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Serum cartilage oligomeric matrix protein (sCOMP) is elevated in patients with knee osteoarthritis: a systematic review and meta-analysis

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SUMMARY

Objective: To be used in diagnostic studies, it must be demonstrated that biomarkers can differentiate between diseased and non-diseased patients. Therefore, the purpose of this study was to answer the following questions: (1) Is serum cartilage oligomeric matrix protein (sCOMP) elevated in patients with radiographically diagnosed knee osteoarthritis (OA) compared to controls? (2) Are there differences in sCOMP levels when comparing differing radiographic OA severities to controls?
Methods: Systematic review and meta-analysis. *Data Sources*: A systematic search of CINAHL, PEDro, Medline, and SportsDiscus was completed in March 2010. *Keywords*: knee, osteoarthritis, sCOMP, radiography. *Study inclusion criteria*: Studies were written in English, compared healthy adults with knee OA patients, used the Kellgren Lawrence (K/L) classification, measured sCOMP, and reported means and standard deviations for sCOMP.
Results: For question 1, seven studies were included resulting in seven comparisons. A moderate overall effect size (ES) indicated sCOMP was consistently elevated in those with radiographically diagnosed knee OA when compared to controls (ES = 0.60, $P < 0.001$). For question 2, four studies were included resulting in 13 comparisons between radiographic OA severity levels and controls. Strong ESs were calculated for K/L-1 (ES = 1.43, $P = 0.28$), K/L-3 (ES = 1.05, $P = 0.04$), and K/L-4 (ES = 1.40, $P = 0.003$). A moderate ES was calculated for K/L-2 (ES = 0.60, $P = 0.01$).
Conclusions: These results indicate sCOMP is elevated in patients with knee OA and is sensitive to OA disease progression. Future research studies with a higher level of evidence should be conducted to investigate the use of this biomarker as an indicator for OA development and progression.

Introduction

Characterized by irreversible joint destruction such as cartilage degradation, osteophyte development and joint space narrowing, osteoarthritis (OA) affects millions of individuals each year[1–4]. Knee OA, either affecting the patellofemoral or the tibiofemoral joint, is the most common cause of disability in the United States[2,5], causing pain and loss of function[1,3,6–8]. Currently, there are few diagnostic tools used to identify individuals with knee OA. The diagnosis of OA is based on patient reports of pain and stiffness, and the presence of osteophytes and joint space narrowing as viewed on radiographs. Although many patients will demonstrate both symptomatic and visual indicators of OA, there is not a direct correlation between clinical indicators and actual joint damage[2,9]. Given the limitation of current diagnostic tools and that early osteoarthritic changes such as articular cartilage abnormalities are silent[10], OA is often unrecognized until it has reached an irremediable and disabling level[2]. The ability to develop intervention strategies with the hope of delaying irreversible joint damage remains difficult due to the lack of sensitive and valid pre-radiographic diagnostic tools[2]. Identifications of

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sensitive diagnostic tools to recognize pre-radiographic OA are necessary in order to develop and implement intervention strategies aimed at delaying irreversible joint damage[2].

Several serum and/or synovial fluid biomarkers have been identified in the literature to diagnose pre-radiographic OA[3,4,11–14]. For a biomarker to be useful in diagnosing early joint damage, it must be sensitive to differences between healthy individuals and those with OA, and also among varying degrees of severity of joint disease[4,15,16]. Examples of these biomarkers include keratan sulfate[12] and pentosidine[11], both which tend to be elevated in patients with OA. Another biomarker that is theorized to have significant diagnostic value for beginning OA, is serum cartilage oligomeric matrix protein (sCOMP)[2].

Serum COMP is a non-collagen biomarker for cartilage degradation present in articular cartilage, and other tissues such as ligament, meniscus, synovial membrane, and tendon[1,17–21]. Numerous studies have investigated the relationship of sCOMP in patients with and without knee OA[3,4,12,14,22,23]. Validation of this relationship will provide scientists and physicians with a prospective pre-radiographic diagnostic indicator that may be clinically applicable and may assist in the development of treatment interventions for early stage OA.

The purpose of this systematic review was to answer the following questions: (1) Is sCOMP elevated in patients with radiographically diagnosed knee OA compared to controls? (2) Are there differences in sCOMP levels when comparing differing radiographic OA severities to controls?

Methods

Search strategy

A computerized literature search was completed in March of 2010 utilizing: CINAHL (from 1981), PEDro (from 1929) Medline (from 1966), and SportDiscus (from 1985). The search terms used were, *knee*, *osteoarthritis*, *sCOMP*, and *radiography*. All abstracts from the search results were reviewed. If the abstracts did not contain enough information to include or exclude the study from the review, the study was reviewed in its entirety. In addition, all reference lists were cross-referenced for relevant studies not included in the original searches.

Criteria for study selection

The inclusion criteria for the studies used in this systematic review were:

- Subjects with radiographically diagnosed knee OA and disease free control groups.
- Studies using the Kellgren Lawrence (K/L) scale to classify knee OA.
- Studies that measured sCOMP or used sCOMP as an outcome.
- Studies reporting means and associated measures of variability.
- Studies using human adults (18+ years or older).
- Studies published in the English language.

Assessment of publication bias

A funnel plot was used to provide an illustrative assessment of publication bias. In addition, Duval and Tweedie's Trim and Fill method and Orwin's Fail-Safe N were used to further interpret possible publication bias. The Duvall and Tweedie's Trim and Fill method looks for missing studies on the left side of the mean effect using a fixed effects model[24]. The asymmetric studies from the right hand side of the mean effect are trimmed, the unbiased effect is located, then the studies to left of the mean are then filled in[24]. This method results in an adjusted cumulative effect, and provides a conservative estimate of the total number of studies that are "missing". Orwin's Fail-Safe N test was employed to assess the robustness of the observed overall effects of the moderators on sCOMP[25].

Sensitivity analysis

The "one-study removed method" was used to test the stability of the cumulative effect across the included studies by determining if the results of one particular study substantially influenced the overall effect[24]. The analysis systematically removes each study and replaces it so that the influence of each study can be individually evaluated. If the removal of any given study results in little change, it can be concluded that the pooled result is robust[24]. For the second question, we performed an additional sensitivity analysis to determine the influence of sample size on the overall effect for each of the individual K/L comparisons. Study comparisons were dichotomized into "large ($>$10 subjects per group) or "small" ($<$10 subjects per group). As a group, "large" studies and then "small" studies were selectively removed in order to assess for changes in the overall result based on sample size.

Assessment of study quality

The study quality was assessed independently by two authors using a quality index for non-randomized studies[26]. This index was adapted from a previously published version by Downs and Black[27]. Based on the study designs for the included studies, the quality index assessment tool[26] was selected in order to compare case-control and retrospective-cohort studies.

A total of 16 items were used to assess study quality for each study. The quality index assessment tool addressed areas such as: clarity of objectives, main outcomes, subject characteristics and main findings, as well as, external validity and internal validity concerning bias and confounding[26]. Any discrepancies in scores between authors were discussed and a mutual score was reached. Using previously published criteria[26], those studies achieving $\geq$75% of the criteria were considered high quality, 60–74% were considered moderate quality, and $\leq$60% were considered low quality.

Data extraction and statistical analysis

The variable of interest for this study was sCOMP. The reported unit of measure is typically ng/ml, but sCOMP levels have been reported using μg/ml and U/L. For meta-analysis, all sCOMP units of measure were used for data extraction and statistical analysis. Furthermore, in some cases sCOMP levels are not normally distributed. Recognition of this will allow for the data to be transformed using a logarithmic transformation, assuring the assumptions of the general linear model[23,28]. For the purposes of this meta-analysis, we recognize that a normal distribution might not have been present before data analysis; however, we did not or could not modify the data to control for this.

For this systematic review of the literature, K/L severity classification system for OA was used as an inclusion criterion. This classification system was chosen as it is a common classification system used to grade OA[29]. Studies using other forms of OA severity classification systems were excluded to ensure consistent comparisons across all studies.

To determine if sCOMP was elevated in patients with radiographically diagnosed knee OA compared to controls, bias-corrected Hedges's g[30] effect sizes (ESs) were calculated to estimate differences between OA and control groups and 95% confidence intervals