سامية محمد مصطفى

شبكة المعلومات الجامعية

بسم الله الرحمن الرحيم

سامية محمد مصطفى

شبكة المعلومات الجامعية

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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سامية محمد مصطفى

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

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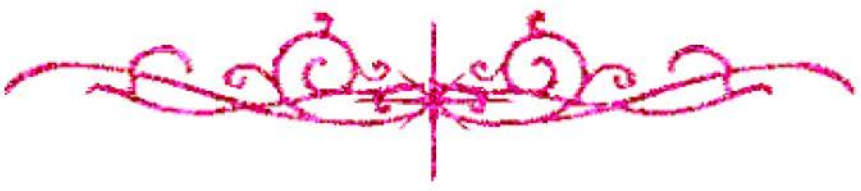

سامية محمد مصطفى

شبكة المعلومات الجامعية

بالرسالة صفحات لم ترد بالأصل

EFFECT OF HYALURONIC ACID ON CHONDROCYTE RESPONSE TO TUMOR NECROSIS FACTOR-α AND INTERLEUKIN-1

Thesis

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By

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بسم الله الرحمن الرحيم

﴿قالوا سبحانك لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم﴾

صدق الله العظيم

البقرة (٣٢)

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CONTENTS

Abbreviation

3D	Three diminsion.
ACR	American collage of rheumatology.
C65	Chondroitin-6-sulphate
Cacl2	Calcium chloride.
CMC	Carpo- metacarpal joint.
Co2	carbon dioxide
COX-1	Cyclo-oxygenase-1.
COX-2	Cyclo-oxygenase-2.
CP	Courté Periodé.
CT	Computerized tomography.
DAG	glycosaminoglycan
DIP	Distal interphalangeal joint.
DMAB	Dimethylaminobenzalhyde
DMEM	Dulbeccos' modified Eagks' medium
DMOAD	Disease modifying osteoarthritis drugs.
ECM	Extracellular matrix.
Elisa	Enzyme linked immune assary
FBS	Fetal bovine serum.
GAGPs	Glycosaminoglycans polysulphoric acid.
GP-c	Glycosaminoglycans peptide- complex.
HA	Hyaluronic acid.
IGF-1	Inhibitory growth factor-1.
IL-1	Interleukin-1.
IL-6	Interleukin-6.
INF-γ	Interferon-γ.
Kda	Kilodalton.
Ks	Keratan sulphate.
LIF	Leukemia inhibitory factor.
M	Molar

MCP	Metacarpo-phalangeal joint.
Mg	milligram
MMP-1	Metalloproteinase-1.
MRI	Magnetic resonance image.
MW	Molecular weight
Nacl	Sodium chlorid
NSAIDs	Non- steroidal anti-inflammatory drugs.
OA	Osteoarthritis .
PG	Proteoglycan.
PIP	Proximal interphalangeal joint.
PPs	Pentose polysulphate.
Rpm	ramp per minute
SF	Synovial fluid.
TENS	Transcutenouse electrical nerve stimulation.
TIMP-1	Tissue inhibitor metalloproteinase-1.
TMB	Tetramethylbenzidine.
TNF-α	Tumor necrosis factor -α.
WBC	White blood cell.
WW	wet weight
μg	Microgram
μL	Microlitre

INTRODUCTION

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Osteoarthritis (OA) is the most common form of arthritis , although the prevalence varies among different populations, it is a universal problem of mankind. It accounts for as much disability in the elderly as any disease[1].

It is the second most common cause of long-term disability among adults in the United States [2]. OA is characterized by deterioration and loss of the articular cartilage, subchondral sclerosis, osteophytes formation,and is often accompanied by a variable grade of inflammation of the synovial membrane .

Most of current researches are directed to understand the pathogenesis of OA, particularly the changes that occur in the articular cartilage with the hope that such understanding may ultimately lead to therapy that can retard the articular cartilage degeneration and/or promoting cartilage repair [3]. At present, pharmacological therapy for OA is only palliative i.e concentrating on treating only the symptoms rather than interfering with the disease progression. Non Steroidal Anti-inflammatory Drugs (NSAIDs) are the most commonly prescribed agents for treatment of both pain and inflammation in OA. Although NSAIDs are well tolerated by some patients, many others suffer from serious adverse effects (gastrointestinal bleeding &interstitial nephritis), especially the elderly ,the population with the highest prevalence of OA [4].

Because of the side effects of NSAIDS, safe and effective alternative therapies are needed. Nowadays two therapies are currently in use. For some patients, growing evidence suggests a simple analgesic such as acetominophen may be as effective as an NSAID in the symptomatic treatment of patients with OA[4]. However, its effect is insufficient to relieve the joint pain in many others.

In addition, the problems with NSAIDs` side effects has led to the development of selective cyclooxygenase-2(Cox- 2) inhibitors to minimize the

local and systemic effects of the traditional NSAIDs [5,6]. These agents are effective in some patients, but do not meet the needs of all, also it is still not clear whether any NSAID alters the progression of OA or not. Therefore, a need remains for therapy that may has an analgesic effect, provide an anti-inflammatory effect if necessary, and also can retard the progression of the disease.

One alternative therapy is developed which is viscosupplementation of the joint by intraarticular injection of hyaluronan (HA). The concept of viscosupplementation for the joint was developed by Balazs, et al(1993) [7]. These investigators established two facts : 1- In normal human joints, with aging, elasticity and viscosity of the synovial fluid(SF)decrease. 2- In arthritic joints, elastoviscosity of SF is considerably decreased as a result of diminished interaction between HA molecules (as with aging), in addition to reduction of its concentration and molecular weight(MW). These investigators contend that loss of the elastoviscocity of SF contributes to the progression of OA. Because HA permeates the superficial layers of the articular cartilage, synovial tissues, joint capsule and intra-articular ligaments, they suggest that the biological role of HA in the joint is to provide protection ,lubrication and mechanical stability to the collagen network, and to the entire joint tissue surface. They suggested that augmentation of synovial fluid with HA would restore the synovial fluid properties and reduce the progression of OA.

Preliminary clinical studies were performed in induced model of OA in dogs using high molecular weight mass(non inflammatory fraction of Na hyaluronan) ,had positive results, as the cartilage wound healed, the inflammatory reaction in the synovial tissue decreased and the capsular pain was reduced [8]. Since that time a number of improved hyaluronan preparations have been developed for ophthalmological, veterinary and muscloskeletal indications. However, all preparations are similar in composition but the difference is only in MW of the molecule used. It was found that low MW preparations were less

effective in controlling the inflammation and pain in OA joint than high MW preparations[9].

To date this therapy has been shown significantly to decrease pain in patients with OA of the knee [10] , and its effect may be continue after the last injection to several weeks[11].

In *vitro* and in *vivo* studies on HA support the concept that elastoviscous hyaluronan solutions can exert anti-inflammatory and analgesic activities. The anti-inflammatory effect could be mediated through inhibition of mononuclear cell phagocytosis [12], cell migration [13],and reduction of prostaglandin release[14].

The analgesic effect would appear to be mediated both directly by entrapment of the pain producing substances within its polymeric network and/or coating the pain receptors[15],and indirectly through the anti-inflammatory effect. Both direct and indirect mechanisms would appear to be depending on the molecular weight and concentration of the HA preparation used[16].

Animal models of joint arthropathies have generated conflicting data on the disease modifying effects of HA, some studies indicating that it slows the progression of OA [17] while others suggest that it may exacerbate tissue damage through relief of joint pain, promoting weight-bearing usage of the unstable joints[18,19].

Intra-articular HA appear to be well tolerated by patients and is relatively safe compared to the other forms of the pharmacological treatment in OA[20]. Most studies confirm that HA relieves joint pain, but it is still not clear if it actually slows progression of joint damage in OA, However the efficacy and the mode of action of this agent is still controversial.