

Deactivated Phospholipids in an Osteoarthritic Joints: Lost Surface Lubricity

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Abstract

This study is designed to determine phospholipids (PLs) dysfunction on cartilage surface and in synovial fluid (SF) in an osteoarthritic (OA) joints. The (PLs) in (SF) were measured for normal samples, with early eOA and late IOA stages of (OA) and rheumatoid arthritis (RA). During cartilage inflammation enzymatically activated β 2-Glycoprotein I was transformed into antibody conformation (see Fig. 3). Deactivated PLs molecule lost ability to form bilayers and liposomes content in synovial fluid (SF) in osteoporotic joints is significantly higher (2-3 times) above the normal concentration of PLs. Additionally, the osteoporotic cartilage surface showed surface lubricity (f) 0.015 about three times higher, compared to the normal cartilage.

Key words: cartilage; osteoarthritis (oa); β 2-glycoprotein i (β 2-gpi); active and deactivated phospholipid

Introduction

Phospholipids, PLs, molecules with the capacity to adsorb to solid surfaces and/or fluid interface a property that allows them to act as multifunctional chemical compound. The concept that surface-active phospholipids (SAPL) provide effortless sliding of many tissues, including joints, pleura, pericardium and peritoneum was pioneered by Hills research [1, 2]. Phospholipids are highly self-organized

biomolecules in aqueous media, and their structure allows them to form spontaneously vesicles, lamellar phases, and surface membranes function as efficient lubricant, Fig. 1. The analyses of the composition of the SAPLs in the human knee joints reveal that they mostly contain unsaturated phospholipids; 30% palmitoyl-linoleoylphosphatidylcholine (PLPC), 23% dilinoleoyl-phosphatidylcholine (DLPC), 17.5% palmitoyl-oleoyl-phosphatidylcholine (POPC) and 16% stearoyl-linoleoylphosphatidylcholine (SLPC), 8% saturated dipalmitoyl-phosphatidylcholine (DPPC) [3].

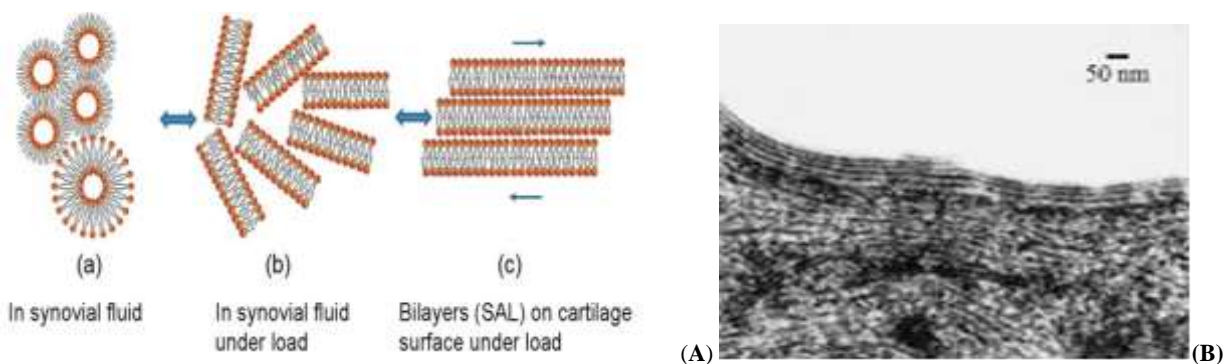


Figure 1: Formation of phospholipid phases in synovial fluid and bilayers on cartilage surface under load at a pH ~ 7.4. A (a) The lipid spheres and vesicles in synovial fluid, A(b) formations of lamellar phases separate opposing cartilage surfaces and A(c) cartilage upper surface bilayers facilitating lamellar-repulsive lubrication with lamellar slippage of the bilayers. (B) Morphology of the articular surface of human knee showing adsorbed phospholipid bilayers [2].

Strongly adsorb and cohesive SAPL linings to act as lubricant, barrier against abrasion, corrosion and possibly against invasion by microorganisms. As the 'sealant', it could be the true barrier rather than the cells providing its mechanical support [1, 2]. The multilamellar structure of phospholipids, namely the surface amorphous layer (SAL), covers the natural surface of articular cartilage found in diarthrodial joints [4, 5]. A very high porosity (75 to 80 %) to be a critical factor in providing excellent hydration, more specifically hydration lubrication properties displayed by articular cartilage [2, 3]. Morphology of the articular surface of human knee showing adsorbed phospholipid bilayers, Fig.1 (B) [2].

The surface-active phospholipids (SAPL) coating on the articular surface possesses highly desirable lubricating properties for efficient joint function. The inflammation and breakdown of cartilage cause bony and surface deterioration and was name osteoarthritis disease. The uppermost lipid bilayer (i.e., surface amorphous layer (SAL)) of articular cartilage surface is degraded during cartilage inflammation osteoarthritic disease [4, 5, 6].

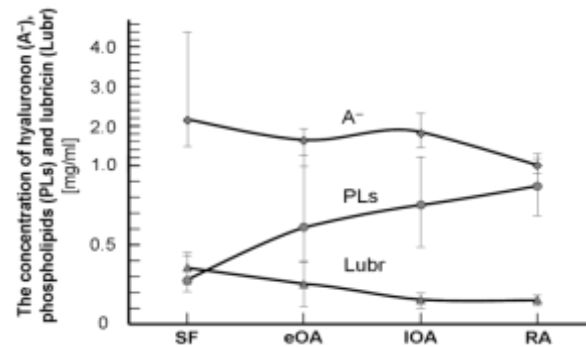


Figure 2: The levels of hyaluronan (A⁻), phospholipids (PLs) and lubricin (Lubr) in human synovial fluid (SF) in patients with healthy joints control (SF) and joint diseases with early osteoarthritis (eOA), late osteoarthritis (IOA) and rheumatoid arthritis (RA) were 2 to 3 times higher above the normal range.

Compared to patients with healthy joints control (SF), patients with early (eOA) and those with late (IOA) had higher levels of most PLs species (2 to 3 times) above the normal range (see Fig. 2). The concentration of components of synovial fluid (SF), such as hyaluronan (A⁻), lubricin, and surface-active phospholipids, from unaffected controls (or normal), (eOA), (IOA), and RA in the human synovial fluid are shown in Fig. 2. During osteoarthritis, OA, and rheumatoid arthritis, RA, contain less hyaluronan (A⁻) and lubricin and are contain more with phospholipids. Also, the MW distribution of (A⁻) shifted toward the lower range in OA and RA SF. These results indicate that activities in OA and RA SF are enhanced, leading to decreased levels of lubricin and hyaluronan (A⁻) [4-7].

Materials and Methods

The phospholipid species were quantified by mass spectrometry (ESI-MS/MS) [4]. The research was carried out using synovial fluid derived from undamaged controls and patients with early and late osteoarthritis and rheumatoid arthritis. After comparing control synovial fluids, SF of patient with early and late OA had higher levels of most PLs species. Most of the PLs data for this paper was taken from Kosinska et al [4, 5].

Results and Discussion

Molecules of β 2-Glycoprotein I, (β 2-GPI) (MW of 50 kDa) circulate in the body in the range 50-500 μ g/ml and autoimmune virus transforms β 2-GPI in an antibody, Figure 3. The (β 2-GPI) participates in antiphospholipid antibody syndrome (APS) through binding of (β 2-GPI) to the anionic charged phospholipid ($-PO_4^-$) group. At a pH around 7, (β 2-GPI) amino acids (arginine, lysine and tryptophan) are positively charged ($-NH_3^+$): an acid-base interaction occurs between the protonated amino acid functional group ($-NH_3^+$) and the phosphate ($-PO_4^-$) membrane group: $(\beta_2\text{-GPI-NH}_3^+) + (\text{PLs-PO}_4^-) \rightarrow (-\text{NH}_3^+ \text{PO}_4^-)$ interaction and electrostatic attractions is strong enough to destroy the PLs bilayer on the articular surface and deactivate all phospholipids in the synovial fluid (SF). β 2-GPI is a highly adhesive protein that binds to various cell receptors, β 2-GPI binds with negatively charged phosphate groups ($-PO_4^-$) at pH \sim 7.4. During cartilage inflammation enzymatically activated β 2-Glycoprotein I was transformed into antibody an open hockey-stick-like conformation (see Figure 3) [8, 9].

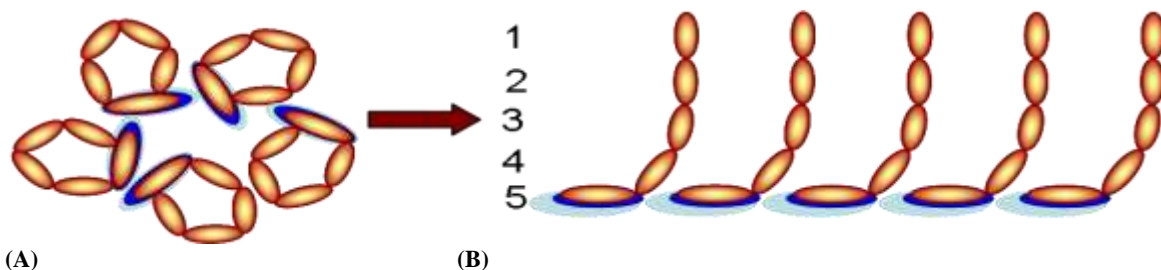


Figure 3; (A) Conversion of β 2-Glycoprotein I (β 2-GPI) of the circular conformation (closed molecules) into (B) an open hockey-stick-like conformation, each molecule has five domains (1-5).

In Figure 3 (A) the closed circular conformation of plasma (β 2-GPI) as it circulates in plasma in a healthy joint, and (B) the open hockey stick-like

conformation in APS syndrome and (β_2 -GP I) is binding to negatively charged ($-\text{PO}_4^-$) phospholipids. The autoantibodies will bind and stabilize (β_2 -GPI) in its hockey-stick-like conformation.

Phospholipid binding takes place in the domain (5) of β_2 -GPI, **Figure 3 (A)**, which contains positively charged groups ($-\text{NH}_3^+$) at pH ~ 7 . In the blood plasma, the β_2 -GPI molecule is in a closed form in which the domain (1) interacts with the domain (5). For a pH of about 7, amino acids in the domain (5) (arginine, lysine, and tryptophan) with a functional group ($-\text{NH}_2$) are positively charged ($-\text{NH}_3^+$), hence the acid-base

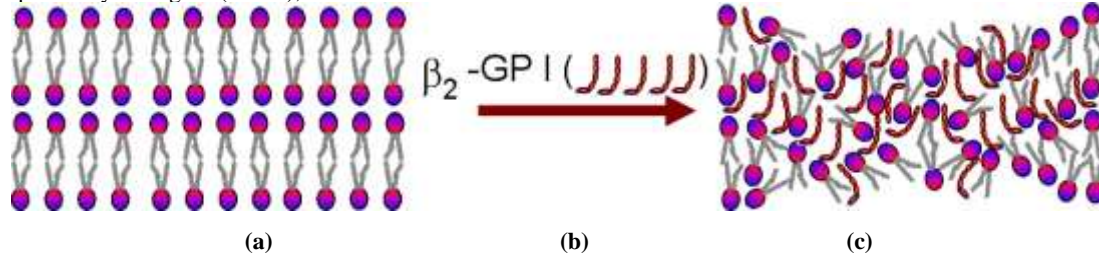
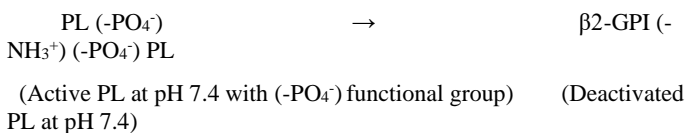


Figure 4 : (a) PL bilayers on the cartilage surface, (b) open stick-hockey conformation of β_2 -glycoprotein I, (c) phospholipid molecules deactivated by stick-hockey conformation of β_2 -glycoprotein I

Wettability measurement of the contact angle (theta) clearly demonstrated a highly significant decrease in hydrophobicity, falling from 103 degrees for 13 bovine controls (78 degrees for five human controls) to 56 degrees for arthritic hips. These changes were reflected in the quantities of SAPL (and proteolipid) recovered from the same articular surfaces by solvent rinsing, yields of SAPL being 60% lower from osteoarthritic hips [1, 11]. These results indicate that the outermost lubricating layer of SAL deposited onto lubricating surfaces is deficient in OA.

Conclusion

PLs are the foundation in joints boundary lubrication (Fig. 1). In conclusion, we have provided mechanism deactivation functional group ($-\text{PO}_4^-$) of PLs by β_2 -GPI is believed to totally destroy the cartilage surface amorphous layer (SAL). Deactivated PLs molecules form a new insoluble compound β_2 -GPI ($-\text{NH}_3^+$) ($-\text{PO}_4^-$) PL with no ability to lubricate.

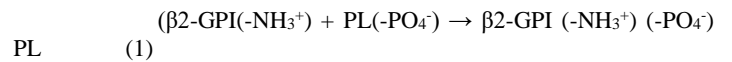


Additionally, hyaluronan and lubricin are unable to take supportive function of lubricant without active phospholipids presence. This fact is in support Hills hypothesis that hyaluronan and lubricin are molecular carriers for insoluble SAPL [1]. Cartilage degradation of membrane anionic phospholipids by antibodies (β_2 -Glycoprotein I) belong to Anti Phospholipid Syndrome (APS) disorder. The work showed surface active phospholipid adsorbed to the articular surface contributes to joint lubrication, but deactivation functional group ($-\text{PO}_4^-$) of PLs ruins their smartness.

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interaction between the group of protonated amino acids ($-\text{NH}_3^+$), and the phosphate group ($-\text{PO}_4^-$):



The electrostatic interactions are strong enough to destroy the PL bilayer on the cartilage surface and deactivate all phospholipid molecules in the synovial fluid (**Figure 4**), whose association constant, $K_{\text{ass}} = 10^5$ [7, 10].

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