#PeptideWC2022

PEPTIDES FOR PAIN AROUND THE BODY

@drpmr

Anne Abrahamson, MD

FELLOW SSRP

Grosse Ile

The township encompasses several islands in the Detroit River, of which the largest is named as Grosse Ile. Named by French explorers in 1679, Grosse Île means "Big Island"

10 miles long and 1 mile wide

About 10,000 residents

2 bridges to access the island

Post office, grocery store, gas station, airport, horse barn

Pain

What makes it chronic?

There are a lot of theories – alternations in the dorsal spinal cord and brain are one of the key mechanisms

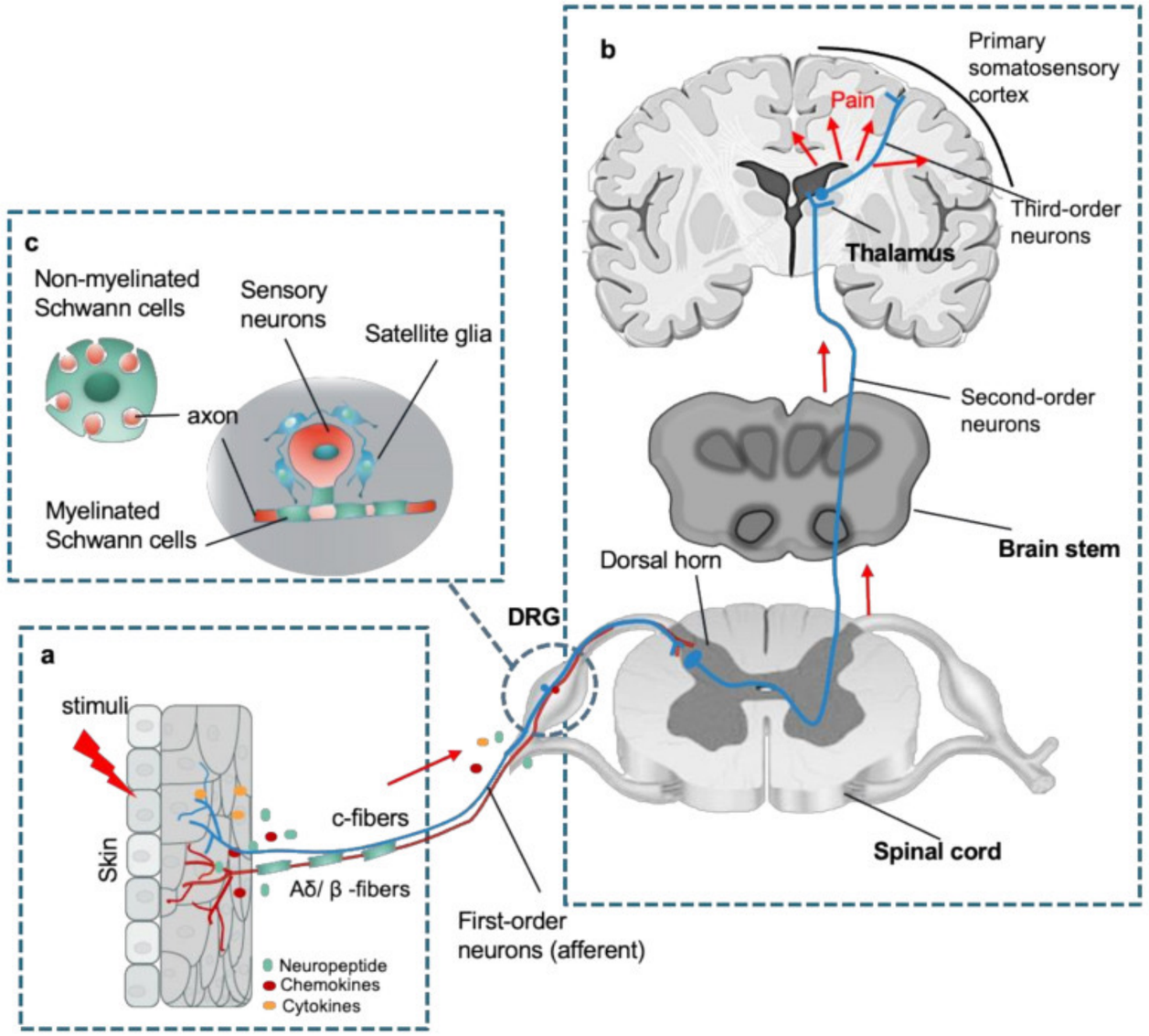
The brain is rewired
Misfiring neural pathways
Leads to unusual pain where certain neural networks are sensitized to overreact
= allodynia

-> signaling gets rewired on a *cellular level*

Emerging studies have revealed that bidirectional signaling between the immune and nervous systems
Contribute to the initiation and maintenance of chronic pain providing molecular insights

Int J Mol Sci. 2021 Feb; 22(3): 1448. Published online 2021 Feb 1
Immune Actions on the Peripheral Nervous System in Pain
doi: 10.3390/ijms22031448

PNS



Overview of PNS in the sensory pathways

Peripheral nerve endings sense a stimulus

Chemicals such as inflammatory mediators
And neuropeptides are released

Axon enters the spinal cord (first order neuron)

Contacts second order neuron in gray matter

Action potential generated travels up to the
Brainstem and thalamic nuclei

Sensory signal reaches third order neuron
From the thalamus which project pain signals
To several cortical and subcortical regions

Int J Mol Sci. 2021 Feb; 22(3): 1448.
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Pain

Focus on the misfiring signaling

Work on cellular level with PEPTIDES to provide relief

peptides change the polarity or inflammatory state of those cells

sends message to turn off activated astrocytes and activated microglial cells in the dorsal root ganglia, dorsal horn, in the spinal cord, in the somatosensory area in the parietal lobe

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SEPTEMBER 8, 2022

Episode 53 - Chronic Pain from the Cellu ...

Sex, Drugs, and Epigenome

PEPTIDE WORLD CONGRESS 2022

Back pain: Psychological treatment shown to yield strong, lasting pain relief, alter brain networks

Two thirds of patients found relief; benefits lasted one year

Date: September 29, 2021

Source: University of Colorado at Boulder

Summary: A study of chronic back pain patients finds that more than two-thirds of those who underwent a novel, 4-week psychological treatment were pain-free or nearly pain-free afterward. Those in the treatment group also saw brain regions involved in pain processing quiet. For many, the benefits lasted at least one year.

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Article

University of Colorado at Boulder. "Back pain: Psychological treatment shown to yield strong, lasting pain relief, alter brain networks: Two thirds of patients found relief; benefits lasted one year." ScienceDaily. ScienceDaily, 29 September 2021.

Pain Reprocessing Therapy (PRT) seeks to turn off the alarm

Article provides a deeper understanding of pain - can correlate to cellular level

Benefits of Healing Peptides

Individual peptides will have certain benefits, however there are some correlations between them when looking from a generalized perspective:

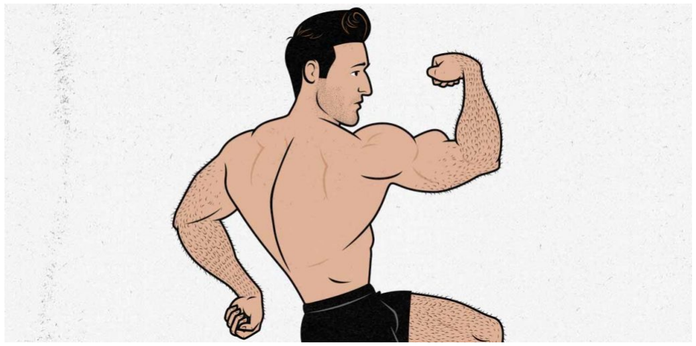
- Increased
  - muscular recovery
  - joint recovery
  - cellular regeneration
  - Angiogenesis (circulation)
  - skin quality
  - Sleep quality
- Decreased
  - inflammation

Benefits of Healing Peptides

Peptides promote healing and fast recovery from injuries that can set you back in the gym

However, peptides do more than just repair damaged tissue or ligament in professional athletes and bodybuilders

Peptides are effective for ordinary, everyday men and woman seeking to combat the symptoms of aging



Pain Peptides

My Top 3

BPC

Body Protection Compound

15 amino acids

TB-4

Thymosin Beta-4 aka TB-500

43 amino acids

PPS

Pentosan Polysulfate

Pain Peptides

A few others

*** Not all inclusive ***

GLUCAGON-LIKE PEPTIDE-1 GLP-1

30 amino acids

HYALURONIC ACID

HA

CEREBROLYSIN

Multi modal neuropeptide

BPC

Best for healing

BPC 157 is a favorite amongst thousands of athletes and bodybuilders because of its ability to trigger *angiogenesis*, which is the formation of new blood cells. This process can trigger *faster healing* and faster generation of cells.

Broad effects thus the name

Benefits

Studies have found that BPC can help in the healing of joints, ligaments, tendons and muscle as well.

Accelerates the healing of many different wounds, including tendon and bone healing and healing of damaged ligaments

Dosing

Dosing of around 1-10 mcg per kilogram of body weight seems to be a good place to start, however best to try and find the perfect dose for you personally.

This peptide has been shown to reduce pain in areas of damaged tissues, lessening the need for *narcotic* type medications

BPC-157

In 1993 ,Dr. Sikiric of Croatia isolated the peptide from human gastric juice

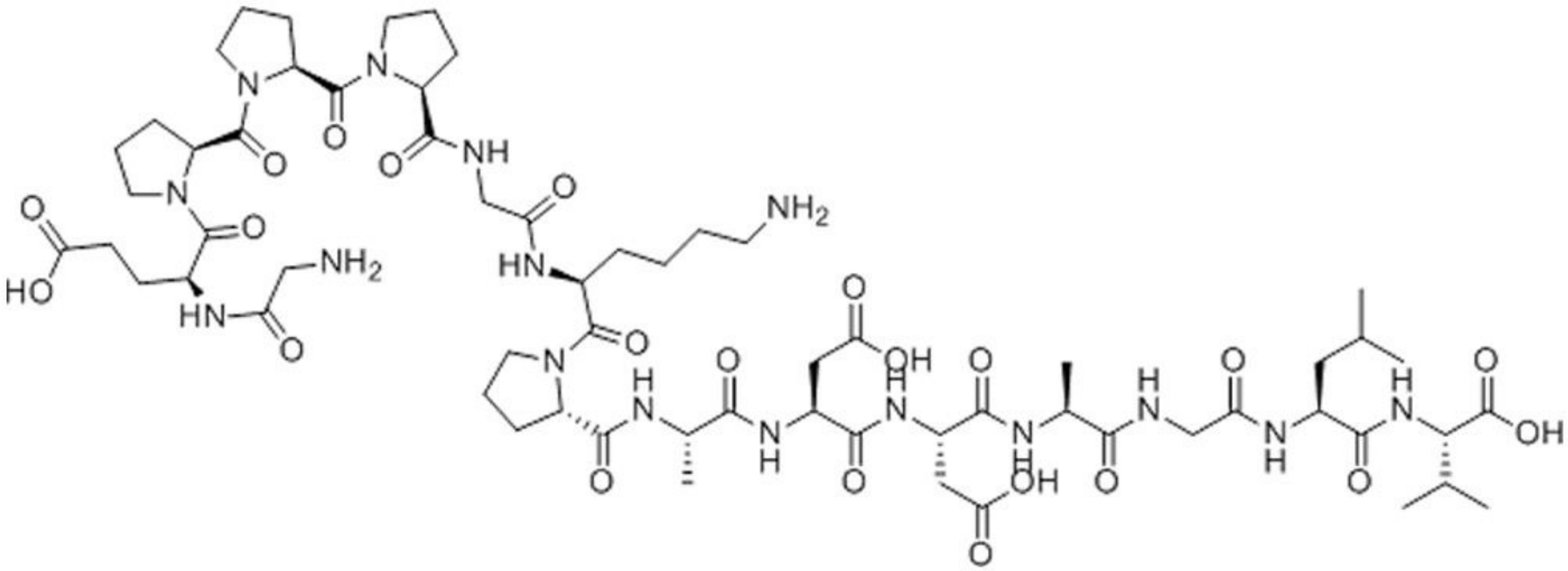
BPC works by accelerating the rate of angiogenic repair

Angiogenesis is a key dynamic process for wound healing

Most effective therapeutically IM or SQ

Can use Intraarticularly

Oral ok if using for GI benefits



BPC

Pentadecapeptide – 15 chain sequence of amino acids

The peptide was banned by the World Anti-Doping Agency in 2022

BPC-157

Most Frequent Uses:

- Promotes tissue and wound healing
  - Skin
  - Muscle
  - Bone
  - Ligament/tendon
- Sport injuries
- Gastric protection
  - Anti-ulcer
  - IBDs
  - Cytoprotective
  - Improves GI mucosal barrier – use in Leaky Gut Syndrome
  - Decreases NSAID and ETOH effects on gastric mucosa
- Improving burn healing rate
- Antioxidant
- Neuro and cardio protection
- Adjunct in cancer cachexia treatment

BPC-157

• IMPROVES JOINT HEALTH

BPC 157 promotes healthy tendon and ligament healing by accelerating the growth and spread of fibroblasts, which are cells found in connective tissues that are involved in the creation of collagen.

• MENDS MUSCLES & TENDONS

BPC 157 has muscle and tendon mending properties, which can help repair sports related injury where the tissues need to be rejuvenated or an injury from working out at the gym.

• ACCELERATES BONE HEALING

With its well-known fracture and wound healing aspects, BPC 157 injection therapy is known to promote bone repair and improve overall bone health.

• PROTECTS AGAINST INTESTINAL & GUT DAMAGE

BPC 157 can help overcome problems related to short gut (short bowel syndrome: SBS) and can help repair damaged tissues caused by inflammatory bowel disease (IBD). It can also act as an anti-ulcer peptidergic agent and an NSAIDs (nonsteroidal anti-inflammatory drugs) antidote. NSAIDs can be toxic to the gut and frequent use can lead to ulcers and an irritation of the bowels. BPC 157 can counteract symptoms associated with taking aspirin, such as bleeding.

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IA INJECTION OF BPC 157 FOR KNEE PAIN

ORIGINAL RESEARCH

Intra-Articular Injection of BPC 157 for Multiple Types of Knee Pain

Edwin Lee, MD, FACE; Blake Padgett

ABSTRACT

Introduction • Knee pain, a common complaint in primary care, has many causes, the most common of which is osteoarthritis (OA). Other common causes are meniscus tears, tendinosis, ligament tears or sprains, rheumatoid arthritis, lupus and septic arthritis. Also, referred pain from hip joint pathology like slipped capital femoral epiphysis can result in knee pain.[1] The use of peptides BPC157 and thymosin-beta-4 (TB4) has not been studied in the treatment of knee pain.

Methods • A retrospective study was done at the Institute for Hormonal Balance in Orlando, Florida, USA to see whether intra-articular injection of the peptide BPC 157, alone or combined with TB4, helped relieve knee pain. A 1-year chart review from 2019 to 2020 was performed. Since this was a retrospective study, patient follow-up varied, with most patients having had an injection of peptide into their knee 6 months to 1 year prior to the study. Of the 17 patients in the study, 16 were contacted by phone to follow up on the status of their knee pain. Only 1 patient could not be reached for the survey. Patients were asked to rate their pain prior to injection, the length of time the peptides helped ease the pain and the degree to which the injection helped them. No specific tools were used to measure their improvement in function, quality of life, stiffness or activities of daily living. The survey's main goal was to determine whether BPC157 helped with multiple types of knee pain in a primary care setting.

Results • Of the 16 patients, 12 had received only BPC 157 as an intra-articular injection. In this group, 11 of the 12 patients (91.6%) had significant improvement in knee pain, whereas 1 patient (8.3 %) had no improvement. The other 4 patients received a combination of 2 peptide injections of BPC 157 and TB4. Of the patients who received both peptides, 75% showed significant improvement, but 25% had no relief of their knee pain. Overall, 14 of 16 patients (87.5%) had relief of their knee pain when BPC 157 or a combination of BPC 157 and TB4 was used.

Conclusion • This small study suggests that intra-articular injection of BPC-157 helps with multiple types of knee pain.

Clinical Implications • BPC157 is a peptide with regenerative properties that can be used to relieve multiple types of knee pain.[2,3] Future studies are needed to look at the different causes of knee pain with follow-up magnetic resonance imaging scans (MRIs) to document the peptide's benefits. BPC157 has the potential to repair tears, build cartilage and reduce the number of knee surgeries. Because of its reparative properties, treatment with BPC157 offers advantages over the use of steroids.

Results • BPC157 is a peptide with regenerative properties that can be used to relieve multiple types of knee pain.[2,3] Future studies are needed to look at the different causes of knee pain with follow-up MRIs to document the peptide's benefits. BPC157 has the potential to repair tears, build cartilage and reduce the number of knee surgeries. Because of its reparative properties, treatment with BPC157 offers advantages over the use of steroids. (*Altern Ther Health Med.* 2021;27(4):8-13).

Edwin Lee, MD, FACE; Assistant Professor, Internal Medicine at the University of Central Florida College of Medicine, Orlando, Florida USA. **Blake Padgett,** Junior at the University of Florida.

Corresponding author: Edwin Lee, MD, FACE
E-mail: info@DrEdwinLee.com

INTRODUCTION

The science of peptides has grown since 1902, when the word "peptides" was introduced at a scientific meeting in Germany.[4] In general, peptides have a short half-life and have multiple effects.[5,6] Researchers working on the Human Proteome Map have estimated that the human body has close to 300 000 peptides and think we know only a fraction of what these peptides do.[7] Although peptides interact with

Reference: Intra-Articular Injection of BPC 157 for Multiple Types of Knee Pain, Lee, Edwin, MD, Alternative Therapies Jul/Aug 2021 Vol 27 No. 4

PEPTIDE WORLD CONGRESS 2022

BPC-157

2021 – Intra-articular injection of BPC 157 for multiple types of knee pain

Knee pain – most common cause is osteoarthritis
Single most common cause of disability in the elderly

Retrospective study to see whether intra-articular injection of BPC 157 alone or combined with TB4 helped relieve knee pain

Conclusions – suggests that intra-articular injection of BPC-157 helps with multiple types of knee pain

BPC-157 is a peptide with regenerative properties

BPC-157 has potential to repair tears, build cartilage and reduce the number of surgeries

Thus BPC-157 offers advantages over the use of steroids

Small study - prolonged effects over six months compared with the short-lived benefit of steroids

Altern Ther Health Med. 2021:27(4):8-13

BPC-157

Figure 1. Overall pain in all 16 patients; 14 out of 16 (87.5%) had improvement in knee pain.

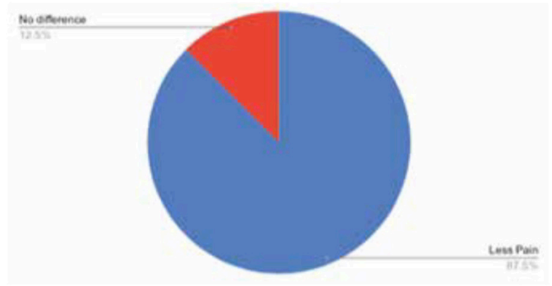


Figure 2. Overall mobility in all 16 patients; 75% had improvement in mobility.

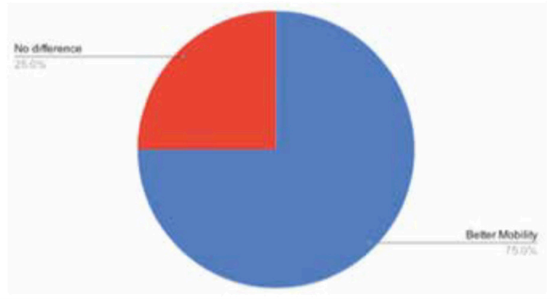
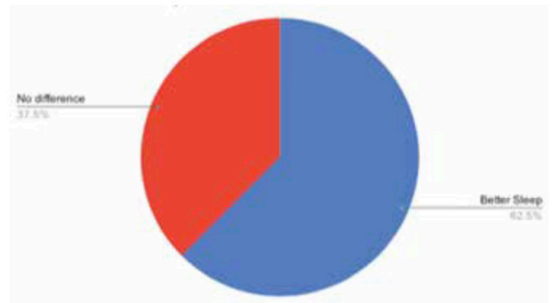


Figure 3. Overall sleep in all 16 patients; 62.5% had better sleep.



Key points:

87.5% of pts had overall improvement in knee pain

75% of pts had overall improvement in mobility

62.5% of pts had overall better sleep

Altern Ther Health Med. 2021:27(4):8-13

BPC-157

Dosage:

- SubQ General Dosage:
  - 300-600 mcg daily for 30 days
  - If injury specific = split dosing into 20-300 mcg BID
  - Available 2mg/ml, 5ml injectable solution

- Oral
  - 500 mcg daily for 30 days
  - Stability and bioavailability questionable

- Results can be spontaneous and improve over 2-4 weeks treatment
- Reported safe in recommended dosages

- As of January 1, 2022, BPC-157 is prohibited under the World Anti-Doping Agency (WADA) Prohibited List.

TB4

Best Against Inflammation

Thymosyn Beta 4 is another great peptide used for healing. TB4 is found naturally in humans and animals. Veterinarians initially found use for it in horses before doctors used in it humans

Naturally occurring peptide that comes from the thymus gland

FDA-approved as an orphan drug in 2004 and 2013

Actin

TB4 increases actin which can increase cell mobilization, cell division and fight inflammation

Wide range of regenerative activities such as accelerating recovery from skin wounds, TBI, stroke, MS

Dosing

TB4 dosing can have quite a large dose, ranging from 5 to 20 mg per week

Reduces inflammatory markers and pain

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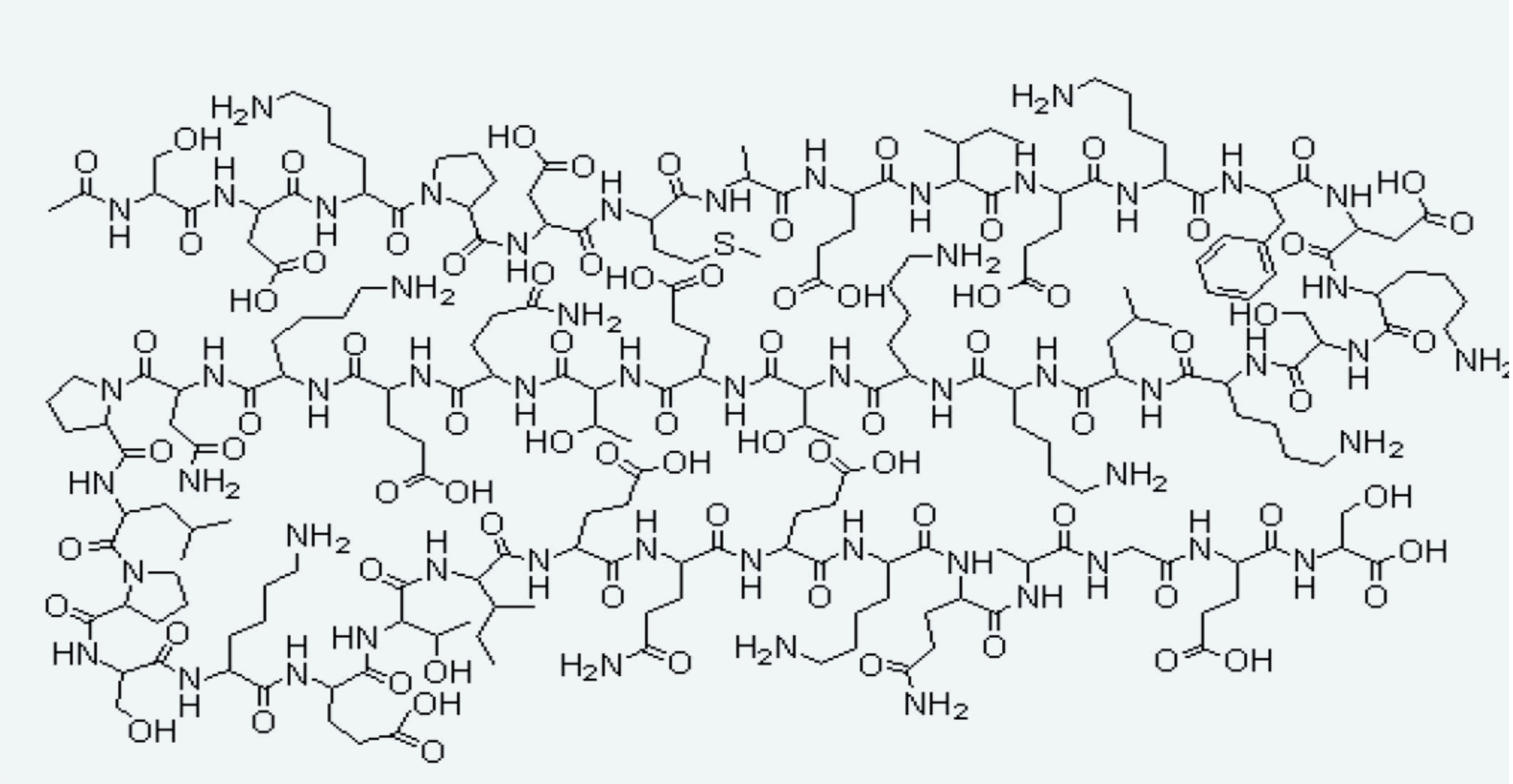

TB4 43 amino acids

Thymosin beta-4 is considered a performance enhancing substance and is banned in sports by the World Anti-Doping Agency due to its effect of aiding soft tissue recovery and enabling higher training loads.

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TB-4

Thymosin beta-4 is a peptide found in most cells and tissues

- Originally isolated from calf thymus
- Main intracellular G-actin sequestering peptide
- Up-regulates actin
- Forms a ternary complex with actin and profilin

- Increases cells involved in healing
- Improves cell migration to site of injury
- Promotes matrix metalloproteinase expression during wound repair
- Promotes angiogenesis, is cytoprotective
- Helps decrease scar tissue formation
- Improves T cells

TB-4

Most Frequent Uses:

- Sports/athletic injury
- Soft tissue repair
  - Tendon/ligament/muscle repair
- Cardioprotective – especially post MI
- Pressure ulcers / venous stasis ulcers
- Immune support (as monotherapy or in conjunction with Thymosin alpha 1)
- Nephroprotective
- Brain issues if autoimmunity suspected
- Neuroinflammation – microglial inflammation
- Multiple sclerosis
- Ischemic stroke
- Spinal cord injuries
- TBI; concussion support (in conjunction with BPC 157)
- Eye disorders
  - Diabetic retinopathy
  - Dry eye disorders
  - Ocular tissue injuries including corneal wound healing and repair
  - Corneal transplants

TB-4

Other Uses:

- Sepsis
- Chemical burns
- Diabetes
- NAFLD – non-alcoholic fatty liver disease
- Lung inflammation / fibrosis
- May improve hair growth

TB-4

Study in 2015 found:

TB4 as a restorative/regenerative therapy for neurological injury and neurodegenerative disease

TB4 promotes PNS plasticity and neurovascular remodeling leading to recovery

TB4 significantly improves functional and behavioral outcomes

TB4 can target many diverse restorative processes via multiple molecular pathways

Expert Opinion Biol. Ther. (2015) 15 suppl 1 S9-12
Michael Chopp & Zheng Gang Zhang
Dept of Neurology, *Henry Ford Hospital Detroit*, MI

TB-4

Dosage:

- SubQ (SQ) General Dosage:
- 300 mcg – 1 gram daily, SubQ

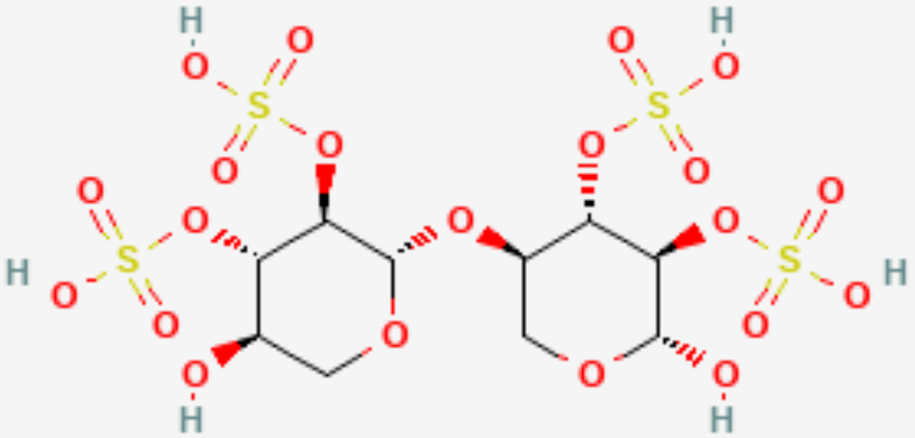
- Can use Intraarticular

- Depending upon clinical presentation – less for immune, more for repair or most for both issues

- Do not dose concurrently for more than 3 months

- Cycle if needed long-term – 3 months on, 6 weeks off or 6 weeks on 6 weeks off

- Individual dosage requirements may vary based on clinical presentation



PPS

Polysaccharide

proposed as **a disease modifying osteoarthritis drug (DMOAD)**

PPS

Brand name Elmiron for tx of interstitial cystitis

Generic name Pentosan polysulfate

It is a polysaccharide with heparin-like properties

Has been studied in knee osteoarthritis – will elaborate

Be aware of chronic exposure to PPS can cause retinal toxicity (seen in oral intake, not SC)

The calcium salt of PPS was one of the first reported structure-modifying osteoarthritis drugs – 1999 study

Structure-modifying osteoarthritis (OA) drugs (SMOADs) defined as agents that reverse, retard, or stabilize the underlying pathology of OA, thereby providing symptomatic relief in the long-term.

DOI: 10.1016/s0049-0172(99)80021-3

PPS for knee and hip arthritis

Proposed mechanisms:

+ improves blood flow to subchondral bone
+ improves synthesis of the cartilage matrix
+ provide less or no cartilage breakdown by inflammatory cytokines
+ maintain proteoglycan content in articular cartilage

Side effects: it a blood thinner

Be careful with use in pts using blood thinner and NSAIDs

Personally, no issues

PPS evidence

Studies

2005 – OA knee study improved pain at rest and joint stiffness less pain with walking

2010 – cartilage improvement seen in OA joints with reduced joint swelling

DOI: 10.1186/1472-6904-10-7

2017 – bone marrow edema resolved per MRI after twice a week x 3 weeks PPS IM

DOI: 10.1186/s12891-017-1754-3

2019 – suppresses release of Nerve Growth Factor (NGF) to reduce pain associated with knee OA

DOI: 10.1371/journal.pone.0222602

With use, Pro athletes report less pain with high level activity

Current ongoing clinical trial

Clinical trial NIH tripled blinded study in progress - twice a week SC PPS, control saline

Primary outcome measures 1) time from initial response through follow up 2) time from initial response to loss of response

A Study to Investigate The Duration of Treatment Effect and Re-treatment With Subcutaneous Injections of Pentosan Polysulfate Sodium Compared With Placebo in Adult Participants With Knee Osteoarthritis Pain

Started December 2021

Estimated completion date October 2024

PPS in Dogs

Study treated 40 geriatric dogs with well-established Clinical signs of chronic OA

3 mg/kg most effective dose weekly IM/SC

doi:10.1111/j.1748-5827.1996.tb02355.x

Also, in a study in dogs with OA due to cranial cruciate ligament deficiency, lower levels of Proteoglycan breakdown products in the synovial Fluids of the OA joints

Found to hasten recovery, as measured by more rapidly improved ground reaction forces over 48 weeks

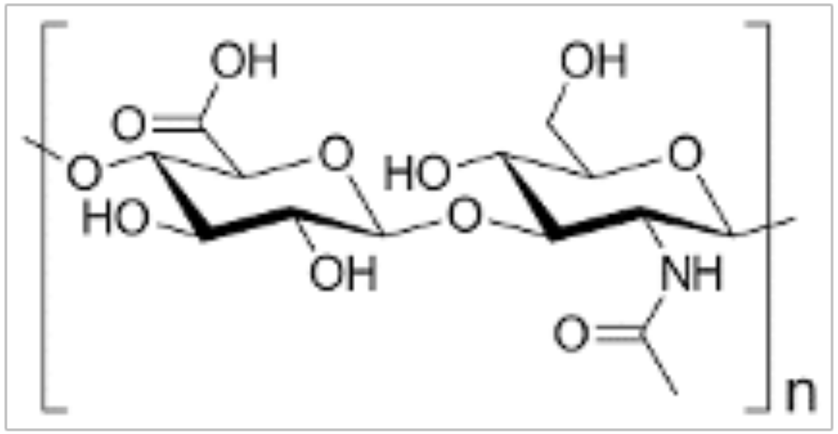
doi:10.1111/j.1532-950x.2007.00256.x

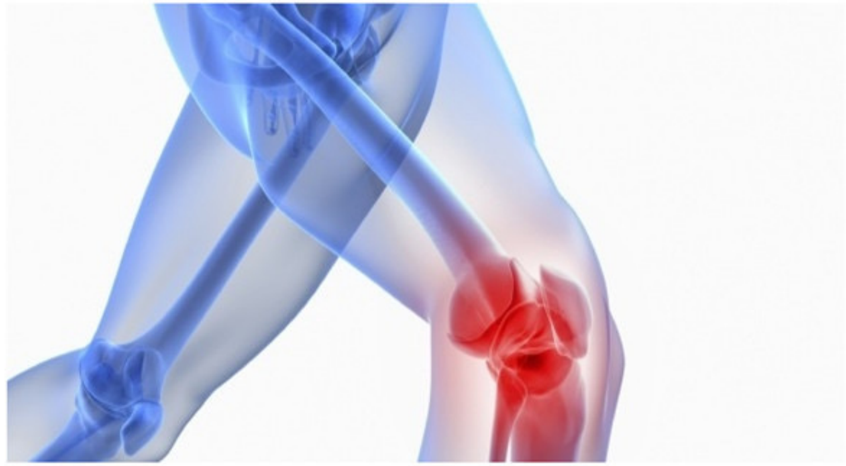
PPS in Horses

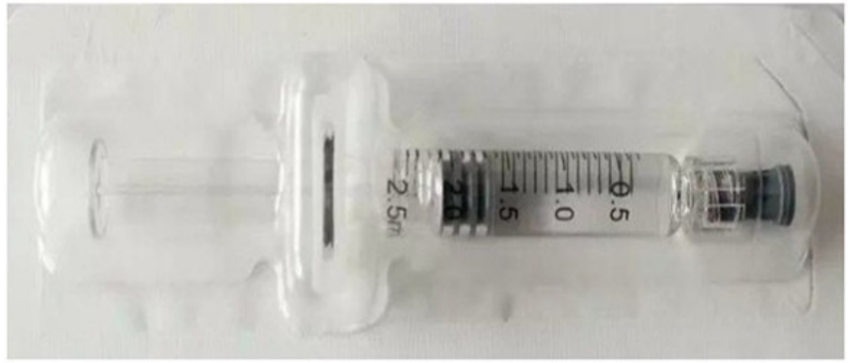
Few published reports describing the use of PPS for equine joint disease, however, it is being used for this indication in Australia

When administered to racing thoroughbreds with Chronic osteoarthritis (2 to 3 mg/kg, IM weekly for 4 weeks then prn), PPS treatment improved but did not eliminate clinical signs of joint disease

Little, CB; Ghosh, P (1996). McIlwraith, CW; Trotter, GW (eds.). *Joint Disease in the Horse*. Philadelphia: WB Saunders Company. pp. 281–292.







HA Hyaluronic acid

Low molecular weight

ubiquitous molecule that naturally occurs within the cartilage and synovial fluid

HYALURONIC ACID
Functions in the joint include:

*lubrication, serving as a space filler to allow the joint to stay open

*regulation of cellular activities such as binding of proteins

*During the progression of osteoarthritis (OA), the endogenous HA in the joint is degraded

*consequently, diminishing the mechanical and viscoelastic properties of the synovial fluid in the affected joint

Therefore, exogenous HA injections have been clinically used to alleviate the degradation of endogenous HA in OA patients

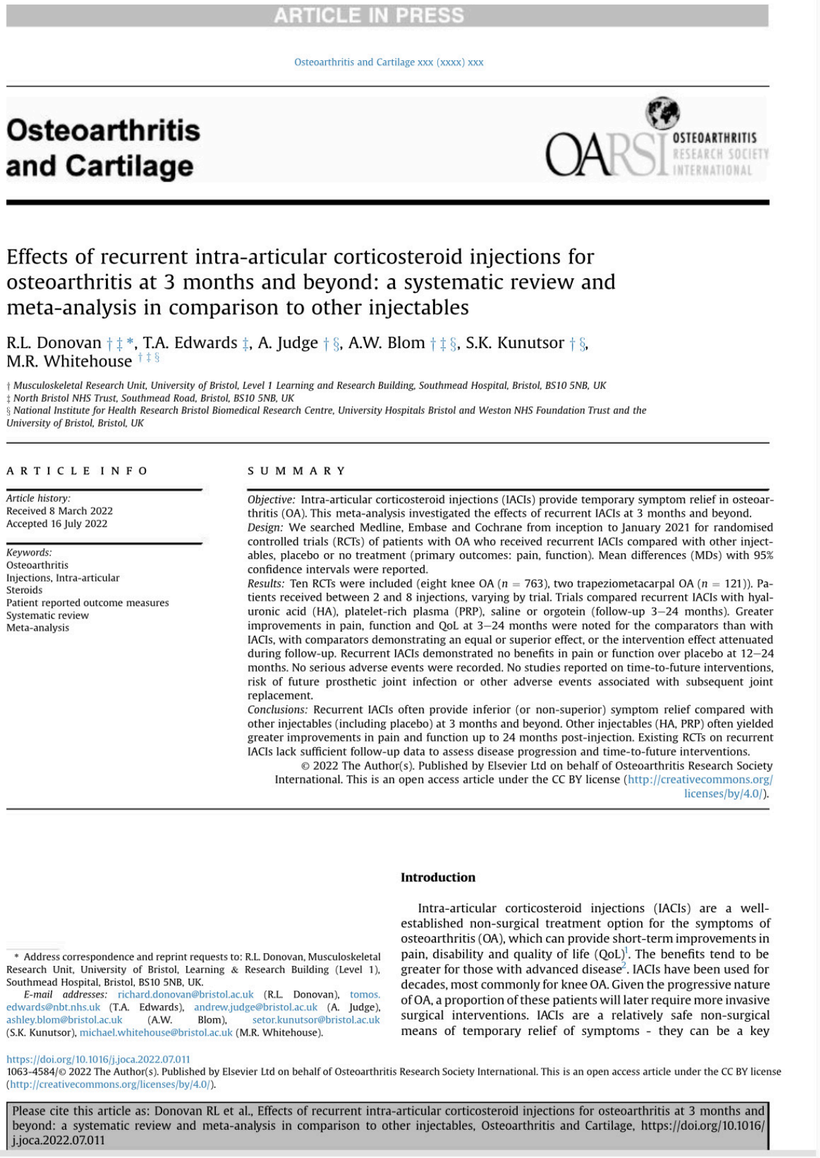
*Although the exogenous HA does not restore and replace the full properties and activities of the depolymerized endogenous HA of the synovial fluid

HA

HA may induce satisfactory pain relief via several mechanisms, including

- Synthesis of proteoglycan and/or glycosaminoglycan
- Anti-inflammatory effect
- Viscoelasticity maintenance

As some studies reporting an overall beneficial effect while others report that there is only a small benefit.



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Osteoarthritis and Cartilage xxx (xxxx) xxx

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Effects of recurrent intra-articular corticosteroid injections for osteoarthritis at 3 months and beyond: a systematic review and meta-analysis in comparison to other injectables

R.L. Donovan † ‡ *, T.A. Edwards ‡, A. Judge † §, A.W. Blom † ‡ §, S.K. Kunutsor † §, M.R. Whitehouse † ‡ §

† Musculoskeletal Research Unit, University of Bristol, Level 1 Learning and Research Building, Southmead Hospital, Bristol, BS10 5NB, UK
‡ North Bristol NHS Trust, Southmead Road, Bristol, BS10 5NB, UK
§ National Institute for Health Research Bristol Biomedical Research Centre, University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol, Bristol, UK

ARTICLE INFO

Article history:
Received 8 March 2022
Accepted 16 July 2022

Keywords:
Osteoarthritis
Injections, Intra-articular
Steroids
Patient reported outcome measures
Systematic review
Meta-analysis

SUMMARY

Objective: Intra-articular corticosteroid injections (IACIs) provide temporary symptom relief in osteoarthritis (OA). This meta-analysis investigated the effects of recurrent IACIs at 3 months and beyond.
Design: We searched Medline, Embase and Cochrane from inception to January 2021 for randomised controlled trials (RCTs) of patients with OA who received recurrent IACIs compared with other injectables, placebo or no treatment (primary outcomes: pain, function). Mean differences (MDs) with 95% confidence intervals were reported.
Results: Ten RCTs were included (eight knee OA (n = 763), two trapeziometacarpal OA (n = 121)). Patients received between 2 and 8 injections, varying by trial. Trials compared recurrent IACIs with hyaluronic acid (HA), platelet-rich plasma (PRP), saline or orgotein (follow-up 3–24 months). Greater improvements in pain, function and QoL at 3–24 months were noted for the comparators than with IACIs, with comparators demonstrating an equal or superior effect, or the intervention effect attenuated during follow-up. Recurrent IACIs demonstrated no benefits in pain or function over placebo at 12–24 months. No serious adverse events were recorded. No studies reported on time-to-future interventions, risk of future prosthetic joint infection or other adverse events associated with subsequent joint replacement.
Conclusions: Recurrent IACIs often provide inferior (or non-superior) symptom relief compared with other injectables (including placebo) at 3 months and beyond. Other injectables (HA, PRP) often yielded greater improvements in pain and function up to 24 months post-injection. Existing RCTs on recurrent IACIs lack sufficient follow-up data to assess disease progression and time-to-future interventions.

Introduction

Intra-articular corticosteroid injections (IACIs) are a well-established non-surgical treatment option for the symptoms of osteoarthritis (OA), which can provide short-term improvements in pain, disability and quality of life (QoL)[1]. The benefits tend to be greater for those with advanced disease[2]. IACIs have been used for decades, most commonly for knee OA. Given the progressive nature of OA, a proportion of these patients will later require more invasive surgical interventions. IACIs are a relatively safe non-surgical means of temporary relief of symptoms - they can be a key

* Address correspondence and reprint requests to: R.L. Donovan, Musculoskeletal Research Unit, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Bristol, BS10 5NB, UK.
E-mail addresses: richard.donovan@bristol.ac.uk (R.L. Donovan), tomos.edwards@nbt.nhs.uk (T.A. Edwards), andrew.judge@bristol.ac.uk (A. Judge), ashley.blom@bristol.ac.uk (A.W. Blom), setor.kunutsor@bristol.ac.uk (S.K. Kunutsor), michael.whitehouse@bristol.ac.uk (M.R. Whitehouse).

https://doi.org/10.1016/j.joca.2022.07.011
1063-4584/

OA and Cartilage

2022 systematic review and meta-analysis

Effects of recurrent IA steroid injections for OA at 3 mo

Conclusions: Recurrent IACIs often provide inferior short-term improvements in pain, disability and QOL

When compared to

Other injectables, HA, PRP, often yielded greater improvements in pain and function up to 24 months post-injection

Donovan RL et al., Effects of recurrent intra-articular corticosteroid injections for osteoarthritis at 3 months and beyond: a systematic review and meta-analysis in comparison to other injectables, Osteoarthritis and Cartilage, doi.org/10.1016/j.joca.2022.07.011

Bowman et al. Clin Trans Med (2018) 7:6
https://doi.org/10.1186/s40169-017-0180-3

Clinical and Translational Medicine

REVIEW Open Access

Recent advances in hyaluronic acid based therapy for osteoarthritis

Steven Bowman[1†], Mohamed E. Awad[2†], Mark W. Hamrick[3,4], Monte Hunter[1] and Sadanand Fulzele[1,4*]

Abstract

Osteoarthritis is a debilitating disease that has increased in prevalence across the world due to the aging population. Currently, physicians use a plethora of treatment strategies to try and slow down the progression of the disease, but none have been shown to ubiquitously treat and cure the disease. One of the strategies uses the high molecular weight molecule hyaluronic acid as either an injectable or oral supplement for treatment. Hyaluronic acid (HA) is a relatively new treatment that has shown varied results through several clinical trials. It can be used as a scaffold for engineering new treatments and several new preparations have just been added to the market. A comprehensive search was conducted through several search databases according our inclusion and exclusion criteria. This review included 44 prospective clinical trial investigating the feasibility and efficacy of HA injection for knee, hip, and ankle osteoarthritis. This review will take a closer look at hyaluronic acid and its properties, as well clinical effectiveness and future options.

Keywords: Osteoarthritis, Hyaluronic acid (HA), Treatment, Tissue engineering

Introduction

Osteoarthritis (OA) is a degenerative joint disease that frequently affects the hands and weight bearing joints of the body [1]. In United States, 52.5 million adults have been diagnosed with osteoarthritis according to data analyzed between 2010 and 2012 in the National Health Interview Survey (NHIS) [2]. In addition, OA is considered as one of the main causes of functional disability in (estimated) 22.7 million US adults [3]. The patient with OA is suffering not only from the persistent pain, stiffness and limited mobility. However, it also directly affects their quality of life with physical and/or mental co-morbidity [4]. OA substantially increases health care expenditures which is estimated around $ 128 billion [5]. When considering productivity loss due to OA, estimates are between 0.25 and 0.50% of the Gross Domestic Product (GDP) [5].

Osteoarthritis (OA) is poorly understood because of its vast complexity and interplay of various biological factors such as: genetic alterations, sex hormone deficit, and aging [6]. Many recent evidence has focused on molecular markers that implicated in the stress-induced senescent state of chondrocytes [7]. The term "Chondrosenescence" has been currently used to describe the age-dependent deterioration of chondrocyte function [8]. The therapeutic approaches for OA are limited because of its complex pathophysiology. According to the Osteoarthritis Research Society International (OARSI) Guidelines and recommendations for OA management, a core set of evidence based-modalities of therapy has been established [9]. These modalities included non-pharmacological such as patient education and awareness, physical exercise and rehabilitation aids. The pharmacological modalities vary from prescription of acetaminophen, non-selective NSAIDs (Nonsteroidal anti-inflammatory drugs) and selective COX-2 inhibitors agents and even opioid prescription. NSAIDs are the most prescribed agents for OA [10]. Despite NSAIDs established effectiveness in relieving the pain with OA its long term use is associated with potential harmful adverse effects. In addition, there is a wide heterogeneity in their personalized response because of the pharmacogenomics interactions [11]. The other potential non-operative therapeutic

*Correspondence: sfulzele@augusta.edu
†Steven Bowman and Mohamed E. Awad contributed equally to this work
[1] Department of Orthopedics, Augusta University, 30904 Augusta, Georgia
Full list of author information is available at the end of the article

Recent advances in HA based Therapy for OA 2018

2018 review of 44 prospective clinical trials

Investigating the feasibility and efficacy of HA injection for knee, hip and ankle osteoarthritis

Its effectiveness is due to the many methods of actions it deploys, including lubrication, anti-inflammatory and chondroprotective effects

Can pair with other drugs to maximize effect

Treatment does not provide immediate relief to most – studies have shown that it takes about 5 weeks before pts feel the *full* effect of tx

Pts definitely report some relief sooner

Recent advances in HA based therapy for OA
Bowman et al. Clin Trans Med (2018) 7:6
doi: 10.1186/s40169-017-0180-3

HA

Dosage:

Intraarticular

- Supplied: 1 mg/mL + HA 10 mg/mL
- 5 mL vial

- Inject 0.5 to 0.75 mL IA weekly x 4 weeks

- Then inject once a month for 5 months

- Can be combined with AOD 9604

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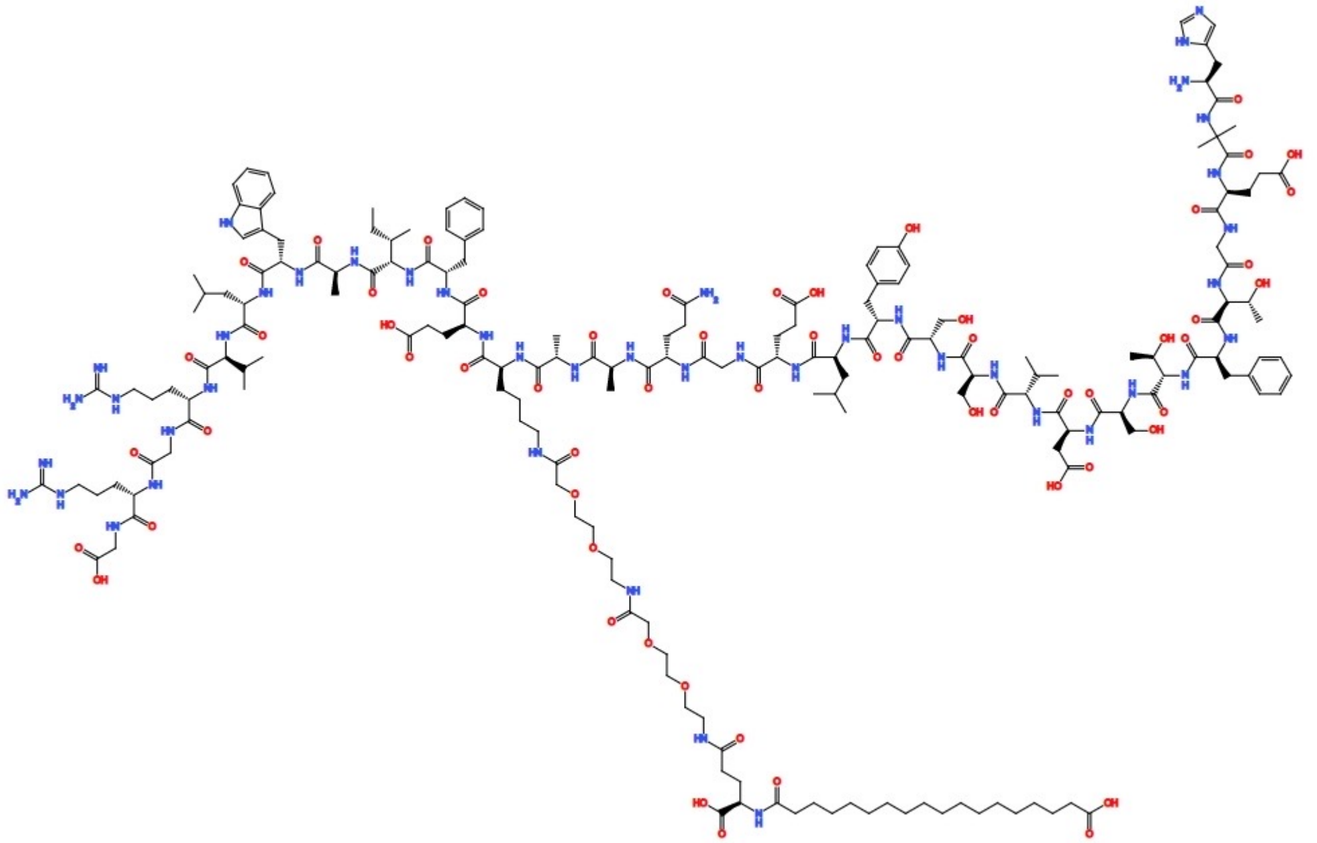

GLP-1 **Glucagon-like peptide-1**

30 amino-acid long peptide hormone

Element was purified in 1932 from gut extracts

Named INtestine seCRETion INsulin (incretin)

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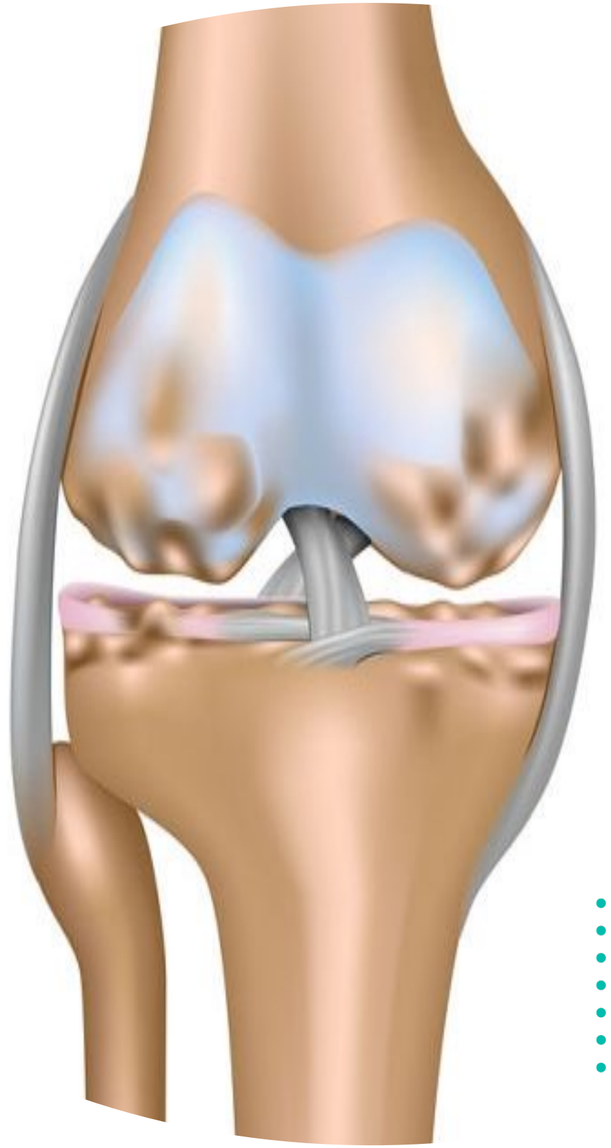
GLP-1/GLP-1R AXIS TO TREAT OA

Currently no disease modifying therapy
Available for osteoarthritis

Affects millions of people worldwide

In OA, chondrocytes, synovial cells and other joint cells become activated when exposed to an abnormal environment



Reference: Targeting the GLP-1/GLP-1R axis to treat osteoarthritis: A new opportunity? C. Meurot, Journal of Orthopaedic Translation 32(2022) 121-129

Journal of Orthopaedic Translation 32 (2022) 121–129

Contents lists available at ScienceDirect

Journal of Orthopaedic Translation

journal homepage: www.journals.elsevier.com/journal-of-orthopaedic-translation

Targeting the GLP-1/GLP-1R axis to treat osteoarthritis: A new opportunity?

C. Meurot [a], C. Jacques [b], C. Martin [a], L. Sudre [a], J. Breton [a], R. Rattenbach [a,c], K. Bismuth [a], F. Berenbaum [c,d,*]

[a] 4P-Pharma, Lille, France
[b] Sorbonne University, INSERM UMRS_938 and Labex Transimmunom, CDR St-Antoine Paris, Paris, France
[c] 4Moving Biotech, Lille, France
[d] APHP, Sorbonne University, Rheumatology Department, INSERM UMRS_938, CDR St-Antoine Paris, Paris, France

ARTICLE INFO

Keywords:
Osteoarthritis
Glucagon-like peptide-1 (GLP-1)
Glucagon-like peptide-1 receptor (GLP-1R)
Liraglutide
Cartilage
Synovial tissue

ABSTRACT

Osteoarthritis (OA) is a degenerative joint disease affecting millions of people worldwide. In OA, chondrocytes, synovial cells and other joint cells become activated when exposed to an abnormal environment, including mechanical stress, inflammatory cytokines or disorganization of matrix proteins. Several analogues of the hormones called incretins have been developed and are used notably for treating type 2 diabetes mellitus. Data has accumulated to suggest that incretinomimetics, which bind to the glucagon-like peptide-1 receptor (GLP-1R), have beneficial pleiotropic effects such as immunomodulation, anti-inflammation and neuronal protection. Thus, because of their anti-inflammatory properties, GLP-1–based therapies could benefit OA patients. This review focuses on the GLP-1R pathway, molecular mechanisms and phenotypes related to OA pathogenesis.

The translational potential of this article: The search for new therapeutic targets to treat people suffering from OA remains urgent as there is currently no disease-modifyingtherapy available for this disease. This review discusses how GLP-1 analogues could be potential DMOADs for treating OA thanks to their anti-inflammatory, immunoregulatory and differentiation properties.

1. Introduction

Osteoarthritis (OA) is the most common degenerative joint condition and the leading cause of disability, affecting over 300 million individuals worldwide [1,2]. In the absence of disease-modifying treatments, the US Food and Drug Administration (FDA) has characterized OA as a serious disease [3]. OA affects the joints, including knees, hands, hips and spine, and is the leading cause of impaired mobility in older people [1]. Risk factors for knee and hip OA include age, sex, obesity and cardiometabolic factors, all of which are central features of metabolic dysfunction. However, other risk factors for OA include trauma, sports activities and anatomical abnormalities. The overlap between OA and metabolic dysfunction prompted scientists to propose that OA might be a component of the metabolic syndrome [4,5]. Traumatic joint injury is another risk factor for the development of OA (post-traumatic osteoarthritis [PTOA]), associated with earlier disease onset than age-related OA and more readily affecting younger patients [6]. The mechanical injury is accompanied by release of cytokines such as interleukin 1 or 6 (IL-1 or 6), with both acute and long-term deleterious cellular effects: necrosis, apoptosis, autophagy and/or senescence [6]. In addition, mechanical activation of chondrocytes, which occurs during injury, activates extracellular matrix degradative enzymes including matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) [6]. Inflammation has a fundamental role in OA initiation and development. The inflammation found in OA is low grade and is induced and sustained by the innate immune response, metabolic syndrome and inflammaging [7].

Type 2 diabetes mellitus (T2DM) and OA are common diseases that are frequently associated. The prevalence of OA in patients with T2DM is 52%, whereas the prevalence in the general population is 27% [8]. The well-established association between OA and diabetes is explained at least in part by hyperglycemia, which, at the level of joint tissues, causes cellular and tissue toxicity [9]. In the past century, the discovery and characterization of the incretins, a family of gastrointestinal hormones that stimulate insulin production, has enabled the development of new therapies for treating T2DM, a chronic disease characterized by elevated blood glucose level caused by insulin resistance [10,11]. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide

* Corresponding author. UMR_S938, CDR Saint-Antoine, INSERM, Sorbonne Université, 184 Rue du Faubourg Saint-Antoine, 75012, Paris, France.
E-mail address: francis.berenbaum@aphp.fr (F. Berenbaum).

https://doi.org/10.1016/j.jot.2022.02.001
Received 3 September 2021; Received in revised form 31 January 2022; Accepted 1 February 2022

GLP-1/GLP-1R AXIS TO TREAT OA

2022 review in Journal of Orthopedic Translation

focuses on the GLP-1R pathway, molecular mechanisms and phenotypes related to OA pathogenesis

This review discusses how GLP-1 analogues could be potential DMOADs (disease modifying osteoarthritis drug) for treating OA due to their anti-inflammatory, immunoregulatory and differentiation properties

Focus on GLP-1/GLP-1R axis in the normal and pathological physiology of joints tissues

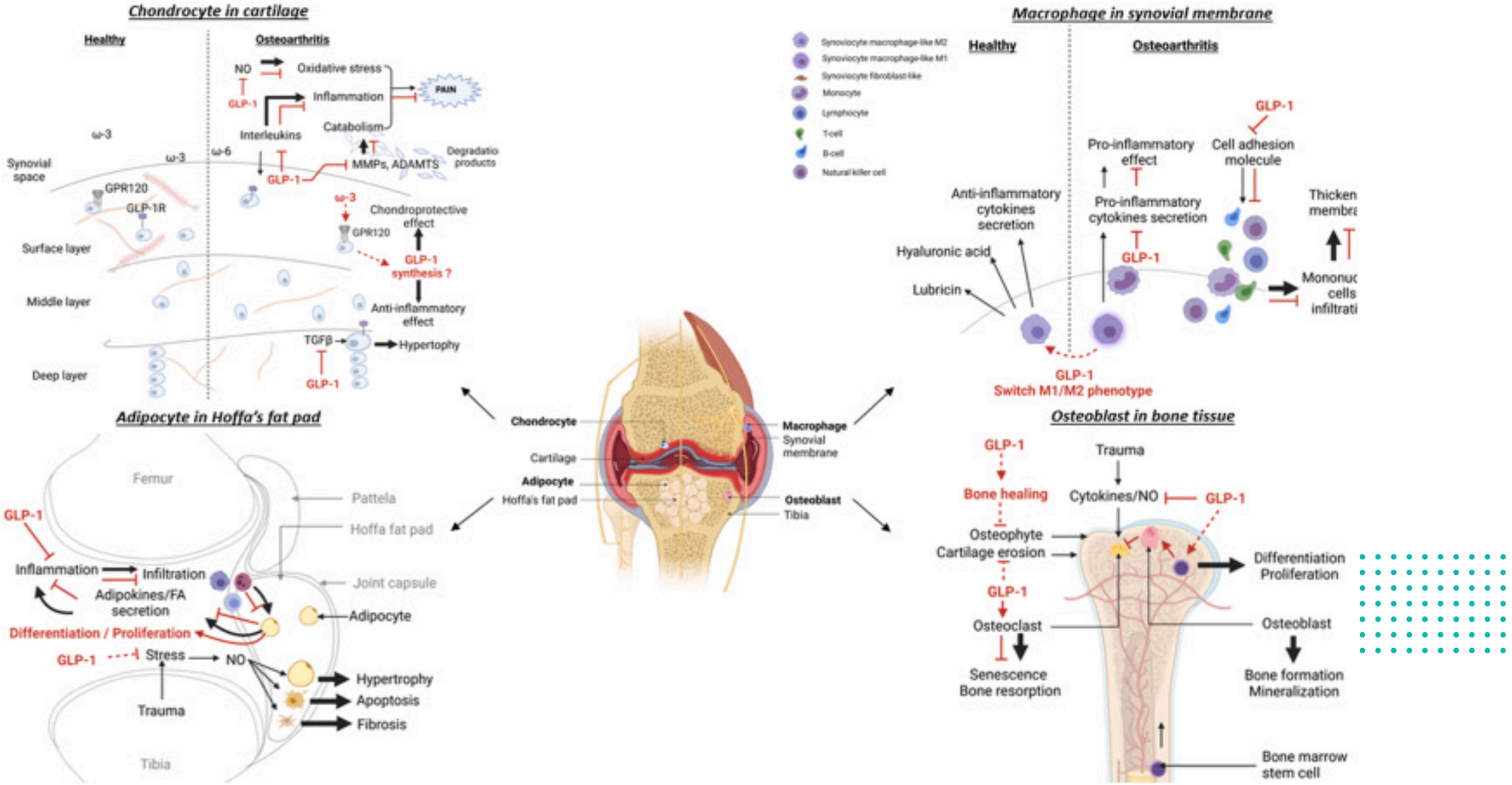
Reference: Targeting the GLP-1/GLP-1R axis to treat osteoarthritis: A new opportunity?
C. Meurot, Journal of Orthopaedic Translation 32(2022) 121-129

GLP-1/GLP-1R AXIS TO TREAT OA

GLP-1 functions and GLP-1R signaling pathways in osteoarthritis

Healthy	OA conditions	GLP-1 effects	Signaling pathways involved in GLP-1 effects
Homeostasis	Inflammation Cytokines synthesis	Anti-inflammatory (10, 16,30–32, 49–50, 63)	NF-κB PKA/CREB MAPK
Cartilage synthesis Matrix production	Hypertrophic differentiation ER stress	Anabolism/chondrogenic differentiation (43) Anti-oxydative stress (16)	? ? PI3K/Akt MAPK
Cartilage degradation	Catabolism Apoptosis Decreased Autophagy Senescence	Anti-catabolic (ROS, AGEs) Prevent apoptosis (35) ? ?	PI3K/Akt MAPK PI3K/Akt AMPK ? ?
Osteogenesis	Subchondral bone remodeling Osteophytes Reduced mineralization	Proliferation/ Differentiation (62–66) Maturation (69) Migration (63) Autophagy	Erk 1/2 MAPK β-catenin RANKL Wnt/β-catenin ? TGF-β
Adipogenesis	Adipokines synthesis Fatty acid synthesis Inflammation	Proliferation/ Differentiation (75,77) Fatty acid degeneration (47) Anti-inflammatory	PKC ? NF-κB PKA/CREB Erk 1/2
Nociception	Neuro-inflammation Pain Neuronal apoptosis	Neurotrophic/ Neuroprotector (92) Anti-inflammatory (86) Improved pain sensitivity (88) (release of β-endorphin) Analgesic (85) Anti-apoptotic (90)	Erk 1/2 NF-κB PKA/CREB cAMP MAPK Erk 1/2 PI3K/Akt AMPK

Ref: Targeting the GLP-1/GLP-1R axis to treat osteoarthritis: A new opportunity? C. Meurot, Journal of Orthopaedic Translation 32(2022) 121-129



Proposed targets of GLP-1 in joint tissues

The cell specific roles and molecular effects of GLP-1 in the GLP-1R dependent pathway may help counteract the pathogenesis of osteoarthritis in cartilage, synovial membrane, Hoffa's fat pad and bone tissue

The main effects lead to inhibition of cytokine secretion into the synovial fluid, thus decreasing inflammation and consequently reducing other downstream effects such as oxidative stress, pro degradative mediator secretion, phenotype modification and impairment/destruction of joint cells (apoptosis, senescence)

Reference: Targeting the GLP-1/GLP-1R axis to treat osteoarthritis: A new opportunity? C. Meurot, Journal of Orthopaedic Translation 32(2022) 121-129

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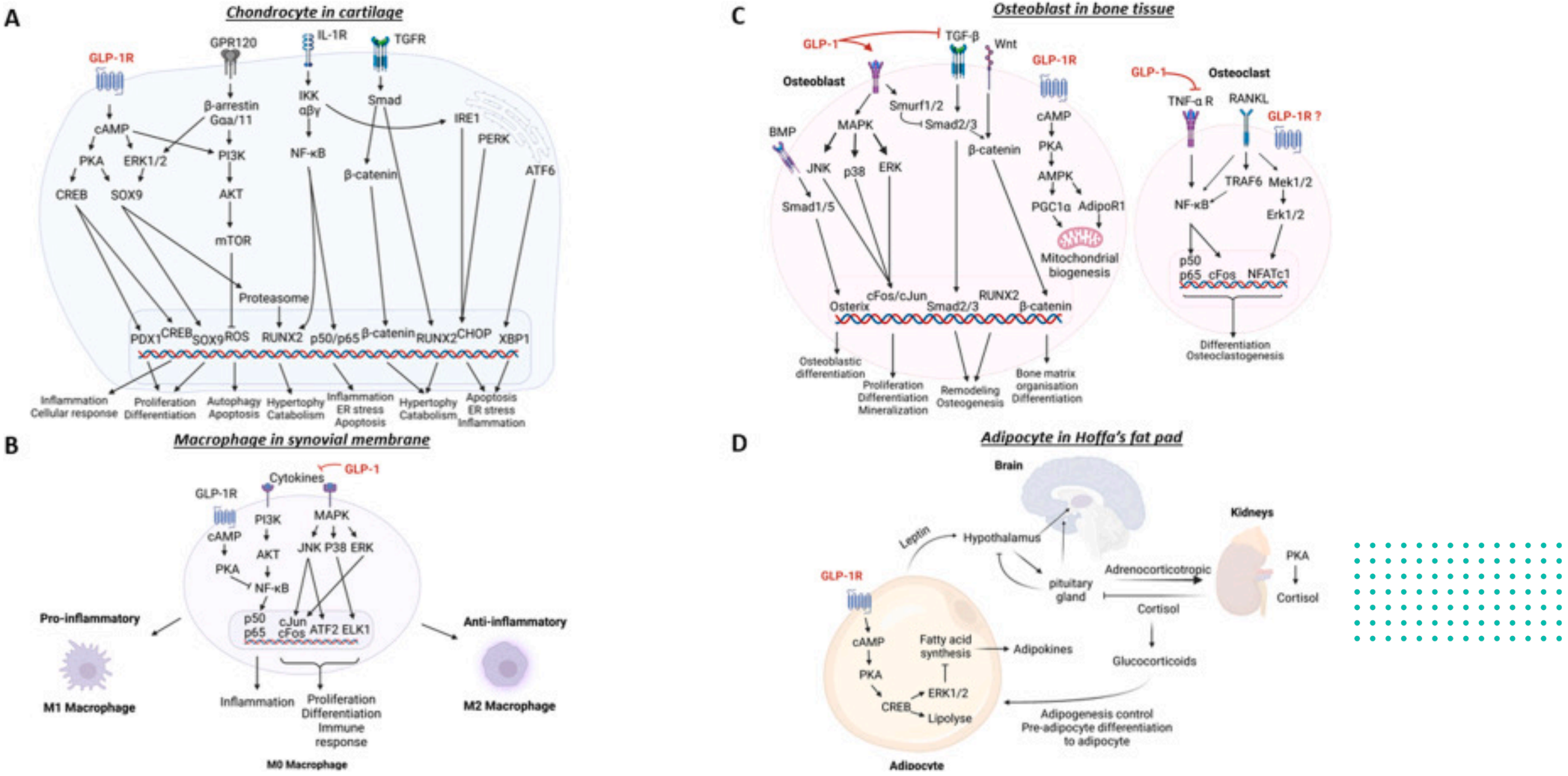

GLP-1R signaling pathways in different cell types of the joint

Proposed models of intracellular network associated with activation of GLP-1R regulating chondrocytes, macrophages, osteoblast/osteoclasts and adipocytes

GLP-1 binds to the GLP-1R and induces cAMP release which principally activates (PKA/CREB) and ERK1/2 pathways which are available to stimulate the expression of several genes involved in protective or repair effects. Other effects mediated by GLP-1 include lipolysis, bone metabolism, or mitochondrial biogenesis. The strong anti-inflammatory activity allows GLP-1 to promote a switch of M1 to M2

Reference: Targeting the GLP-1/GLP-1R axis to treat osteoarthritis: A new opportunity?
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GLP-1/GLP-1R AXIS TO TREAT OA

This strong anti-inflammatory activity allows GLP-1 to promote a switch of macrophage phenotype from M1 pro-inflammatory to M2 anti-inflammatory.

In adipocytes, the secretion of leptin is captured by the hypothalamus and the pituitary gland, which will induce the secretion of cortisol by the kidneys and allow for better management of adipogenesis.

In bone cells, GLP-1 promotes the osteoblastogenesis process

Reference: Targeting the GLP-1/GLP-1R axis to treat osteoarthritis: A new opportunity? C. Meurot, Journal of Orthopaedic Translation 32(2022) 121-129

GLP-1/GLP-1R AXIS TO TREAT OA

CONCLUSION:

The search for new therapeutic targets to treat people suffering from OA remains urgent as there are no disease-modifying therapy available for this disease

The recent discovery of anti-inflammatory, immunoregulatory and differentiation properties at the joint tissue and cellular levels of GLP-1 analogues raises the hypothesis of their potential interest to treat OA

Reference: Targeting the GLP-1/GLP-1R axis to treat osteoarthritis: A new opportunity? C. Meurot, Journal of Orthopaedic Translation 32(2022) 121-129

CEREBROLYSIN

Cerebrolysin is a multimodal neuropeptide preparation that crosses the blood brain barrier and displays neuroprotective properties in aging and disease.

Previously shown that cerebrolysin **reduced mechanical allodynia in a model of persistent inflammation and pain**

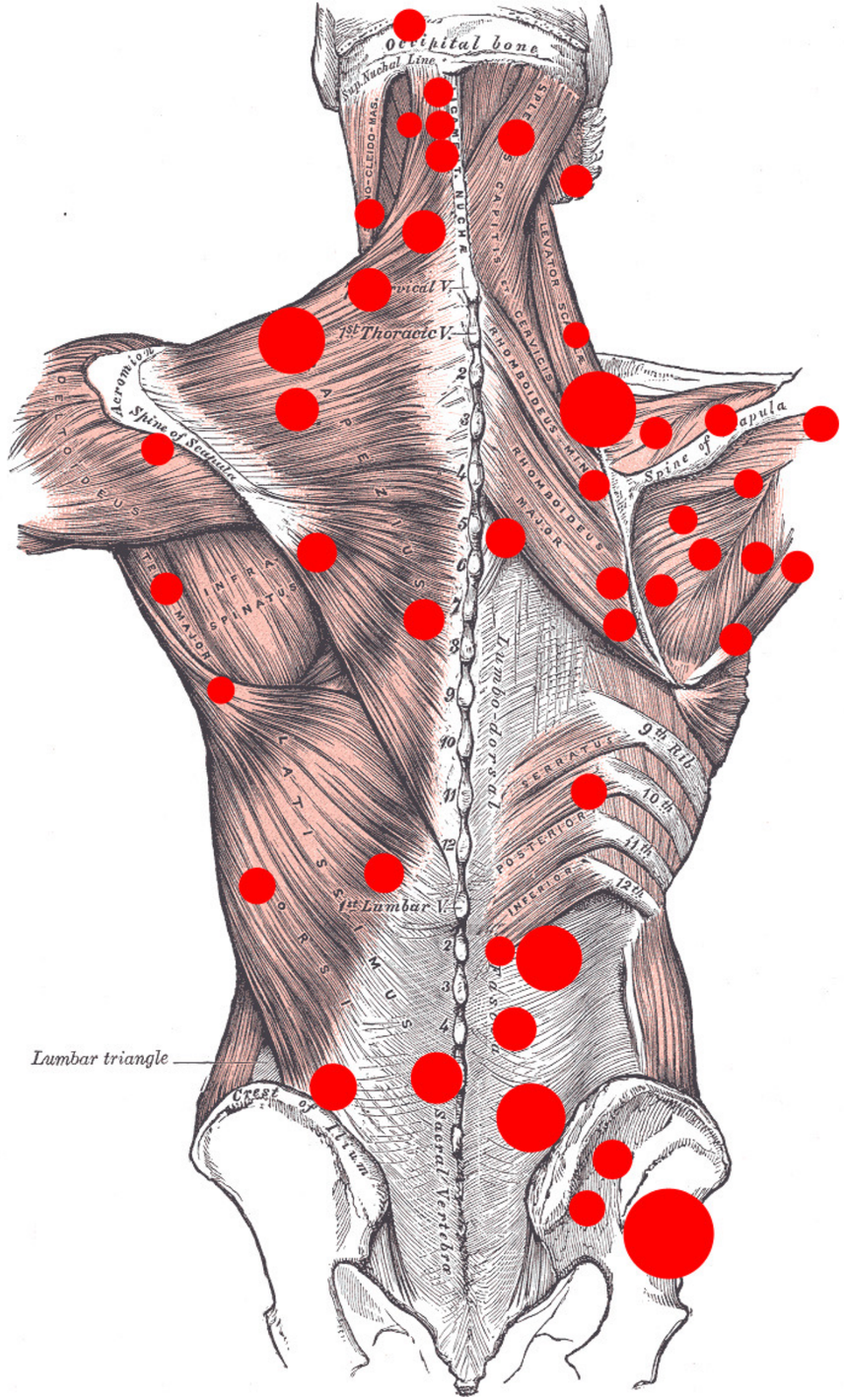
Cerebrolysin improves peripheral inflammatory pain
Drug Development Researc
Morales-Medina, March 2019
Doi.org/10.1002/ddr.21528

Cerebrolysin Trigger Point Therapy

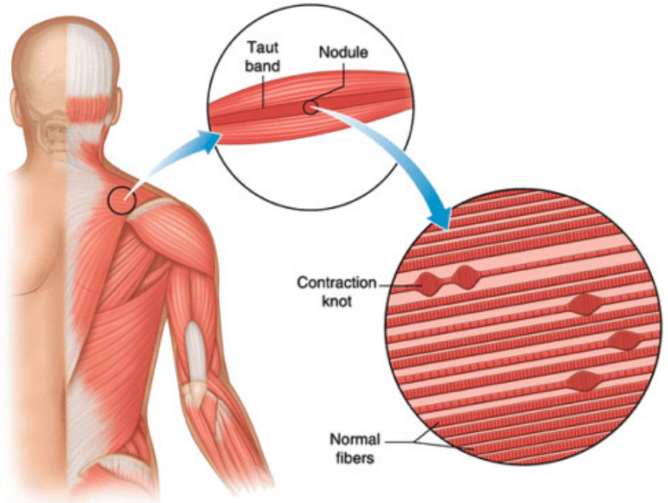
Trigger Point Injections

Treats painful areas of muscles that contain trigger points, or knots of muscles that form when muscles do not relax

Many times, knots can be felt under the skin



Cerebrolysin
Trigger Point Therapy

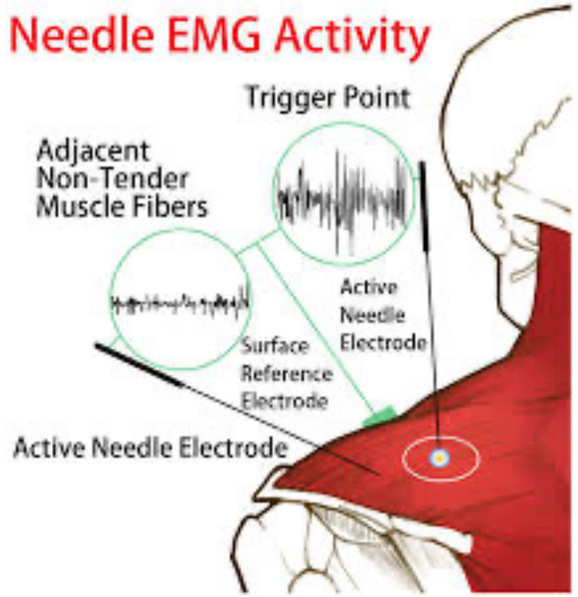


Trigger point complex

Trigger Point Injections

Trigger points may irritate the nerves around them and cause referred pain, or pain that is felt in another party of the body

Use EMG guidance for injection therapy



CEREBROLYSIN

Can be used IV as well!

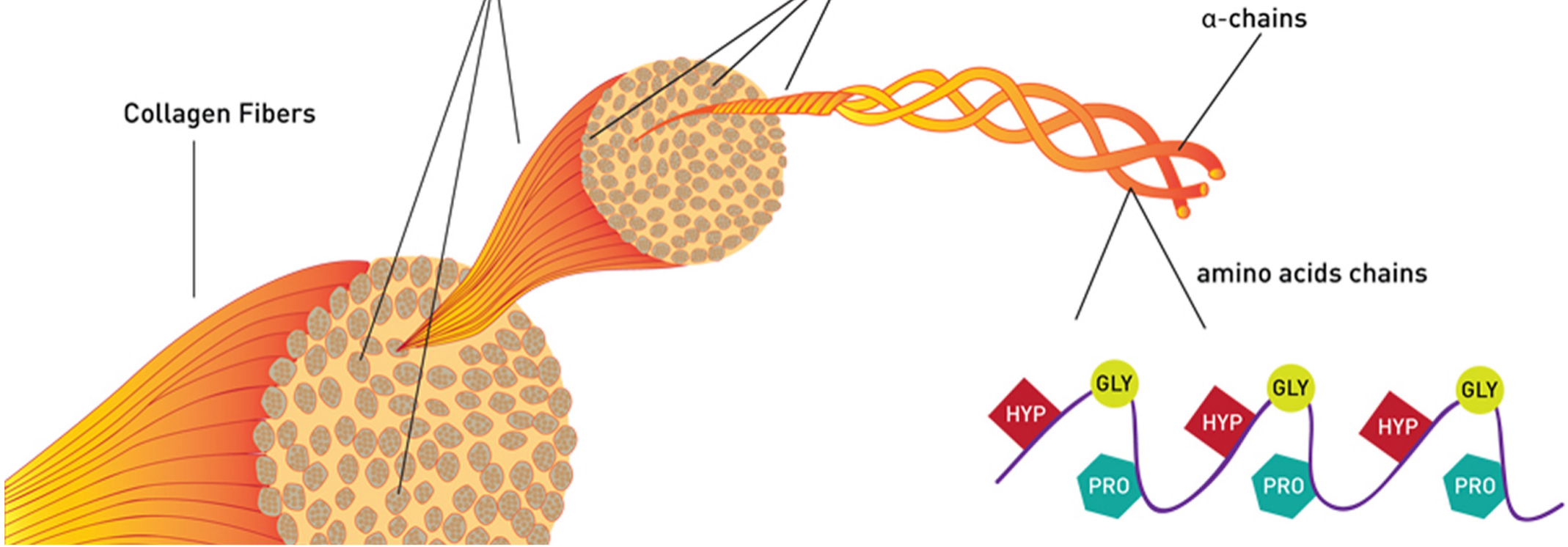
Barrier: availability

CEREBROLYSIN

Dosage:

- SubQ/IM General Dosage:
    - 215 mg (1 cc) daily 7 days, for a four week cycle
- IV
    - 215 mg/mL – 5 cc IV drip 2 times a week for 2 weeks

Source: Dr. Seeds Peptide Protocols Volume 1



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COLLAGEN

Collagen is the most abundant protein in the body

Collagen is the main structural protein found in the connective tissue

30% of the total protein mass in humans in comprised of collagen

Collagen plays a role in immune modulation

Consists of three peptide chains

Lose a teaspoon a year - gradual but substantial

Studies recommend adults consume 2.5 to 15 g/d (webmd)

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Collagen

Consume by mixing it into smoothies, shakes, baked goods or in your coffee or tea

When you age, the reduction of collagen in your body increases the risk of **Osteoarthritis**.

Evidence shows that collagen supplementation helps alleviate **joint pain** and improves **joint function** in patients with Osteoarthritis

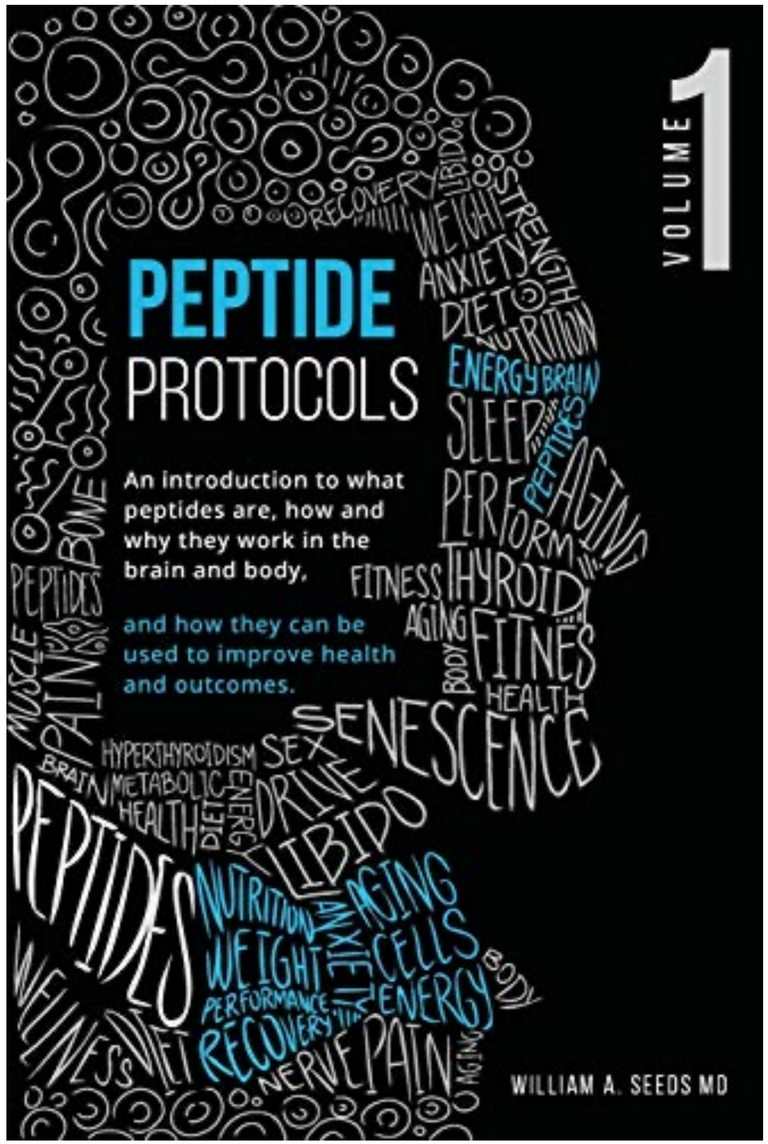
As collagen decreases with age, you may experience an increased risk of sarcopenia

Collagen has a place in pain
Collagen has a place in joint disease

Dosing

Protocols

Reference



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May 06, 2022 05:07 AM Eastern Daylight Time

DUBLIN--(BUSINESS WIRE)--The "Global Peptide Therapeutics Market & Clinical Trials Insight 2028" report has been added to **ResearchAndMarkets.com's** offering.

"Global Peptide Therapeutics Market & Clinical Trials Insight 2028"

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Peptides are naturally occurring, small biological molecules made of short chains of amino acids linked by a peptide bond, performing multiple functions within the cell. Peptide drugs have been in use for almost a century now, though initially they were only used to replicate the action of natural hormones for metabolic diseases, for example, the first of this kind that was approved for clinical usage was insulin for the management of diabetes. However, decades of research and development of peptides have resulted in the discovery of peptides that have the ability to penetrate the cell with advanced actions, all of which have shown excellent results for various therapeutic functions.

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THANK YOU!

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