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Relationship between weight loss in obese knee osteoarthritis patients and serum biomarkers of cartilage breakdown: secondary analyses of a randomised trial

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SUMMARY

Objective: To explore effects of weight loss and maintenance on serum cartilage biomarkers denaturation neoepitope for Collagen2 (Coll2-1) and Fibulin3 fragment (Fib3-2), as well as correlations between Coll2-1 and Fib3-2 and symptomatic improvement, in a knee osteoarthritis (KOA) population.

Design: 192 obese KOA patients followed a 16 week weight loss intervention and 52 weeks weight maintenance (ClinicalTrials.gov identifier: NCT00655941). Assessments were at 0, 8, 16 and 68 weeks. Serum Coll2-1 and Fib3-2 were determined with ELISA, and symptoms by the Knee Osteoarthritis Outcome Score (KOOS) questionnaire.

Changes from week 0 and association between changes from baseline in body weight and Coll2-1, Fib3-2, and the 5 KOOS domains were assessed at all time points.

Results: Coll2-1 changes from baseline showed a decrease at week 8 ($P = 0.0002$), no change at week 16 ($P = 0.49$), and an increase at week 68 ($P = 0.036$). Fib3-2 showed an increase from baseline at week 8 ($P = 0.0015$) and 16 ($P < 0.0001$), but none at week 68 ($P = 0.23$).

No statistically significant correlations were found between changes in body weight and Coll2-1 and Fib3-2 at any time point ($r < 0.05$; $P > 0.49$).

At all time-points there were significant positive correlations between changes from baseline in Coll2-1 and in $KOOS_{Sports/Recreation}$ (week 8, 16, 68: $r = 0.17$; $P = 0.03$; $r = 0.16$; $P = 0.04$; and $r = 0.17$; $P = 0.04$, respectively).

Conclusion: The clinical improvement after a substantial weight loss and weight maintenance in KOA patients was not associated with decrease in markers of cartilage breakdown Coll2-1 or Fib3-2, even with indications of a slightly negative effect.

Introduction

Loss of cartilage is a cardinal feature of knee osteoarthritis (KOA)[1], and disease-modifying treatment still needs to be identified. Weight loss is recommended as treatment of symptoms in concomitant obesity and KOA[2] and has symptomatic effect, but so far effects of weight loss on KOA cartilage assessed by imaging are not conclusive[3–6]. As an alternative, assessment of circulating biomarkers of cartilage breakdown or turnover may provide clues to possible effects of weight loss on KOA cartilage. Earlier we found a slight weight-change related reduction in serum Cartilage Oligomeric Matrix Protein (sCOMP) with weight loss in KOA, while urine C-terminal telopeptide of Collagen 2 (uCTX2) and of Collagen 1 (uCTX1) increased, independent of weight loss magnitude[7].The latter biomarkers are recently questioned as reliable markers for cartilage breakdown[8,9].

The main and characteristic collagen type in articular cartilage is Collagen type 2 (Coll2). The denaturation neoepitope Coll2-1

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which, when oxidated following the catabolic processes, appears on the nitrated form Coll2-1NO2, originates from the helical part of the collagen type II, thereby representing collagen type II degradation[10,11]. When looking for a reliable marker for collagen type-2 catabolism, Coll2-1 is therefore a valid choice. Coll2-1 fragments are shown to be elevated in OA compared to healthy controls[11,12], and is not associated with age[11]. Following knee or hip joint replacement for OA, a decrease in serum Coll2-1 towards the values found in healthy controls has been shown[12]. Further, serum Coll2-1 associates with joint degeneration in horses[13], and Col2-1 concentration decreases following curcumin treatment knee OA[14]. Thus Coll2-1 is considered a reliable measure for state of breakdown processes of collagen-2 fibres in articular cartilage, and may indicate possible disease modification induced in cartilage by treatment like weight loss.

Another suggested marker for OA activity is Fibulin3 turnover measured by the Fibulin3 fragment Fib3-2, which is raised in OA compared to healthy individuals[15,16]. Fibulins are glycoproteins present in extracellular matrix[17] in many parts of the body like the walls of smaller blood vessels, in basal membranes, myofascia, and cartilage[17–19]. Matrix metalloproteases (MMPs) are known to break down the short fibulins like Fibulin3[20], and a link between OA matrix degradation and Fibulin3 breakdown products is plausible.

We have previously demonstrated efficacy of a 16-week weight loss program in obese KOA patients concerning symptomatic improvements[21]. Further, we have shown that a subsequent 52 weeks maintenance by either continuous dietetic support, exercise, or 'no attention' sustained symptomatic relief with only slight weight regain[22]. Here we aim to explore any possible effects of weight loss and maintenance on circulating levels of serum Coll2-1 and Fib3-2, as well as any correlation between Coll2-1 and Fib3-2 and symptomatic improvement, in the same population.

Materials and methods

Study

This is a secondary report from the CAROT study – Influence of weight loss or exercise on CARtilage in Obese KOA patients Trial (ClinicalTrials.gov: NCT00655941), designed as a pragmatic randomized controlled trial, with pain and treatment response as primary outcomes[22]. 192 patients were included fulfilling aged 50 years and above, confirmed KOA based on pain and at least OA in one joint compartment on standing radiographs, and a body mass index (BMI) $\geq$ 30 kg/m^2. Participants were excluded if they had any of the following: lack of motivation to lose weight, inability to speak Danish, planned anti-obesity surgery, total knee alloplasty (TKA), or receiving pharmacologic therapy for obesity. The patients were given an initial 16 week intensive diet intervention in a supervised program, inducing a clinically significant weight loss. The intensive diet intervention consisted of 8 weeks of full meal replacement (Cambridge Weight Plan TM, Northants, UK) with either 810 or 415 kcal/day followed by 8 weeks with gradual reintroduction of "normal food" in a hypo-energetic diet of 1200 kcal/day[21]. Following 16 weeks weight-loss program, the participants were allocated to a 52-week maintenance program consisting of either (1) continued dietary consultancy, (2) knee exercise therapy, or (3) no attention[23]. The participants were randomised at baseline (i.e., before the dietary intervention) but not informed about the group allocation until the end of the 16 week dietary intervention. The exercise group was mainly concerned with improving knee function and not at improving fitness or muscle strength. The programme was designed to transfer from facility-based to unsupervised home-based exercises and a more elaborate description has been published[22]. The continued dietary consultancy was one meal replacement product daily and weekly educational session with a dietician. The details have also been published[22]. The total study duration was 68 weeks. Assessments, including body weight and blood samples, and self-assessment via the Knee injury and Osteoarthritis Outcome Score (KOOS)[24], were carried out at week 0 (baseline), 8, 16, and 68.

Variables

Body weight

Body weight was measured on a decimal weighing scale (TANITA BW-800, Frederiksberg Vægtfabrik, Denmark) to the nearest 0.1 kg, and without shoes and larger clothing.

KOOS

At each visit, the patient filled in the KOOS[24]. The KOOS questionnaire consists of 5 subscales (Pain; Symptoms; Function in daily living; Knee-related quality of life; and Function during Sports and Recreation) each with scores ranging from 0 (worst) to 100 (best). The results of the weight loss and maintenance on KOOS have been published[22].

Biomarkers

Samples from the same patient at different time point were for each biomarker measured on the same ELISA plate.

Coll2-1. Blood samples were taken fasting in the morning. Serum samples were produced from these, frozen at −20°C, and stored at −80°C until measurements of all samples in one batch. Coll2-1 was measured with ELISA (Coll2-1 kit, Artialis, Liège, Belgium, www.artialis.com). The sensitivity for Coll2-1 was 17 nM, and the intra-assay and inter-assay variation was below 10%. The working range of quantification of this assay was comprised between 31.85 and 2000 nM.

Fib3-2. Fib3-2 was measured with ELISA (Fib3-2 kit, Artialis, Liège, Belgium, www.artialis.com). The sensitivity for Fib3-2 was 8 pM, and the intra-assay and inter-assay variation was below 11%. The working range of quantification of this assay was comprised between 15.6 and 500 pM.

Outcomes

The outcomes were changes in the proposed biomarker for articular cartilage breakdown Coll2-1, assessed as changes from baseline, and change in proposed OA disease-marker Fib3-2.

Statistical analyses

Since the aim of this study was to explore a possible change in biomarkers of cartilage turnover in relation to weight loss and weight loss maintenance, we decided a priori to include only participants with complete baseline Coll2-1 and Fib3-2 data, thus defining a modified intention-to-treat (mITT) population.

We analysed the changes from week 0 using repeated measures mixed effects models, allowing for imbalanced data (i.e., no imputation for missing data beyond baseline) with maintenance group (Control, Diet, and Exercise) and week (8, 16, and 68) as fixed effects including their interaction, and participant as random effects. The models were adjusted for the baseline value. We focused on the group × week interaction, and on the main effects of week (thus ignoring group allocation).

The association between changes from baseline in body weight and Coll2-1, Fib3-2 concentrations, and the 5 KOOS domains were assessed at all time points using Spearman correlation.

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