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Undenaturated collagen type I in the treatment of painful osteoarthritis of the knee

Worldwide, osteoarthritis is the most common joint disorder. In western countries, radiographic evidence of this disease is present in the majority of persons by 65 years of age and in about 80 percent of persons more than 75 years of age. The number of patients with OA has increased by nearly 30% over the past 10 years. Pain and other symptoms of OA may have a strong effect on quality of life, affecting both physical and psychological functions. It is now well recognized that OA is not solely a disease of cartilage. In addition to the synovium and subchondral bone, it also affects menisci, ligaments, capsule, and muscle (1). The degradation of cartilage occurs as a result of complex interactions between the mechanical factors and biochemical changes in the affected joint.

Current treatment of OA includes exercise, heat/cold therapy, joint protection, weight loss, physiotherapy/occupational therapy and medications (2-4). The most common medications include acetaminophen, NSAIDs and symptomatic slow acting drugs for osteoarthritis – SYSADOA as glucosamine, chondroitinsulphate, unsaponified avocado/soybean and diacerhein. Drugs from SYSADOA group are widely used also in USA as dietary supplements. Currently, glucosamine and chondroitin are the two most commonly used dietary supplements in humans to alleviate pain associated with OA (5). However, recent randomized controlled trials and meta-analysis of these supplements have shown only small-to-moderate symptomatic efficacy in human OA (6). New meta-analysis of clinical studies with glucosamine or chondroitin showed, that only the long-term daily administration for over 2 or 3 years may delay radiological progression of OA of the knee (7).

In the past twenty years some clinical studies demonstrated the beneficial effects of native collagen type II in the treatment of patients with rheumatoid arthritis (8, 9, 10, 11). Recently, Crowley et al. (12) compared the efficacy of undenaturated collagen type II (UC-II) and glucosamine + chondroitin (G+C) in the treatment of patients with knee OA. The results of this randomized, double-blind clinical study indicate that UC-II treatment was more effective, resulting in a significant reduction in all assessments (WOMAC score, VAS score, Lequesne's functional index), from the baseline at 90 days; whereas, this effect was not observed in G+C treatment group.

Our previous open clinical study in patients with osteoarthritis (OA) has shown that native, undenaturated type I collagen (COL-I) (dietary supplement Colafit made by Dacom Pharma, Czech Republic) is effective in the treatment of OA. Colafit is a pure collagen type I *of fibrous structure* isolated from bovine Achilles tendon. Collagen type I is the most abundant collagen of the human body. It is found in tendons, skin, artery walls, the endomysium of myofibrils, fibrocartilage, and the organic part of bones and teeth. Lahm et al (13) found that not only collagen type II, but also collagen type I is synthesized by the cells of the diseased cartilage tissue, shown by increasing amounts of collagen type I mRNA especially in the later stages of osteoarthritis.

The present randomized double-blind, placebo-controlled clinical trial evaluated the safety and efficacy of COL-I in the treatment of OA of the knee.

Patients and methods

The study was conducted at 2 sites in Slovakia and enrolled 58 patients with painful knee OA (29 treated with COL-I and 29 with placebo) who satisfied Kellgren radiographic criteria grade 2 or grade 3. After a 1-week NSAID or analgetics washout period, patients received either COL-I (8 mg pure lyophilized collagen type I in capsule) or placebo for 3 months, followed by an off-treatment period of 1 month to determine the carryover effects of the drug. The 100mm visual analogue scale (VAS), Western Ontario and McMaster Universities Index (WOMAC Index) were evaluated at the beginning of the study, after 3 moths of treatment and other 1 month follow-up. At the beginning of the study the consent form was discussed, signed and a physical

examination was performed. Exclusion criteria were: inflammatory joint diseases, septic arthritis, gout, diabetes, intra-articular corticosteroid or hyaluronan injections in the target knee within the last three months, abnormal kidney or liver function test. Medication/supplement use and medical history were recorded. Paracetamol up to 4g per day was allowed as a rescue therapy during the study. The possible side effects and medications used throughout the study period were recorded. The patients were also asked for verbal evaluation of the efficacy of the treatment by choosing from the following possibilities: excellent, good, mild or unsatisfactory.

Results.

The results indicate that COL-I treatment was effective resulting in significant reduction in the WOMAC score and VAS score from the baseline after 3 months treatment and after 1 months follow-up. Treatment with COL-I reduced the total WOMAC score by 38% as compared to 10% in placebo treated group and 37% vs 8 % after 1 month follow up (COL-1 vs placebo, $p<0.001$) (Fig.1). COL-I treatment decreased VAS score by 41% after 3 month treatment vs 13 % placebo and after 1 month follow-up 37% vs 11 % (COL-1 vs placebo, $p<0.001$) (Fig. 2). No side effects associated with treatment were observed. Efficacy of the treatment evaluated by patients showed significantly better efficacy in COL-I treated group compared to placebo group (Fig. 3). Concomitant medication of the pain was recorded only in 2 patients (paracetamol in an average dose 600 mg/day, not longer then 2 weeks) comparison with placebo group in which 5 patients needed the rescue pain treatment (600 mg paracetamol 1-2 weeks).

Discussion

Our previous open clinical study in patients with osteoarthritis (OA) has shown that native, undenaturated type I collagen (COL-I) is effective in the treatment of OA. This double blind, placebo controlled study proved these results and showed the clinical efficacy of treatment on disease specific measures of OA of the knee. Interestingly, the results of our study are similar or better in comparison with result published by Crowley et al. (12) with undenaturated collagen type II. Collagen type II reduced the WOMAC score after 3 months treatment by 33% from the baseline value, collagen type I in our

study by 38%. Reduction of VAS score in our study with collagen type I was 40% in the study of Crowley et al (12) the reduction of VAS score was 41%. We suggested that these collagens could act by similar mechanism in knee OA. The precise biochemical mechanism involved in COL-I induced pharmacological anti-arthritic effects in humans is not clearly established. Type I collagen is more abundant then collagen type II, besides cartilage occurs also in the other joint structures as ligaments, tendons, joint capsule, subchondral bone but also osteoarthritic cartilage. COL-I contains the amino acids required for the synthesis and repair of connective tissue throughout the body. Anti-inflammatory and antiarthritic effets of collagen type I may be explain by mechanism of oral tolerance developed after oral application of collagen.

In conclusion our study showed that undenaturated collagen type I is effective in the treatment of painful OA of the knee.

References

1. **Brandt KD, Radin EL, Dieppe PA, et al.: Yet more evidence that osteoarthritis is not a cartilage disease. Ann Rheum Dis. 2006 ; 65:1261-4.**
2. **Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S: Exercise for osteoarthritis of the hip. Cochrane Database Sys Rev.2009; 8: CD007912.**
3. **Das SK, Faroogi A: Osteoarthritis. Best Pract Res Cli Rheumatol 2008; 22:657-75.**
4. **Bruyère O, Burlet N, Delmas PD, Rizzoli R, Cooper C, Reginster JY. Evaluation of symptomatic slow-acting drugs in osteoarthritis using the GRADE system. BMC Musculoskelet Disord. 2008 ; 16:165.**
5. **Brown LP. Pet Nutraceuticals; Inter-Cal Nutraceuticals. US: Arthritis Foundation. 2005.**
6. **Distler J, Anguelouch A.: Evidence-based practice: review of clinical evidence on the efficacy of glucosamine and chondroitin in the treatment of osteoarthritis. J Am Acad Nurse Pract. 2006;18:487-93.**

7. **Lee YH, Woo JH, Choi SJ, Ji JD, Song GG : Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: a meta-analysis. Rheumatol Int. 2010; 30: 357-63.**
8. **Trentham DE, Dynesius-Trentham RA, Orav EJ, et al.: Effects of oral administration of type II collagen on rheumatoid arthritis. Science. 1993; 261:1727-30.**
9. **Barnett ML, Combitchi D, Trentham DE: A pilot trial of oral type II collagen in the treatment of juvenile rheumatoid arthritis. Arthritis Rheum. 1996; 39: 623-8.**
10. **Ausar SF, Beltramo DM, Castagna LF, et al. : Treatment of rheumatoid arthritis by oral administration of bovine tracheal type II collagen. Rheumatol Int. 2001; 20:138-44.**
11. **Wei, W, Zhang LL, Xu J-H, et al: A multicenter, double-blind, randomized, controlled phase III clinical trial of chicken type II collagen in rheumatoid arthritis. Arthritis Res Therapy 2009; 11: R180.**
12. **Crowley DC, Lau FC, Sharma P et al: Safety and efficacy of undenaturated type II collagen in the treatment of osteoarthritis of the knee: a clinical trial. Int J Med Sci 2009; 6: 312-321.**
13. **Lahm A, Mrosek E, Spank H, Erggelet C, Kasch R, Esser J, Merk H. Changes in content and synthesis of collagen types and proteoglycans in osteoarthritis of the knee joint and comparison of quantitative analysis with Photoshop-based image analysis. Arch Orthop Trauma Surg. 2010 Apr;130(4):557-64. Epub 2009 Oct 17.**

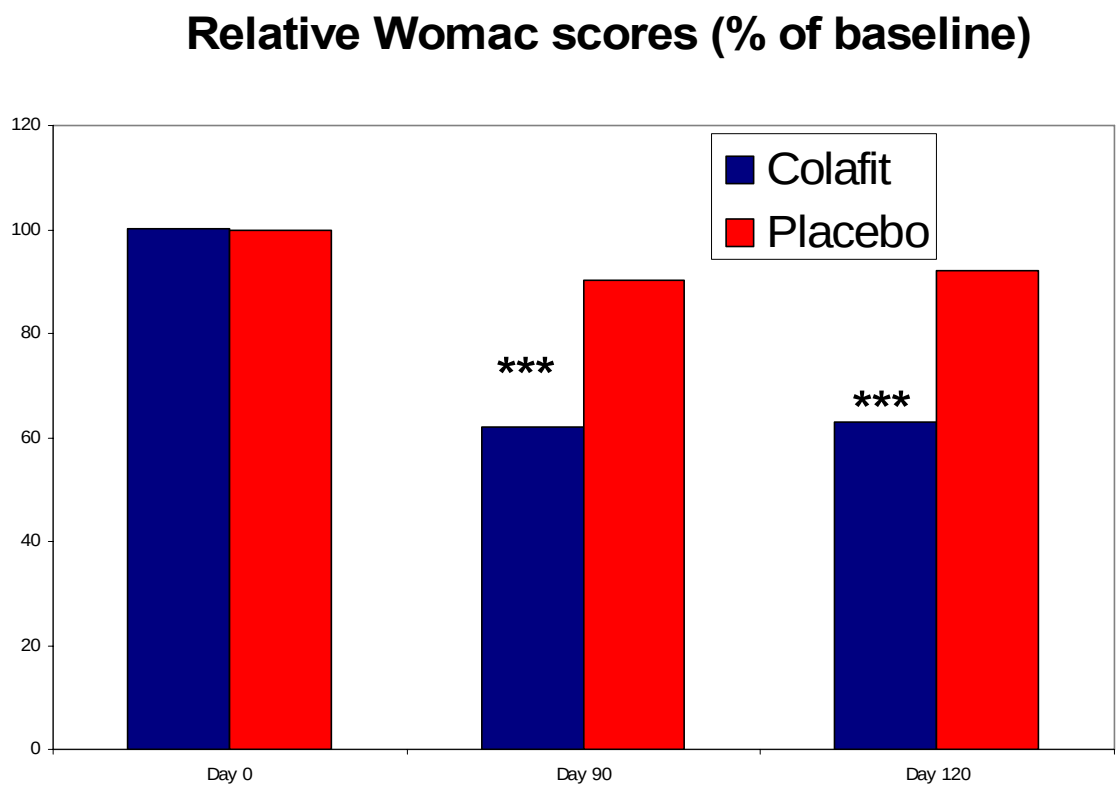

Fig.1.
*****Significantly different from basaline value, p<0.001.**

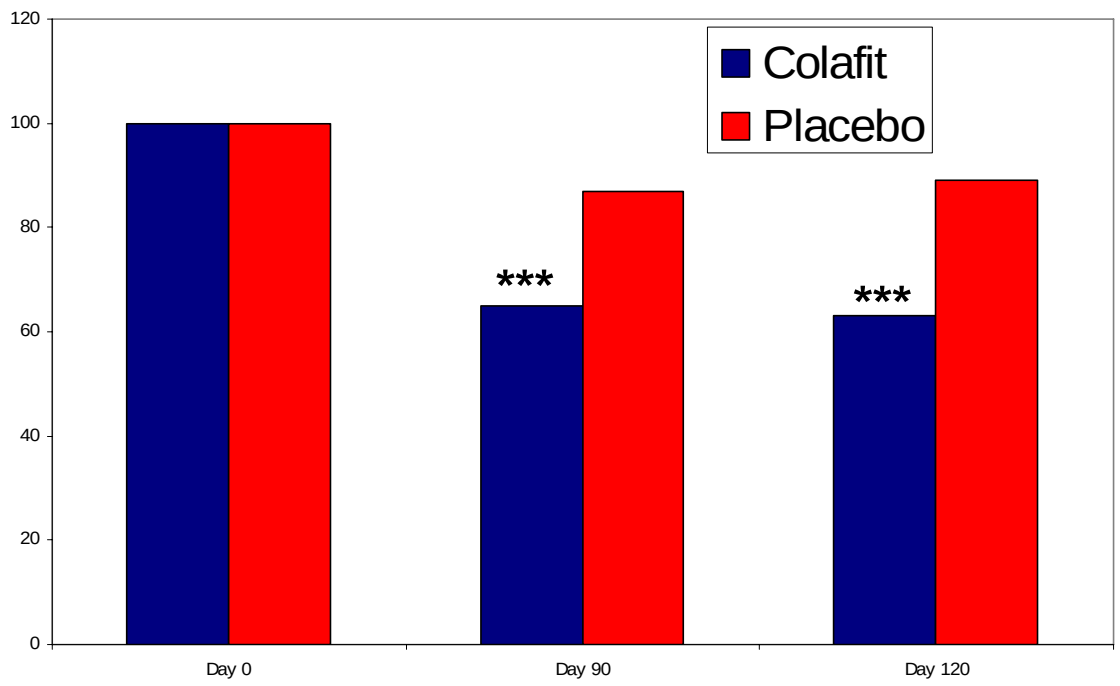

Fig.2.
*****Significantly different from basaline value, p<0.001**

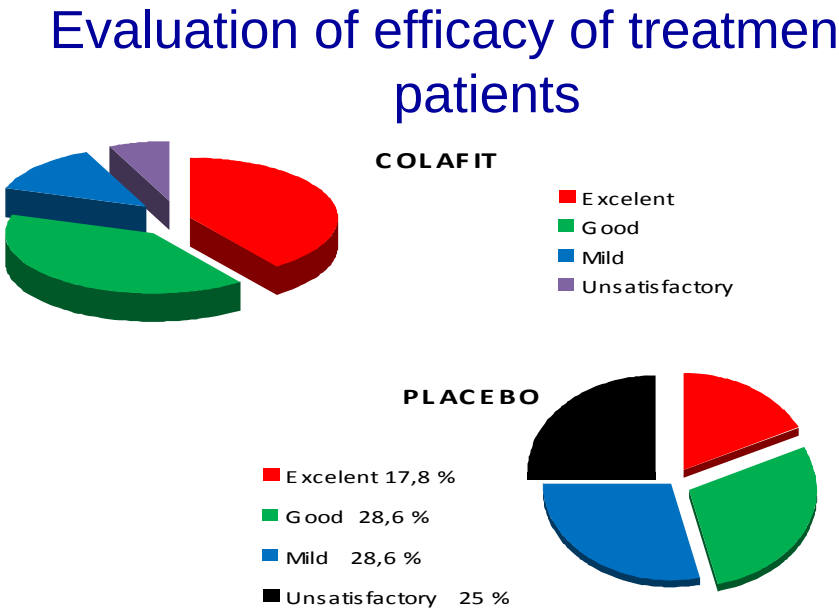

Fig. 3. Evaluation of efficacy of treatment by patients.

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