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Review

Symptomatic and chondroprotective treatment with collagen derivatives in osteoarthritis: a systematic review

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SUMMARY

Objective: Osteoarthritis (OA) is one of the most prevalent musculoskeletal diseases. Collagen derivatives are candidates for disease-modifying OA drugs. This group of derivatives can be divided into undenatured collagen (UC), gelatine and collagen hydrolysate (CH). Collagen derivatives are marketed as having direct chondroprotective action and reducing complaints of OA. This review summarizes the evidence for the effectiveness of symptomatic and chondroprotective treatment with collagen derivatives in patients with OA.

Methods: Eligible randomised controlled trials (RCTs) and quasi-RCTs were identified by searching PubMed, Embase and the Cochrane Central Register of Controlled Trials until November 2011. Methodological quality was assessed using methods of the Cochrane Back Review Group.

Results: Eight studies were identified: six on CH, two on gelatine, and one on UC. The pooled mean difference based on three studies for pain reduction measured with the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index comparing CH with placebo was −0.49 (95% CI −1.10–0.12). However, some studies report significant between-group differences in pain when measured with a visual analogical scale (VAS) or other instruments, or when CH is compared with glucosamine sulphate. For disability no significant between-group mean differences were found when comparing CH with placebo. Gelatine compared with placebo and with alternative therapies was superior for the outcome pain. UC compared with glucosamine + chondroitin showed no significant between-group differences for pain and disability. The most reported adverse events of collagen derivatives were mild to moderate gastro-intestinal complaints. The overall quality of evidence was moderate to very low.

Conclusions: There is insufficient evidence to recommend the generalized use of CHs in daily practice for the treatment of patients with OA. More independent high-quality studies are needed to confirm the therapeutic effects of collagen derivatives on OA complaints.

Introduction

Osteoarthritis (OA) is a chronic disease of the joint frequently seen in knee, hip, spine and hand causing pain, stiffness, decreased range of motion, and reduced quality of life. It is a serious health problem reported to affect, for example, 27 million people in the United States[1].

The pathology of OA involves the whole joint in a disease process that includes focal and progressive hyaline articular cartilage loss with concomitant changes in the bone underneath the cartilage, including formation of osteophytes and bony sclerosis, and changes in the synovium and joint capsule[2].

OA is treated mainly by exercise (although only moderately effective), combined with the use of analgesics (acetaminophen) or non-steroidal anti-inflammatory drugs (NSAIDs)[3]. These medications are symptomatic but not disease modifying and have adverse effects. During the last decades, disease-modifying osteoarthritis drugs (DMOADs) have received increasing interest. These new substances are aimed at preventing or diminishing the deterioration of joint tissue[4]. Collagen derivatives are candidate DMOADs

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that are currently being investigated. The three major groups of collagen derivatives are based on the various degrees of hydrolysis of collagen: undenatured collagen (UC), gelatine and collagen hydrolysate (CH), with a molecular weight of 300 kDa, 20–90 kDa and 2–9 kDa, respectively. CH is absorbed intestinally, as shown in preclinical studies in mice. In plasma, it peaks at 6h after ingestion[5]. In 'gut-sac' experiments, it was shown that gelatine is absorbed in high molecular form (1–10 kD) to some extent, notwithstanding the still widespread assumption that proteins are hydrolyzed in the gastrointestinal tract prior to absorption, so that free amino acids enter the circulation predominantly[5]. Administered in fermented milk products, the plasma concentrations of CH increases[6].

The various collagen derivatives are reported to have different working mechanisms. UC is studied mainly in rheumatoid arthritis (RA) patients and mostly collagen type II is used. It is thought to have a working mechanism called oral tolerance, inducing a reduction in autoimmune reactions against collagen of articular cartilage, although not yet conclusively proven in human trials[7]. Since OA is not an autoimmune disease, a potential effect needs to be explained by a different working mechanism, but this has not yet been investigated.

CH and gelatine are thought to have the same working mechanism and differ only in bioavailability. Three possible mechanisms of CH (and gelatine) can be proposed. Firstly, studies using oral administration of radioactive-labelled gelatine in mice and in vitro studies with CH, suggest that peptides can be used as building blocks for the cartilage[5,8,9]. However, the data of these short-term experiments of chondrocytes in monolayer were not confirmed in longer-term studies with chondrocytes in 3D constructs[10,11]. It is not obvious whether the possible effects of CH are caused by the special amino acid content (a relatively large amount of proline and glycine) or by the effects of peptides that crossed the intestinal mucosa.

Furthermore, bone changes play a role in the pathogenesis of OA[12]. It is hypothesized that CH also influences bone metabolism[13,14]. Finally, since chicken CH is reported to reduce blood pressure in animals and humans, a possible working mechanism of CH is via the vascular system[15–17]. This is plausible considering the association between OA and atheromatous vascular disease of the subchondral bone, as suggested by epidemiological studies[18].

Collagen derivatives are heavily marketed in the lay press and recommended to physicians, based on several randomised controlled trials (RCTs). However, no independent high-quality systematic review is yet available, which is needed to provide evidence-based information for physicians and patients. Therefore, this review summarizes the evidence from RCTs and quasi-RCTs that have examined the effectiveness of collagen derivatives for symptomatic and chondroprotective treatment in patients with OA.

Methods

Types of studies, participants, interventions and outcome measures

RCTs and quasi-RCTs were included that assessed the effectiveness of oral intake of collagen derivatives (e.g., UC, gelatine or CH) in patients with OA in any joint in whom the diagnosis was based on clinical, or clinical and radiographic criteria. Preferably, the following comparisons had been made: collagen derivatives vs placebo, collagen derivatives vs no treatment, collagen derivatives vs other pain medication (e.g., paracetamol or NSAIDs), one collagen derivatives vs another collagen derivatives, and collagen derivatives vs other DMOADs. Combined preparations of collagen derivatives with other candidate DMOADs were excluded if the collagen derivatives were not investigated solely in a separate intervention group.

The primary outcomes were pain severity, disability, and adverse events. Secondary outcomes were chondroprotection, quality of life, number of responders assessed with the OMERACT–OARSI responder criteria [19], and health care consumption. No restrictions were applied regarding the measuring methods used for these outcomes, except for the outcome 'number of responders' which has to meet the above-mentioned criteria.

Search methods

The following databases were searched: the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, to November 2011), PubMed (1966–November 2011), and EMBASE (1988–November 2011). No language restrictions were applied. Keywords used were osteoarthritis, degenerative arthritis, CH, gelatine hydrolysate and type II collagen (Appendix 1).

In addition, the reference lists of the selected papers were screened and trial registers were searched. Manufacturers of CH were requested to provide us with any unpublished studies, and experts in the field were contacted and asked to complement our list with any relevant references, abstracts and full-text articles.

Selection of studies

Two of the authors (JPJvV and SMAB-Z) independently examined article titles and abstracts for eligibility (Appendix 2). Then, the full-text reports were screened to determine final eligibility for inclusion in the present review. Any disagreement was resolved by consensus.

Data extraction

Two authors (JPJvV and PAJL) extracted data using a standardised data extraction form. Data were collected on methods, duration of follow-up, participants and setting, interventions, outcome measures and results.

Quality assessment

Two authors (JPJvV and APV) independently assessed the methodological quality using the risk of bias form of the Cochrane Back Review Group[20]. Disagreement was resolved by consensus. A kappa statistic was calculated to assess the interobserver reliability for judging the studies.

Two authors (JPJvV and PAJL) used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the quality of evidence according to outcome[21].

Data synthesis

Continuous data are presented as (standardised) mean differences with 95% confidence intervals (CI). Dichotomous data (e.g., occurrence of adverse effects and number of responders) are expressed as relative risks (RR), odds ratios (OR), risk difference (RD) or number needed to treat (NNT) with corresponding 95% CI. Effect sizes are calculated using mean differences with their standard deviations (Cohen's d).

RevMan analyses (RevMan5) were used to analyse the data. If studies were sufficiently homogeneous concerning study population and intervention, the results of comparable groups were pooled (if possible using a fixed effect model). When statistical heterogeneity measured with I^2 was higher than 40%, a random effects model was used.