianu G, 2014)

Normally,Cartilage undergoes remodelling process stimulated by joint movement or use.Chondrocytes in cartilage respond to micro environment to maintain balance between synthesis and degradation of extracellular matrix.

In osteoarthritis, the mechanism that maintains the matrix equilibrium fails, extracellular matrix components are lost due to increased expression of matrix degradaing enzymes, inhibition of matrix synthesis and excessive production of proinflammatory mediators. (Kim JR et al., 2018)
The combination of decreased matrix synthesis, increased matrix degradation and wear and tear of the weight bearing joints leads to destruction of the articular cartilage. This destructive processes lead to swelling, decreased shock absorbing properties (compliance), softening, fracturing, fibrillation, ulceration and ultimately erosion of the cartilage with exposure of the subchondral bone results in osteophyte formation. (Nemandra Sandiford, 2020)

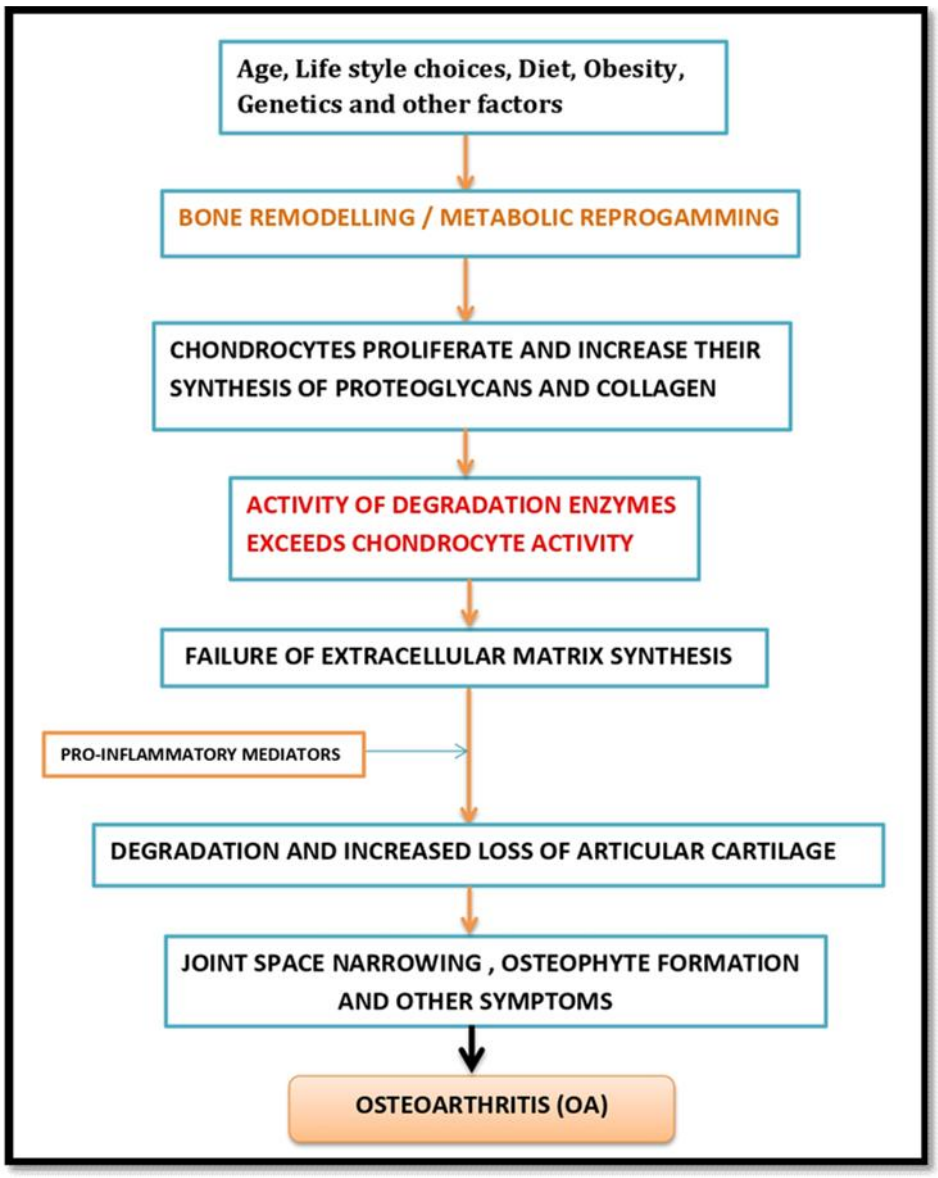

Fig no 1 → Pathogenesis of Osteoarthritis

Pathological changes seen in oteoarthritis

- Progressive loss and destruction of articular cartilage
- Thickening of sub chondral bone
- Formation of osteophytes
- Variable degrees of inflammation of the synovium
- Degeneration of ligaments
- Menisci of the knee
- Hypertrophy of joint capsule (Chen D et al, 2017)

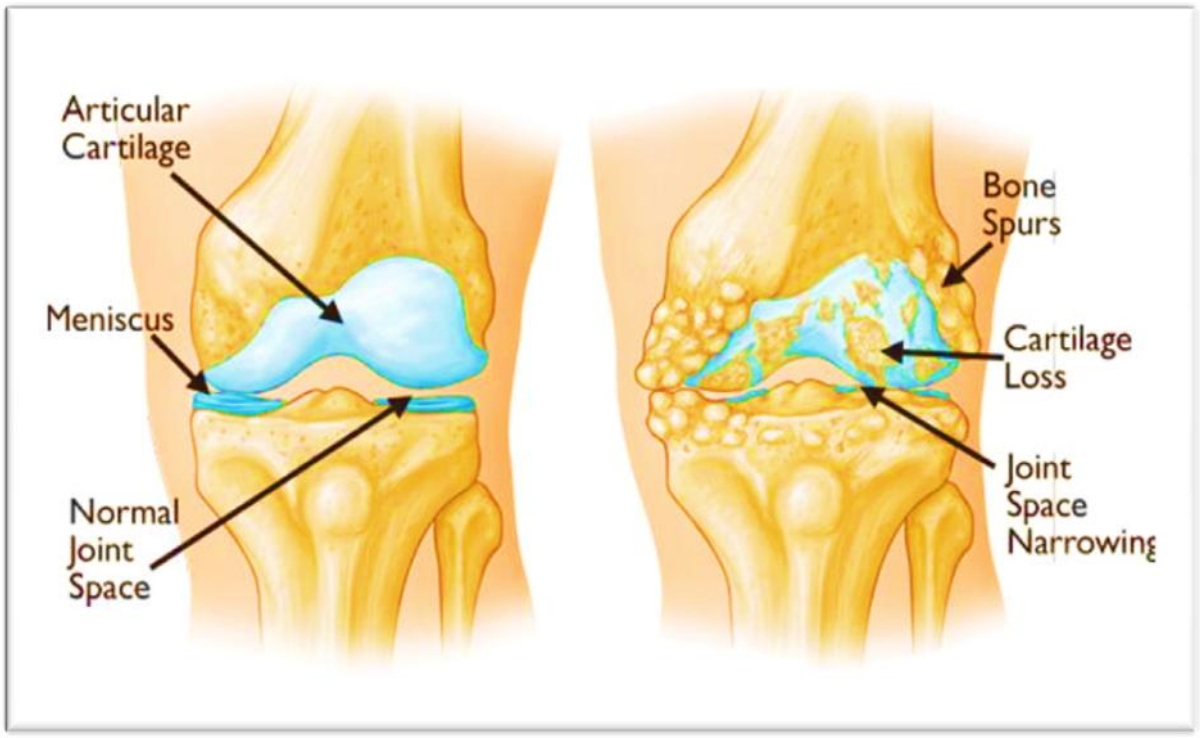

Fig no 2 → Normal joint and Osteoarthritic Joint

Symptoms of osteoarthritis

The characteristic symptoms of osteoarthritis are
- Joint Pain
- Reduced function
- Stiffness
- Joint instability
- Buckling
- Tenderness
- Crepitus with movement of the joint
- Bony swelling (Hunter DJ et al., 2008 ; Racine J and Aaron RK, 2013)

Diagnosis of osteoarthritis

It is primarily a clinical diagnosis, based on the history, physical examination and radiological findings
- Physical examination is important in making diagnosis of osteoarthritis.

- Imaging modalitis include X- ray, MRI, CT scan, Optical coherence tomography (OT), Ultrasoud permit visualization of the structures and can evaluate diagnosis and prognosis.

- Sometimes blood tests are also required to diagnose osteoarthritis. (Braun HJ and Gold GE, 2012)

Role of glucosamine in the treatment of osteoarthritis (OA)

Glucosamine is one of the most studied dietary supplements available today. In the last 30 years, many trials have been conducted and published on the effects of glucosamine on the signs and symptoms of osteoarthritis. (Vangsness CT Jr et al., 2009)

In vitro studies on isolated chondrocytes, or cartilage explants from healthy or OA patients, provide much evidence for the proposed mechanisms regarding how glucosamine supports joint health. It has been shown that glucosamine enhances the production of cartilage matrix components in chondrocyte culture, such as aggrecan and collagen type II.

It increases hyaluronic acid production in synovium explants prevents collagen degeneration in chondrocytes by inhibiting MMPs (matrix metalloproteinase and aggrecanases (predominant cleavage enzymes in the cartilage) (Jerosch J,2011 ; Lippiello L, 2007)

Qui and coworkers studied 178 patients with OA of the knee in a doubleblind protocol comparing treatment for 4 weeks with either daily doses of glucosamine sulfate (1.5 g) or ibuprofen (1.2 g). They concluded that glucosamine was more effective and significantly better tolerated than ibuprofen. (Qiu GX et al., 1998)

Glucosamine has shown potential as a disease-modifying agent in two 3-year, double-blind, ranndomised, placebo-controlled studies in a total of 414 patients with osteoarthritis of the knee (Matheson AJ and Perry CM, 2003)

Two recently published studies have added further information regarding the clinical status of glucosamine in the treatment of OA. The first of these was the National Institutes of Health sponsored GAIT (Glucosamine/chondroitin Arthritis Intervention Trial), which evaluated placebo, glucosamine hydrochloride 500mg three times daily, chondroitin sulfate 400mg three times daily, the combination of glucosamine hydrochloride and chondroitin sulfate, and celecoxib 200 mg/day in a parallel, blinded 6-month multicentre study of response in knee OA.

The second study was the GUIDE (Glucosamine Unum In Die [once-a-day] Efficacy) trial.This 6-month double-blind, multicentre trial, conducted in Spain and Portugal, compared placebo, glucosamine sulfate 1500mg once daily and paracetamol (acetaminophen) 3000 mg/day in patients with OA of the knee (Bruyere O and Reginster JY, 2007 ; Clegg DO,2006; Herrero-Beaumont G et al ., 2007)

Glucosamine

Glucosamine (2-amino-2-deoxy- D- glucose) , a sugar and an aminomonosacchride, a constituent of glycosaminoglycan in the cartilage matrix and synovial fluid, has been used orally for the treatment ofosteoarthritis since the early 1980's.

Glucosamine, a naturally produced ingredient in the body needed to produce glycosaminoglycans. It stimulates the chondrocytes to produce proteoglycans and increase the production of hyaluronic acid resupply of synovial fluid to act as a lubricant (Reginster JY et al , 2007 ; Pavelka K et al ., 2002)

Sources

Glucosamine can be extracted from chitin, found primarily in the exoskeleton of crustaceans (crabs, prawns, and lobsters), as well as in the cell membranes of mushrooms.

It is an important precursor of the glycoprotein and glycosaminoglycan (GAG) synthesis. It is most important for the formation of hyaluronic acid, chondroitin sulfate as well as keratan sulfate, which are the most important components of the extracellular matrix of the articular cartilage and the synovial fluid. (Shmagel A et al, 2019; .Henrotin Y et al., 2012)

Structure

Glucosamine has a molecular weight of 179.17 and is soluble in water , sparingly soluble in methanol or ethanol and practically insoluble in ether or chloroform. More than 50% of glucosamine is nonionized at the pH of the small intestine, allowing rapid absorption. At a pH of 7.4, 75% is in the nonionized form. Following oral administration of glucosamine sulfate, at least 90% is absorbed, with 10% appearing in the feces. (Altman RD, 2009)

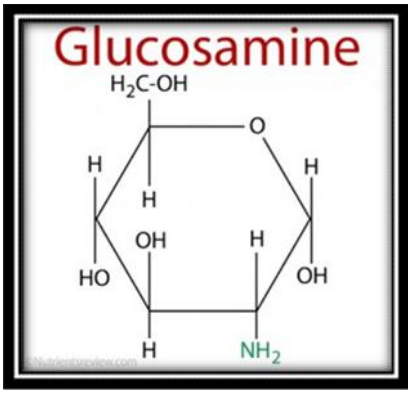

Fig no 3 → Structure of Glucosamine

Synthesis and biochemical pathway

Glucosamine and its acetylated derivative N-acetyl glucosamine are readily synthesized in the body from glucose. It is synthesized by chondrocytes from glucose to produce glycosaminoglycans and to stimulate proteoglycan synthesis.

Glucosamine is a prominent component of the hexosamine pathway, an important process of glycolysis. This metabolic pathway is essential for the biosynthesis of amino sugars to produce glucosamine, catalysed by enzyme glutamine: fructose 6-phosphate amidotransferase (GFAT).

Besides this "endogenous" production, glucosamine provided exogenously can be introduced to cells through glucose transporters (especially GLUT-2), and phosphorylated intracellularly by hexokinase to Glucosamine-6-phosphate.

The next step is the acetylation of glucosamine-6-phosphate to N-acetylglucosamine -6-phosphate (N-Acetyl-GluN-6-P), catalyzed by glucosamine-phosphate-N-acetyltransferase.

Then, this compound is transformed into uridine-5-diphosphate-Nacetyl-glucosamine (UDP-N-Acetyl-GluN) by the enzyme UDP-N-acetyl-glucosamine pyrophosphorylase.

UDPN-Acetyl-GluN is the precursor for the biosynthesis of amino sugars which serve as building blocks for glycosaminoglycans, proteoglycans, and glycoproteins (Ivanovska N and Dimitrova P, 2011 ; McCarty MF et al., 2019 ; Salazar J, 2014)

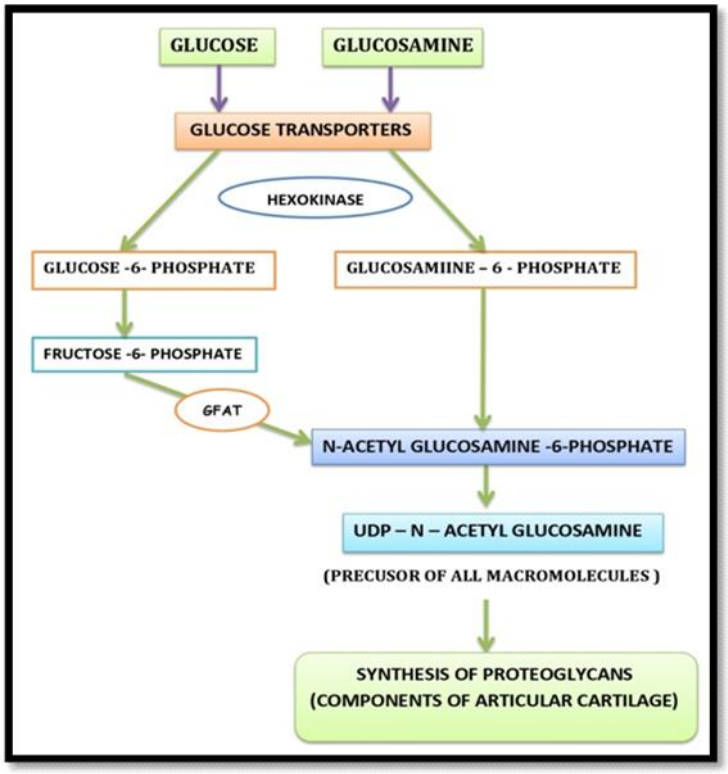

Fig no 4 → Biochemical Pathway of Glucosamine

Actions of glucosamine

After administration, it reaches the articular cartilage and the possible mechanisms of action of glucosamine for the treatment of osteoarthritis are

1.It is preferentially incorporated by chondrocytes into the components of glycosaminoglycan chains in the intact cartilage.
2. Stimulates the synthesis of physiological proteoglycans
3. Decreases the activity of catabolic enzymes, including metalloproteases
4. Suppression of IL-1 induced inflammatory reaction by decreasing NF- kappa B activation.
5.Suppression of superoxide radical generation (Pavelka K et al .,2002 ;Neil KM et al., 2005)

1) Glucosamine – incorporated by chondrocytes to produce proteoglycans

Glucosamine is a building block for articular cartilage's extracellular matrix. Specifically, it is used to produce GAGs and proteoglycans, critical components of articular cartilage ground substance (James CB and Timothy L. UhL, 2001)

Glucosamine can be imported by cells and incorporated into newly synthesized glycosaminoglycans. UDP- N-Acetyl glucosamine , the end product of hexosamine pathway, is the precursor for synthesis for glycosaminoglycan synthesis (Alexander Shikhman, 2006)

2) Decreases the activity of catabolic enzymes

Studies suggests that enzymatic breakdown of the extra-cellular matrix might be reduced by the addition of glucosamine. This was suggested by down-regulation of transcript abundances and reduced MMP enzymatic activity, which preserves the cartilage matrix in the catabolic osteoarthritis situation (Uitterlinden Ej et al., 2006 ; Cibere J et al.,)

3) Suppression of il-1 inflammatory reaction

Glucosamine inhibits NFκB activation induced by IL-1β . IL-1β is a proinflammatory cytokine released by synovial cells, chondrocytes and invading macrophages in inflamed joints. IL-1β plays a critical role in the inflammatory process and the connective tissue destruction observed in osteoarthritis. It has been shown that glucosamine significantly suppresses the Interleukin-1 beta (IL-1β) signalling pathway, an essential mediator of the inflammatory responses, by inhibition of NF-κB activation, which in turn leads to a decrease of both inflammatory and degenerative mediators of the disease. Additionally, it has been reported that GlcN inhibits various proinflammatory mediators such as, cyclooxygenase-2 (COX-2), nitric oxide (NO), and matrix metalloproteinases (Largo R et al., 2003; Gilzad Kohan H et al., 2015)

4) Suppression of superoxide radical generation

It is well-established that the levels of reactive oxygen species and oxidatively damaged proteins are elevated in the synovium of patients with arthritis. Glucosamine is capable of scavenging reactive oxygen species, such as superoxide anion, hydrogen peroxide, and hydroxyl radical (Reginster JY et al., 2001; Rubin BR et al., 2001)

Pharmacokinetics of glucosamine

The absorption of orally administered glucosamine is nearly 90%. After absorption, it is incorporated into plasma proteins during first- pass metabolism.

About 90% of glucosamine administered orally as a glucosamine salt gets absorbed from the small intestine and from there it is transported, via the portal circulation, to the liver. It appears that a significant fraction of the ingested glucosamine is catabolized by first-pass metabolism in the liver and 10% appearing in the feces (Neil KM et al., 2005; Thakral R et al., 2007)

Dose and formulation

There are different forms of glucosamine in the market. Glucosamine preparations are either extracted from chitin (from crustacean shells) by acid hydrolysis (and thus patients with shellfish allergies should be cautioned to avoid the use of glucosamine) or chemically synthesised.

Glucosamine is a weak organic base, which must first be stabilised as a salt. Different forms of glucosamine commonly available on the market:

-Glucosamine hydrochloride (from crab shells),
-Glucosamine sulphate (from shrimp shells) and
-Chemically synthesised glucosamine (as sulphate form)
-N-acetyl-glucosamine

The absolute daily dosing of glucosamine varies according to the preparation type, owing to the differences of the molecular size of the associated salt.

The recommended daily dosing of glucosamine generally ranges from 1250 mg 1500 mg.

Single oral dose of glucosamine (1500 mg) approximately produces plasma concentration of 10 µmol, while taking a dose (500 mg) three times daily produces approximately a plasma concentration of 3 µmol (Persiani S et al.,2007; Ahmed M A ,2007; Yousry H H,2015)

Side effects

Side effects after glucosamine administration are rare and may include stomach upset, heartburn, nausea, diarrhea or constipation , hypersensitivity. (Dahmer S and Schiller RM, 2008).

Conclusion

Osteoarthritis is a chronic arthropathy characterized by the degeneration and loss of articular cartilage, resulting in disruption of its mechanical properties and those of subchondral bone as well as modifications in the surrounding soft tissue. The loss of cartilage has been thought to be the pathophysiologic mechanism of osteoarthritis. It results from failure of chondrocytes to maintain homeostasis between synthesis and degradation of extracellular matrix components. Glucosamine, a constituent of glycosaminoglycans in cartilage matrix and synovial fluid, could have various pharmacological actions in articular cartilage and joint tissues. Glucosamine is one of the most studied dietary supplements available today. In the last 30years, many trails have been conducted and published on the effects of glucosamine on the signs and symptoms of osteoarthritis. Endogenous and exogenously administered glucosamine is thought to be involved in the synthesis of glycosaminoglycans, proteoglycans and inhibits the degradation of cartilage by suppressing catabolic enzymes. Most currently available glucosamine supplements are taken orally at a dose of 1500mg. In conclusion, this review article shows that the use of glucosamine is beneficial in decreasing signs and symptoms of osteoarthritis and improves the joint function by enhancing the biosynthetic activity of chondrocytes and preventing cartilage loss in patients with osteoarthritis.

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