Glycosaminoglycans: Their Role in Wound Management

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Chondroprotective agents are substances such as amino acids and mucopolysaccharides[1] (glycosaminoglycans) that support or enhance the connective tissue matrix and, as such, are important structural components of cell membranes[2].

Polysulfated glycosaminoglycans or mucopolysaccharides are natural substances found in the chemical composition of connective tissue and soft tissue in humans and animals. Reference can be drawn to glycosaminoglycans such as chondroitin sulfate, hyaluronic acid, heparin sulfate, heparin and proteoglycans[3]. These compounds are essential in the maintenance of proper elastic integrity within tissues. They have become beneficial in the acceleration of wound healing.

Glycosaminoglycans can be prepared from the principal solids of cartilage (connective tissue which helps to provide support and shape tissue). The principal solids of cartilage are chondromucoid (mucopolysaccharide), chrondroalbumoid and collagen. The chief component of cartilage was found by Miller in 1937 to be chondroitin sulfate(CS). Meyer in 1955 identified chondroitin sulfate as a repeating disaccharide (glucuronic acid and sulfated N-acetylalactosamine) and coined the term "mucopolysaccharide" to describe it[4]. Because mucopolysaccharides such as CS carry sugar molecules and acid groups (COO^-) with each disaccharide unit, the CS structure favors an electrochemical attraction with water. This water loving property affects the structure and mobility of the connective tissue in a positive manner.

This paper will limit its scope to addressing the effects of using a chondroprotective agent as an aid for the management of chronic and acute wounds. The results of an exhaustive literature search suggest that although glycosaminoglycans can have several clinical indications, glycosaminoglycans play an important role in tissue repair and the management of chronic and acute wounds.

The extracellular matrix is composed of various collagens, glycosaminoglycans, and elastin bathed by a tissue fluid found throughout the interstitial space[5]. It is the substratum in which fibroblast and macrophages normally reside, where fibroblast phenotypic transformation occurs, and into which inflammatory cells migrate when called upon during the process of tissue repair[6]. Spontaneous wound healing occurs partly by wound contraction, a process that requires intact functioning fibroblasts, and collagen production[7].

During the past few years many significant developments in the area of glycosaminoglycan-derived products have taken place. Several mammalian glycosaminoglycan products are currently being used in European countries as topical agents for wound healing, treatment of vascular disorders, and anti-inflammatory and anti-athersclerotic applications[8].

There are many biological sources for glycosaminoglycans including porcine tissue, bovine tissue, shellfish and plants. Supply from shellfish is often complicated by erratic supply and

contaminated raw sources. Many plant sources for glycosaminoglycans are available, but when taken orally, digestion of these by humans is more difficult. Glycosaminoglycans derived from animal sources are most frequently used; however, bovine tissues such as trachea and skin provide the most abundant source.

The major glycosaminoglycan in mammals is chondroitin sulfates. There are four types of chondroitin sulfates found in human and animal tissue: Type A is most abundant in all tissues other than the skin, Type B is most abundant in the skin, Type C is found to be most abundant in shellfish and Type D is found in minor quantities in its polysulfated state[9] in all species. Type A is most commonly referred to as chondroitin-4 sulfate, Type B as Dermatan sulfate, Type C as chondroitin -6 sulfate and Type D as chondroitin polysulfate.

Some of the most recent published literature presents observations on the structure-activity relationship of these agents. Glycosaminoglycans are proported to react with the "bricks" of the connective tissue, collagen and elastin, to maintain the normal structural and functional integrity of the joints, arteries, skin and other tissues[10]. These building blocks form cross-linkages with proteins such as collagen, the basis of cartilage. Proteoglycans are the major component of the amorphous ground substance of cartilage. Chondroitin sulfates are an integral part of this macromolecule, possessing an electric charge which favors an electrochemical attraction with water. The fluidity and compressibility of joint/tissue movement is due to this arrangement of water containing molecules. Analysis of young tissue to old tissue reveals biological patterns that indicate young tissue is relatively un-crosslinked, maintaining high elasticity. Measurable differences of sulfonated chondroitin affecting the structure of the tissue may result in tissue stress.

Chondroitin sulfates are produced by cells called chondrocytes, found primarily in cartilage and connective tissue[11]. As human beings age, the chondroitin sulfates that are produced by the chondrocytes decreases contributing to wrinkled skin, arthritis and other ailments. Supplemental chondroitin sulfates have been part of nutritional intake studies. These studies have shown that the consumption of chondroitin sulfate resulted in measurable boosts in their levels within the affected tissues[12].

In a study of twenty patients with keratoconjunctivitis sicca, commonly referred to as dry eye, patients preference was noted for tears solutions containing chondroitin sulfate[13]. Eighteen patients reported marked improvement over the course of the study, in terms of the severity of itching, burning, and foreign body sensation.

A study of 42 human eyes was conducted in Japan to determine the quantitative analyses of glycosaminoglycans in tear fluids; 31 eyes were considered normal and 11 eyes with corneal epithelial disorders[14]. The mean concentration of chondroitin sulfate was significantly lower in patients with epithelial erosion than in normal controls. The results of this study suggest that glycosaminoglycans are synthesized and secreted into the tear fluids and play an important role in the corneal epithelial wound healing in patients with epithelial erosion.

In a degenerative joint study conducted in Italy, the chondroprotective action of chondroitin sulfate was measured by the digestion of hyaluronan by bovine testicular hyaluronidase[15]. It was hypothesized that the administration of chondroitin sulfate could compete for the enzyme hyaluronidase and reduce the degradation process. The study showed that chondroitin sulfate digested a competing amount of the enzyme hyaluronidase; hyaluronidase that is responsible for degenerative disorders of the joints.

In a study measuring endothelial cell protection, the tissue damage was reduced significantly with the use of a viscoelastic containing chondroitin sulfate[16]. The role of chondroitin sulfate in water hemostasis favors tissue hydration which has a well-known beneficial effect on healing[17].

In a double-blind trial, the efficacy and safety of chondroitin sulfate preparations were tested in the treatment of sun-damaged skin in women 40-60 years[18] . A group of 30 women received oral doses, 500mg/daily. Subjective assessment revealed statistically significant improvements in skin condition. Mucopolysaccharides have a repairing effect on solar elastosis.

In another study, a compound comprised of glycosaminoglycans for oral administration was shown to have a repairing effect on sun-damaged skin, brittleness of hair and nails[19]. After 90 days treatment all signs of sun-damage had improved and brittleness of hair and nails were normalized in all cases.

In three separate animal studies by Jasinski[21], Cunitz[22], and Kalbhen[23-24] employing rats and New Zealand rabbits, chondroitin sulfate supported the formation of granulation tissue; promoting accelerated wound healing.

A study in patients with full-thickness burns was conducted using a composite skin replacement composed of Type I collagen crosslinked with a glycosaminoglycan[20]. The composite grafts were placed on full-thickness wounds on the dorsum of arthymic mice. Graft acceptance was 90% without evidence of any inflammation or rejection, resulting in fully healed wound sites.

In conclusion, glycosaminoglycans, specifically such as chondroitin sulfate play an important role as part of the supporting matrix of connective tissue. They function in maintaining salt and water distribution and control a domain, so that a volume of water as much as 1000 times the volume of the proteoglycan can be contained within the molecule. The mechanism of action of exogenous chondroitin sulfate has been shown[25-26]. Its role in water hemostasis favors tissue hydration[27] which has a well-known beneficial effect on healing. Chondroitin sulfate exhibits a water retaining microsponge action similar to that of other mucopolysaccharides, hence it is said to be chondroprotective[28-29].

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