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REVIEW ARTICLE

Biological Markers Associated Osteoarthritis

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ABSTRAK

Osteoartritis ialah penyakit degeneratif sendi yang kerap berlaku pada warga tua seluruh dunia. Prevalen penyakit ini terus meningkat dan menjadi penyebab utama kesakitan serta hilang upaya pada umur tua. Osteoartritis boleh didiagnos melalui X-ray filem ringkas berserta tanda klinikal dan ciri-ciri struktur. Ketidakseimbangan antara sintesis dan degradasi kartilaj telah dinyatakan terlibat dengan perkembangan osteoarthritis, yang dikaitkan dengan kematian kondrosit. Walaupun terdapat banyak sitokin dan petanda biologi yang berkait dengan penyakit ini, ulasan ini akan menyediakan latarbelakang dan perbincangan petanda-petanda biologi yang diketahui terlibat dengan perkembangan osteoarthritis termasuk hasil akhir 'glycation' lanjutan, glutation dan glikosaminoglikan.

Kata kunci: petanda-petanda biologi, penyakit degeneratif sendi, osteoartritis

ABSTRACT

Osteoarthritis is the most common degenerative joint disease that develops in the elderly. The worldwide prevalence continues to rise, leading to pain and disability in older ages. Osteoarthritis can be diagnosed by using plain film X-ray combined with clinical appearance and structural features. The imbalance between cartilage synthesis and degradation has been explained in the development of osteoarthritis, which is associated with chondrocyte death. There are many cytokines and biological markers related to the disease. The present review provides a background and discusses the known biological markers that are related to developing osteoarthritis. These include advance glycation end products, glutathione and glycosaminoglycans.

Keywords: biological markers, degenerative joint disease, osteoarthritis

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INTRODUCTION

Osteoarthritis (OA) is a group of degenerative joint diseases (DJD) and one of the most common disorders worldwide which leads to pain and disability in the elderly (Arden & Nevitt 2006; Garstang & Stitik 2006). Osteoarthritis is considered by chronic loss of hyaline cartilage at the joint articulation and osteophytes formation in the affected joints which leads to progressive pain and limitation of movement and function in aged individuals (Gahunia et al. 1995; Hayashi et al. 2012; Henrotin 2012). The risk factors associated with OA include age, sex, history of joint injury, obesity, genetic factors, and mechanical factors, containing abnormal joint structure and malalignment (Garstang & Stitik 2006). The incidence of OA continues to increase with age and the prevalence of osteoarthritis is greater in men than in women in most joints before 50 yrs of age. Furthermore after 50 yrs, women are more often affected than men, especially in the hand, foot, and knee osteoarthritis (Van der Kraan 2012). Osteoarthritis can be defined by pathology of joint structure comprising chronic loss of hyaline articular cartilage, changes in the subchondral bone; the bone under the cartilage, development of osteophyte and increased bone sclerosis and thickness of the bone under the cartilage (Shane Anderson & Loeser 2010; Gahunia et al. 1995).

Not only change of joint structure, the connective tissue surrounding the joint can be affected. The synovial membrane has increase in inflammatory cytokines. The ligaments are often lax and there is muscle weakness. Currently, the diagnosis of OA comprises both clinical appearance and structural features. Plain film radiograph is widely used as a gold standard to define the damaged articular cartilage (Gahunia et al. 1995). The common radiographic features including decrease joint space, formation of osteophyte, subchondral thickness or sclerosis and abnormalities of bone density.

The etiology of osteoarthritis is not well understood and has multifactorial association (Garstang & Stitik 2006; Henrotin 2012; Hochberg 2012). Age is the most important risk factor of osteoarthritis and the relationship between aging and OA is well known but the mechanisms are still not fully understood (Loeser 2010). At the cell and tissue level, articular cartilage consist of few cells and highly surrounding extracellular matrix (ECM). Chondrocyte is present in articular cartilage and involved in maintaining the balance of matrix synthesis and degradation (Goggs et al. 2003). Many previous studies observed the chondrocyte death related to progressive loss of hyaline articular cartilage which report an increased amount of apoptotic program cell death (Aigner et al. 2001; Almonte-Becerril et al. 2010; Blanco et al. 1998; Dang & Kim 2009). Thomas investigated the incidence of chondrocyte apoptosis in equine articular cartilage specimens and observed the relationship between the process of chondrocyte death and the degree of cartilage degradation. They demonstrated that chondrocyte

apoptosis is associated with degree of cartilage matrix damage and mechanical loading environment of the joint is a significant positive correlation between severity of OA and apoptosis (Thomas et al. 2007). Chondrocyte death has been observed during the development of OA but whether this is an early or late event is still unclear. Therefore, the breakdown of cartilage during the OA pathogenesis is related to chondrocytes death and the loss of ECM (Almonte-Becerril et al. 2010).

REACTIVE OXYGEN SPECIES (ROS)

Reactive oxygen species (ROS) are free radicals, which play an important role in the aging process in both human and animal models (Afonso et al. 2007; Ziskoven et al. 2010). There are group of free radicals oxygen molecules such as hydroxyl group (OH^-), hydrogen peroxide (H_2O_2), superoxide anion (O^-_2) and nitric oxide (NO) (Henrotin et al. 2003; Lepetsos & Papavassiliou 2016). In the articular cartilage, chondrocytes generate several forms of ROS such as superoxide, hydrogen peroxide, reactive nitrogen species and nitric oxide. In normal process, there are various anti-oxidants which control the levels of ROS (Biemond et al. 1984). There are antioxidant system in the human body which include enzymatic and non-enzymatic antioxidants, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidise (GPX), glutathione (GSH), ascorbic acid (vitamin C), α-tocopherol (vitamin E) and carotinoids.

Oxidative stress can also disturbance in the antioxidant defenses mechanism against the level of ROS, which results in cellular damage and disruption of redox homeostasis leading to chondrocyte senescent by causing destruction of proteins, lipids, and DNA directly (Henrotin et al. 2005). Increase in ROS level is related to aging process and plays an important role in the progression of OA. There are various increasing inflammatory cytokines in OA such as IL-1, IL-6 and TNF-α, which encourage production of ROS as a result of increased level of MMPs (Loeser 2009; Loeser 2010).

THE DIAGNOSIS OF OSTEOARTHRITIS

Kellgren and Lawrence in 1957 were the first to use radiographic grading system using plain film radiograph. Nowadays it is the gold-standard for identifying the structural changes in joint structure in patient with OA (Altman & Gold 2007). Radiographic methods of knee OA have usually assessed the disease progression, its least expensive method for detecting joint structural change in patients with OA. The severity of disease normally determined by using the Kellgren and Lawrence grading system, the most widely used and accepted standard for diagnosis of radiographic OA. The grading system consists of 4 grade scales, for grade of 0 suggests that no structural changes of OA and grade 4 is defined as the severe one. The grading scale has been analyzed for illustrating the progression of OA comprising both osteophyte formation and decreased in joint space.

PATHOGENESIS OF OSTEOARTHRITIS

Typical characteristics of osteoarthritis are the progressive loss and damage of hyaline articular cartilage in the articulation in the affected joint. The homeostasis of cartilage matrix synthesis and degradation are the main causes of disease progression (Aigner et al. 2001). The mechanism of matrix degradation is still unclear but associated with both environmental and genetic factors. There are many factors related the disease such as the change of metabolic, biochemical and metabolic homeostasis. In OA cartilage, not only the chondrocytes are produced many cytokines and growth factors but also the synovial tissue. On the anabolic process, the synthesis of extracellular matrix is stimulated by insulin-like growth factor (IGF)-1, transforming growth factor (TGF)-b, fibroblast growth factors (FGFs) and bone morphogenetic proteins (BMPs) (Aigner et al. 2001). From the catabolic process, Matrix metalloproteinase (MMP) is increased and produced the inflammatory cytokines including interleukin (IL)-1, IL-17 and IL-18 and tumor necrosis factor (TNF)-a, which leads to decrease of aggrecan and matrix components, as a result of cartilage matrix degradation (Afonso et al. 2007; Blanco et al. 1998; Loeser 2010).

There are biochemical and structural changes in OA cartilage including The increasing of water content and the matrix macro molecules such as aggrecan can be decrease. The structure of the collagen is damaged, which leads to reduced stiffness and the cartilage more brittle.

BIOLOGICAL MARKERS ASSOCIATED OSTEOARTHRITIS

GLUTATHIONE (GSH)

Nowadays, many studies focused on damaging effects of free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) in osteoarthritis (Valko et al. 2007; Ziskoven et al. 2010). Glutathione (GSH) is one of an endogenous important intracellular anti-oxidant, plays a role in the detoxification of oxygen free radicals. The increasing of ROS levels, the ratio of oxidized to reduced glutathione is changed (Loeser 2010). Glutathione is performed in the cytosol of various cell types and delivered to extracellular matrix and other organelles for example, mitochondria, endoplasmic reticulum and the nucleus (Bertrand et al. 2010; Blanco et al. 2004). GSH occurs not only the reduced state (GSH) but also oxidized state (GSSG). The ratio of GSH/GSSG is necessary to maintain normal functioning and is a good measure of oxidative stress of a tissue and organism (Regan et al. 2008). The protective effect of glutathione against the oxidative stress such as the glutathione is a importance co-factor of numerous enzymes for against oxidative stress, including glutathione peroxidase (GPx), glutathione transferase and others. There are previous studies about glutathione associated osteoarthritis as shown in Table 1. The glutathione represents the major cellular redox

buffer and therefore is a representative indicator for the redox environment of the cell.

GLYCOSAMINOGLYCANS (GAGS)

Glycosaminoglycan (GAG) are one of the most important components of extracellular matrix (ECM) and play multiple roles in different tissues and organs, associated with other pathological conditions such as osteoarthritis, inflammation, diabetes mellitus, spinal cord injury and cancer. GAGs are polysaccharides, devided in five major groups including: chondroitin sulfate (CS), dermatan sulfate (DS), heparan sulfate (HS), keratan sulfate (KS) and hyaluronan (HA) (Studelska et al. 2006). The mechanism of extracellular matrix degradation in joint diseases is not fully understood but the main factor associated is the reactive oxygen species (ROS). An increased level of ROS as a result of decreased levels of GSH leading to reduce the synthesis component of the articular cartilage, which are proteoglycan and hyaluronic acid. Inerot et al. (1978) investigated the structural change of proteoglycans of aging cartilage in the degenerated cartilage of osteoarthritis, found that proteoglycans from the degenerated cartilage were smaller than those from the same-age normal cartilage and had partially lost their ability to bind to hyaluronic acid and form aggregates (Inerot et al. 1978). The recent studies about glycosaminoglycans associated osteoarthritis as shown in Table 1. The structural and composition changes of glycosaminoglycan in OA cartilages could be the result of changes in both the catabolic and anabolic process of chondrocytes during the progression of the disease.

ADVANCED GLYCATION END PRODUCTS (AGES)

Advanced glycation end products (AGEs) are the macromolecules and formed in body during the process of normal aging, suggesting the association with development of osteoarthritis. AGEs produces from non-enzymatic glycation of proteins and lipids leading to formation of collagen cross-links (Nah et al. 2007; Yang et al. 2015) affects the structural properties of cartilage as a result of increased stiffness and brittle in the hyaline articular cartilage (Chen et al. 2005). Increasing of AGEs in cartilage involve in cellular activities such as bone remodeling process, which increase of abnormal proliferation, differentiation, and apoptosis of bone cells, such as osteoclasts (OCs), osteoblasts, and osteocytes (Yaffe et al. 2011; Yang et al. 2015). DeGroot et al. (2001) investigated the relationship between accumulation of AGE levels and chondrocyte turn over of proteoglycans in articular cartilage of human. They found that the accumulation of AGE increased with aged and its has negatively affects synthesis and degradation of proteoglycan as a result of development of OA (DeGroot et al. 2001). It has been suggested that, increased of advanced glycation end products (AGEs) in cartilage related to aging and responsible for decreased the ability of the cartilage to remodel

Table 1: Summary of OA biomarker studies including advance glycation end products, glutathione and glycosaminoglycans in the osteoarthritis.

Author	Biomarkers assessment	Species, tissue, specimens	Result of study
Steenvoorden et al. (2006)	Level of Advanceglycation end products (AGEs) and receptor of Advance glycation end product (RAGE)	Twenty-two donors with focal cartilage degeneration obtained from autopsy cases within 18 hrs of death and Twenty-three age-matched controls subject.	Increased of AGEs level showed in the patients with focal degeneration of cartilage when compared to healthy subjects without cartilage degeneration, therefore AGEs provide to development of osteoarthritis.
Willett et al. (2012)	- Pentosidine as biomarker for Advance glycation end products -Collagen content - Ratio of glycosaminoglycan /collagen	Twenty-eight male, two month old Hartley guinea pig (HGP) model.	Increased of advance glycation end products and pentosidine cross-linking are related with progression of osteoarthritis knee. The accumulation of AGEs in the HGP model of osteoarthritis knee did not develop disease progression.
Vos et al. (2012)	- Pentosidine as marker of Advance glycation end products	Sixty-nine patients with severe stage of osteoarthritis knee and undergoing total knee replacement.	Levels of pentosidine significant increased with age. The inverse relation between AGEs and damage of cartilage in severe stage of osteoarthritis was observed.
Surapaneni and Venkataramana (2007)	- Product of lipid peroxidation (MDA) - Levels of glutathione (GSH) - Activities of superoxide dismutase (SOD); - Glutathione peroxidase (GPX) - Glutathione transferase(GST)	Twenty patients with osteoarthritis.	Increased in MDA levels, SOD, GPX and GST activities showed in patients with osteoarthritis and decreased of GSH, ascorbic acid, plasma vitamin E levels was observed in patients with osteoarthritis when compared to controls.
Ostalowska et al. (2006)	Activities of superoxide dismutase, glutathione reductase, glutathione peroxidase and glutathione-S-transferase)	Fourty-one patients with knee osteoarthritis and twenty-two control subjects.	Increased activities of all enzymes was observed in patient with osteoarthritis knee when compared to the control subjects.
El-barbary et al. (2011)	- Serum malondialdehyde (MDA) - Superoxide dismutase (SOD) - Catalase (CAT) - Glutathione (GSH) level and plasma glutathione-S-transferase (GST) - Ceruloplasmin (Cp) level	Thirty RA, thirty OA patients and fifteen healthy subjects.	Demonstrated the negative correlation between SOD, CAT and GSH level, which Increased of oxidative stress in RA and OA patients have led to changes in the levels of antioxidants.
Hirose et al. (2011)	Collagen and glycosaminoglycan (GAG) contents	Femoral heads of sixteen OA patients underwent hip replacement and twenty reference patients due to OA or fracture of femoral neck of femur.	Increased of cartilage water content in human hip cartilage associated with pathology of osteoarthritis.
Naveen et al. (2014)	The levels of Glycosaminoglycan (GAGs) and total protein	Forty-two; twelfth week old Sprague-Dawley (SD) rats and seven patients diagnosed with osteoarthritis who underwent total knee replacement.	The strong correlation between GAG/total protein level and the cartilage stiffness was observed and suggested that the degenerative changes induced by MIA similar to induce by ACLT and human osteoarthritis.
Kuiper and Sharma (2015)	Glycosaminoglycans (GAGs) contents	Four cadaveric knees.	Increasing age, the proportion of hyaluronan was decreased and significantly more chondroitin-6 sulphate than chondroitin-4 sulphate.

its extracellular matrix, predisposing factor for the development of cartilage damage in OA (Viguet-Carrin et al. 2008). The previous studies of AGEs associated osteoarthritis as shown in Table 1.

CONCLUSION

Osteoarthritis is considered as a group of degenerative disorder, which leads to pain and limitation of functional movement in affected joint. The etiology and mechanism are still unclear but associated with many factors. In the cellular level, there are many cytokines and growth factors involve in the mechanism of osteoarthritis. In this review, we presented the literature review of osteoarthritis and biological marker associated the pathology.

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