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Trials for – Trials Against: Analyzing Efficacy of Glucosamine and Chondroitine for Osteoarthritis

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Abstract

New approach to find effective remedies against osteoarthritis (OA) is actual because total treatment failure. Simultaneous existence of data explaining efficacy of glucosamine and chondroitine against osteoarthritis along with articles certifying failure of such effect raise permanent discussion. This controversy is extended with assessment of proposed infectious theory of osteoarthritis. There are several lines of suspicion for involvement of infectious factors in development of osteoarthritis and for antibacterial properties of glucosamine and chondroitine. From this view possible explanations of the trials' discrepans in GS-CS efficacy-failure against osteoarthritis follow. Along with ethiology different clinical aspects and mechanisms should not be missed in patients with OA, which may be due to infectious factors. Large meta-analysis trials may miss important information considering large non-specific cogorts of patients. There are several teaching points for further investigation in this letter. Large meta-analysis studies cannot take into account all specific groups of patients and general data may miss an important information. In order to realize a nature of osteoarthritis specific homogenous groups for each parameter should be collected and examined. Occasional data may cary light for deep mechanisms of the disease and its therapy.

Keywords: Osteoarthritis; Infectious Factors; Glucosamin; Chondroitine Therapy; Meta-Analysis Limits

Abbreviations: OA: Osteoarthritis; CS: Chondroitine Sulfate; LPS: Lipopolysaccharide; GA: Glucosamine.

Glucosamine (GA) is used by the body to make other chemicals that build tendons, ligaments, cartilage, and the fluid that surrounds joints. Glucosamine along with chondroitine sulfate (CS) was shown to reduce symptoms of moderate severe painful knee osteoarthritis (OA) [1]. Glucosamin sulfate (GS) and CS supplements declined 5-year operative risk after its discontinuation [2]. The special once-a-day formulation, 1500mg of glucosamine sulfate as emphasized in the Glucosamine Unum in Die (once a day) Efficacy (GUIDE) trial tended to be more efficacious than acetaminophen [3]. Combined CS and GA for painful knee osteoarthritis demonstrated non-inferiority versus celecoxib in a multicentre, randomised, double-blind trial [4]. GS and CS were shown to delay X-Ray progression of OA [5,6]. On the other hand, in meta-analyses, the use of GS or CS or products containing a combination of these compounds did not lead to greater reductions in joint pain than placebo [7-9]. Because GA is a precursor for glycosaminoglycans, whch are a major component of joint cartilage, GA supplements are expected to help rebuilding cartilage. But intrarticular concentration of GA after peroral or pareneteral therapy proved to be too low to do it [10]. And clinical relevance of GA supplement is unknown at this time. However, in vitro studies show

evidence that GA reduces inflammation via inhibition of interferon gamma [11-13] and Nuclear factor kappa B subunit 65 (NF-κB p65) [14].

Simultaneous existence of data explaining efficacy of glucosamine against osteoarthritis along with articles certifying failure of such effect raise permanent discussion. How it may be? This controversy is extended with assessment of proposed infectious theory of osteoarthritis [15-18]. There are several lines of suspicion for involvement of infectious factors in development of osteoarthritis [18] and for antibacterial properties of GS and CS [15,16].

From these points follow possible explanations of the trials' discrepans in GS-CS efficacy-failure against osteoarthritis:

- Different microbes are proposed as causative agents for OA. Osteoarthritis in origin and development as a disease due to different pathogens.
- Differences in pathogen activity of certain microorganism or viruses – differences of pathogen phenotypes.
- Differences in drug formula, drug technology and constituents
- Drug antimicrobial activity
- Pathogen resistance
- Fluctuations of disease activity. That was demonstrated in the GAIT trial that did not find differences between medication and placebo group [1]. Only patients with high disease activity showed significant statistical improvement after therapy.
- Possible spontaneous remission of osteoarthritis may occur confusing lack of medication efficacy.

The issues 1-2 delineate pathogen diagnostic of osteoarthritis and may be also autoimmune disease. The issues 3-4 estimate drug characteristics, fifth one reflexes microbial or viral resistance.

The issues 6-7 follow fluctuations of the disease activity. Patients with higher activity are more sensitive to therapy. Patients with lower activity are hardly responsive. A new field seems to be emerging as bacteriological and virological diagnostic of osteoarthritis.

Along with ethiology different clinical aspects and mechanisms should not be missed in patients with OA, which may be due to infectious factors:

- Local symptoms: pain, swelling, limitation, stiffness, myalgia, reffered pain.
- General symptoms: diffuse musculo-skeletal pains, fatigue, tiredness, sick feeling, myalgia. All these phenomena are very common in the patients and are mistakenly not attributed to OA.
- Pathogen associated microbial particles (PAMP's) spread
- Lipopolysaccharide (LPS)-lipopolysaccharide (LBP)-CD14 spread with break through of liver barrier;
- non-direct pathogen distribution
- molecular mimicry with further autoimmunity
- early break through pathogen distribution due to molecular similarity (mimicry) and on this basic antigen elimination failure.
- hypercoagulopathy due to LPS, which brings about endothelial damage and thrombotic events.

There are several teaching points for further investigation in this letter:

- Large meta-analysis studies cannot take into account all specific groups of patients and general data may miss an important information
- In order to realize a nature of osteoarthritis specific homogenous groups for each parameter should be collected and examined.
- Occasional data may carry light for deep mechanisms of the disease and its therapy

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