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Serum Cartilage Oligomeric Matrix Protein (Scomp) Is Elevated In Patients With Knee Osteoarthritis: A Systematic Review And Meta-Analysis

By: J.M. Hoch, C.G. Mattacola, J.M. Medina McKeon, **J.S. Howard**, & C. Lattermann

Abstract

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 ¼ 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 ¼ 1.43, P ¼ 0.28), K/L-3 (ES ¼ 1.05, P ¼ 0.04), and K/L-4 (ES ¼ 1.40, P ¼ 0.003). A moderate ES was calculated for K/L-2 (ES ¼ 0.60, P ¼ 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.

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?
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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 ≥75% of the criteria were considered high quality, 60–74% were considered moderate quality, and ≤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

(CI) to assess the uncertainty in these estimates. Hedge's g adjusts for sample size, which is often referred to as an unbiased estimate[30]. When applicable, separate ESs were calculated for individual K/L classifications compared to controls. All ESs, 95% CIs, and P-values were calculated in Comprehensive Meta Analysis (Comprehensive Meta Analysis Version 2.0, Biostat, Englewood, NJ). The calculated Hedges' g ES is a measure of a population's mean effect estimated under the assumption that the individual variability has a Gaussian distribution. A positive ES indicated elevated sCOMP levels in OA patients as compared to controls. ESs ≤ 0.40 were interpreted as representing a weak effect, ESs between 0.41 and 0.69 were interpreted as representing a moderate effect, and ESs ≥ 0.70 were interpreted as representing a strong effect[31]. An ES was interpreted as statistically significant if <0.05 (in which the corresponding CI would exclude the nil value).

Level of evidence

The level of evidence for the included studies was assessed using the Oxford Centre for Evidence-Based Medicine (CEBM)-Levels of Evidence[32]. The levels of evidence range from 1a to 5, with 1a representing a systematic review of prospective cohort studies, and level 5 representing expert opinion without critical appraisal, bench research or "first principles". The CEBM strength-of recommendation grades are A, B, C, and D. Grade A represents consistent level 1 studies; grade B represents consistent level 2 or 3 studies or extrapolations from level 1 studies; grade C represents level 4 studies or extrapolations from level 2 or 3 studies; and grade D represents level 5 evidence, troublingly consistent or inconclusive studies of any level[32].

Results

Study selection

Computerized and hand searches yielded 57 studies that were included in the initial review (Fig. 1). Based on the inclusion criteria

and presentation of necessary data, a total of seven studies were included in this review (Table I)[3,4,11,12,14,23,33]. The reason(s) for exclusion for the remaining 50 studies can be found in the online Appendix Table I.

Is sCOMP elevated in patients with radiographic knee OA compared to controls?

Seven studies met the inclusion criteria to answer this question (Table I)[3,4,11,12,14,23,33]. The mean quality index assessment for the included studies was 59% (25−87.5%). Three studies[4,14,23] were considered high quality, one[3] was considered moderate quality, and three studies[11,12,33] were considered low quality. Level C evidence exists that sCOMP is elevated in patients with knee OA. This recommendation was reached based on consistent level 4 studies with extrapolations from level 2 or 3 studies[32].

A total of seven ESs and 95% CIs were calculated (Fig. 2). Calculated ESs ranged from 0.06 [(CI) − 0.47−0.60] to 2.70 (1.85−3.54). A total of four ESs were weak, one ES was moderate and two ESs were strong. The results of the random effects meta-analysis revealed a moderate overall ES of 0.60 (0.25−0.94, P = 0.001), indicating sCOMP was consistently elevated in patients with radiographically diagnosed knee OA compared to controls.

Publication bias

The trim and fill[24] analysis indicated one study is missing, and the addition of this study would result in an insignificant weak ES of 0.39 (−0.03−0.81, Fig. 3). In addition, the Orwin's Fail-Safe N indicated a range of 20−50 additional studies (based on the trivial ES range of 0.05−0.10) would be needed to nullify the overall effect. Therefore, the effect of publication bias introduced across the studies is likely trivial. If all relevant studies beyond those analyzed in this meta-analysis were included, the ES would probably remain unchanged.
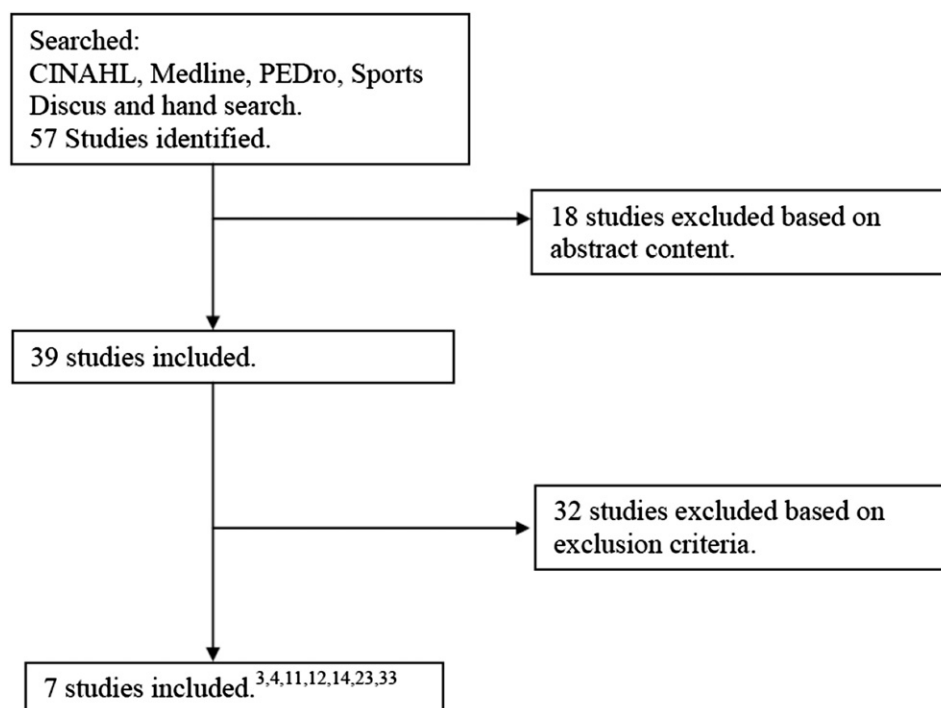

Fig. 1. Summary of search history and included studies.

Table I
Studies systematically reviewed to determine if sCOMP is elevated in patients with radiographically diagnosed knee OA

Authors	Level of evidence (CEBM)	Quality index score (%)	Study design	OA group inclusion criteria	No. control patients	No. OA patients	Dependent variables measured
Cibere et al. (2009)[14],*	2b	81.25%	Exploratory cohort	Aged 40−79 years; pain, aching, or discomfort in or around the knee on most days of the month at any time in the past; any pain, aching, or discomfort in or around the knee in the past 12 months	16	Pre-ROA = 105 ROA = 80† Total = 185	C2C; C1, 2C; CPII; CS846; NTX-I; CTX-II; HA; sCOMP; WOMAC
Clark et al. (2007)[4]	2b	81.25%	Retrospective cohort	Caucasian, knee OA K/L ≥ 2	148	K/L 2 = 109 K/L 3,4 = 34 Total = 143	sCOMP
Fernandes et al. (2007)[3], ‡	4	68.75%	Case control	Aged 40−70 years, mechanical pain in one or both knees for minimum 3 months, and knee crepitus upon clinical evaluation	86	SOA = 75** Pain = 11 NOA = 18** Total = 104	WOMAC; VAS and sCOMP
Jordan et al. (2003)[23]	2b	87.5%	Retrospective cohort	Radiographs and serum COMP samples in database	302	K/L 2 = 313 K/L 3 = 110 K/L 4 = 44 Total = 467	sCOMP
Mundermann et al. (2009)[33]	4	43.75%	Case control	Definite osteophyte presence in the medial or lateral tibiofemoral compartment; a narrowest point inter-bone distance of the medial compartment less than the lateral compartment; pain in and around at least one knee for most of the days in the past months; at least some difficulty with two or more items in the WOMAC physical function scale	41	K/L 1 = 11 K/L 2 = 7 K/L 3 = 12 K/L 4 = 12 Total = 42	Gait analysis; ambulatory load and sCOMP
Senolt et al. (2004)[11]	4	25%	Case control	Undergoing arthrocentesis, no history of renal disease of diabetes mellitus and had normal levels of creatinine	38	K/L 1 = 2 K/L 2 = 18 K/L 3 = 14 K/L 4 = 4 Total = 38	sCOMP and Pentosidine
Wakitani et al. (2007)[12], ††	4	25%	Case control	Patients undergoing knee surgery	24	K/L 1 = 7 K/L 2 = 4 K/L 3 = 6 K/L 4 = 7 Total = 24	Articular cartilage assessment, keratan sulfate, CS6, CS846, HA and sCOMP and synovial COMP

* Pre-ROA = pre-radiographic OA (K/L < 2); ROA = radiographic OA (K/L ≥ 2); C2C = Type II collagen cleavage neopeptide; C1, 2C = Types I and II collagen cleavage neoepitope; CS846 = cartilage proteoglycan aggrecan turnover epitope; NTX-I = N-telopeptide of type I collagen; CTX-II = C-telopeptide of type II collagen; HA = hyaluronan acid; WOMAC = Western Ontario McMaster University Index.

† Only the ROA group was used for this review.

‡ SOA (symptomatic OA) = K/L grades 2, 3, 4; NOA (non-symptomatic OA) = K/L 2 or higher; Pain = K/L 0 or 1; VAS = visual analog scale.

** Only the SOA and NOA groups were used for this review.
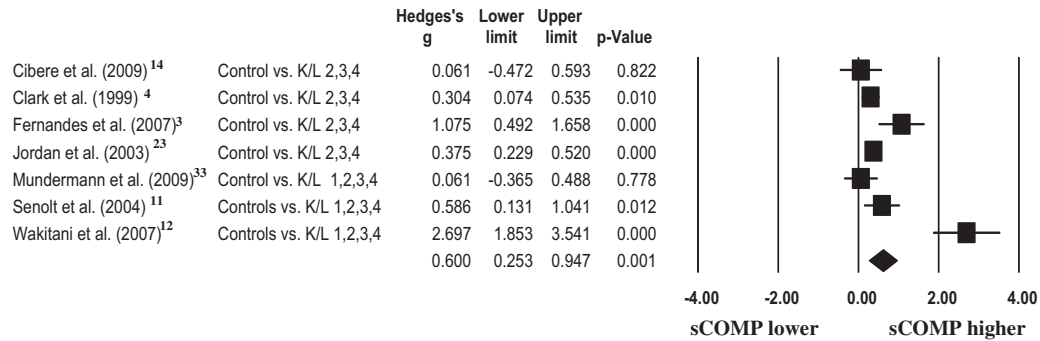
†† C6S = chondroitin 6 sulfate.

		Hedges's g	Lower limit	Upper limit	p-Value
Cibere et al. (2009) [14]	Control vs. K/L 2,3,4	0.061	-0.472	0.593	0.822
Clark et al. (1999) [4]	Control vs. K/L 2,3,4	0.304	0.074	0.535	0.010
Fernandes et al. (2007)[3]	Control vs. K/L 2,3,4	1.075	0.492	1.658	0.000
Jordan et al. (2003) [23]	Control vs. K/L 2,3,4	0.375	0.229	0.520	0.000
Mundermann et al. (2009)[33]	Control vs. K/L 1,2,3,4	0.061	-0.365	0.488	0.778
Senolt et al. (2004) [11]	Controls vs. K/L 1,2,3,4	0.586	0.131	1.041	0.012
Wakitani et al. (2007)[12]	Controls vs. K/L 1,2,3,4	2.697	1.853	3.541	0.000
		0.600	0.253	0.947	0.001

Fig. 2. A Forest plot depicting the calculated ESs of sCOMP in patients with radiographically diagnosed knee OA when compared to controls. The diamond at the bottom of the plot represents the overall ES.

Sensitivity analysis

Following the one-study removed method, the ESs ranged from 0.37 to 0.71. The lowest lower confidence limit was 0.17 and the highest upper confidence limit was 1.20. All P-values were $P < 0.01$. This indicated that there was not one particular study which substantially influenced the overall effect.

Are there differences in sCOMP levels when comparing differing radiographic OA severities to controls?

To be included in data analysis, a study must have presented data for the K/L severities in order to make control comparisons. Using this additional inclusion criteria, four studies[4,11,12,23] were included and 13 comparisons were made (Table I). The mean quality index assessment for the included studies used to answer this question was 56% (25–87.5%). Two studies[4,23] were considered high quality and two studies[11,12] were considered low quality. Level C evidence exists that sCOMP levels are elevated according to OA severity when compared to healthy controls. This recommendation was reached based on consistent level 4 studies with extrapolations from level 2 or 3 studies[32].

A total of 13 comparisons were used, with a calculated overall effect of 1.00 (0.65–1.35, $P < 0.001$). To answer question 2, subgroup ESs were calculated for each of the OA severities (K/L-1,-2, *etc.*)

Fig. 3. A funnel plot of standard error by Hedges's g using Duval and Tweedie's Trim and Fill method to assess publication bias of the studies used to determine if sCOMP is elevated in patients with radiographically diagnosed knee OA when compared to controls.

compared to controls. Strong ESs were observed for K/L-1, K/L-3, and K/L-4 while a moderate ES was observed for K/L-2 (Fig. 4). The subgroup ES for the K/L-1 comparison[11,12] was 1.43 (−1.15–4.02, $P = 0.28$). The subgroup ES for the K/L-2 comparison[4,11,12,23] was 0.60 (0.13–1.06, $P = 0.01$). The subgroup ES for the K/L-3 comparison[11,12,23] was 1.05 (0.06–2.03, $P = 0.04$). The subgroup ES for the K/L-4 comparison[4,11,12,23] was 1.40 (0.47–2.36, $P = 0.003$)[4,11,12,23].

Our results indicate a significant moderate effect for K/L-2, and a significant strong effect for K/L-3 and K/L-4 when compared to controls. Therefore, the subgroup meta-analysis revealed strong trends in elevated sCOMP levels as OA severity levels increase. However, the CIs for the ESs of each subgroup do overlap, therefore caution must be used when interpreting these results.

Publication bias

A publication bias assessment using the trim and fill method[24] was performed for all 13 comparisons. The results indicated publication bias is likely and there are five comparisons missing (Fig. 5). The addition of these five comparisons to the left of the overall mean effect would result in an insignificant weak overall effect of 0.39 (−0.002–0.79), with the CIs crossing zero. Additionally, the results of Orwin's Fail-Safe N indicated a range of 44–100 additional studies (based on the trivial ES range of 0.05–0.10) would be needed to nullify the overall effect. Therefore, the effect of publication bias introduced across the studies is trivial. If all relevant studies beyond those analyzed in this meta-analysis were included, the ES would probably remain unchanged.

Sensitivity analysis

Following the one-study removed method; the ESs remained strong and ranged from 0.78 to 1.30. The lowest lower confidence limit was 0.48, and the highest upper confidence limit was 1.60. All P-values were $P < 0.001$. This indicated that there was not one particular comparison that substantially influenced the overall effect calculated for the question.

A sense of caution must be employed when interpreting the K/L-1 vs control ES, as the two comparisons used to calculate this ES had a combined total of nine subjects in the group, and the CI encompassed zero. Given the recent results of a meta-epidemiological study[34], small comparisons such as those exhibited in the K/L-1 comparison, can inflate the overall effect (see K/L-1 diamond, Fig. 4). In order to determine the effect of the smaller subgroups ($n < 10$) on the overall ESs, we performed a sensitivity analysis comparing the overall effect of large vs small subgroups. The results of this analysis (Fig. 6) indicated small groups had a much larger overall effect (ES = 2.33, CI: 1.09–3.60), compared to larger groups
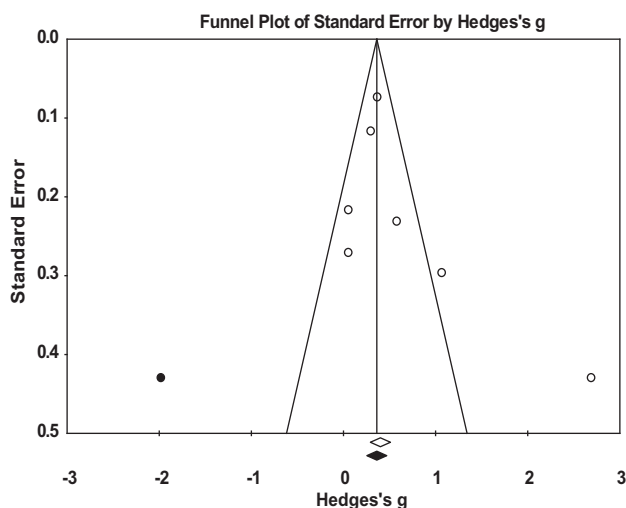
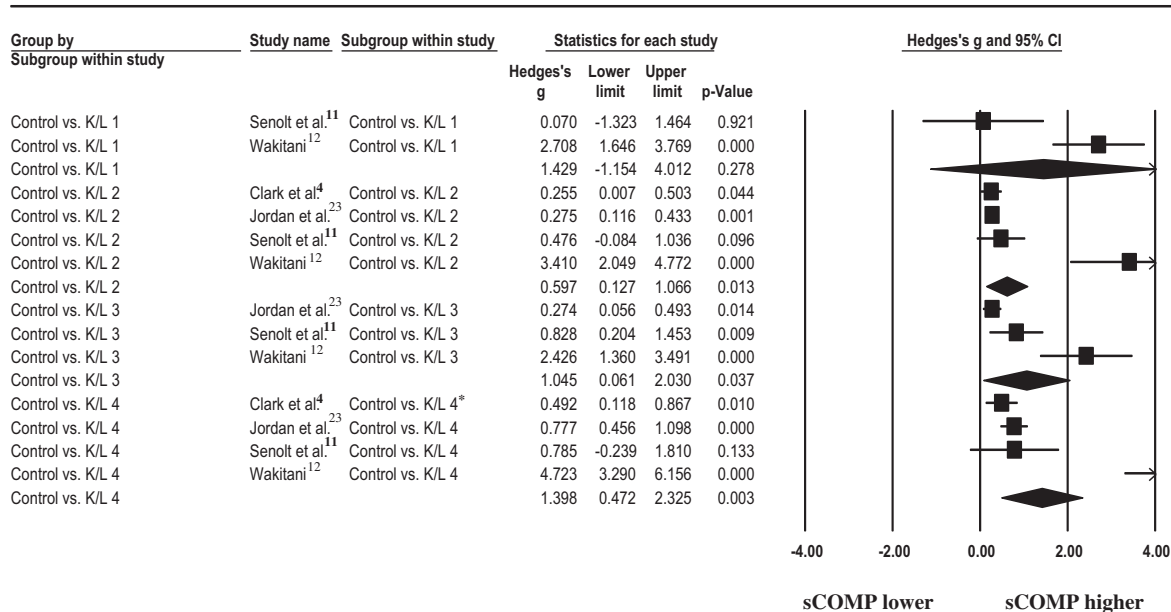| Group by Subgroup within study	Study name	Subgroup within study	Statistics for each study				Hedges's g and 95% CI
			Hedges's g	Lower limit	Upper limit	p-Value	
Control vs. K/L 1	Senolt et al.[11]	Control vs. K/L 1	0.070	-1.323	1.464	0.921	
Control vs. K/L 1	Wakitani[12]	Control vs. K/L 1	2.708	1.646	3.769	0.000	
Control vs. K/L 1			1.429	-1.154	4.012	0.278	
Control vs. K/L 2	Clark et al.[4]	Control vs. K/L 2	0.255	0.007	0.503	0.044	
Control vs. K/L 2	Jordan et al.[23]	Control vs. K/L 2	0.275	0.116	0.433	0.001	
Control vs. K/L 2	Senolt et al.[11]	Control vs. K/L 2	0.476	-0.084	1.036	0.096	
Control vs. K/L 2	Wakitani[12]	Control vs. K/L 2	3.410	2.049	4.772	0.000	
Control vs. K/L 2			0.597	0.127	1.066	0.013	
Control vs. K/L 3	Jordan et al.[23]	Control vs. K/L 3	0.274	0.056	0.493	0.014	
Control vs. K/L 3	Senolt et al.[11]	Control vs. K/L 3	0.828	0.204	1.453	0.009	
Control vs. K/L 3	Wakitani[12]	Control vs. K/L 3	2.426	1.360	3.491	0.000	
Control vs. K/L 3			1.045	0.061	2.030	0.037	
Control vs. K/L 4	Clark et al.[4]	Control vs. K/L 4*	0.492	0.118	0.867	0.010	
Control vs. K/L 4	Jordan et al.[23]	Control vs. K/L 4	0.777	0.456	1.098	0.000	
Control vs. K/L 4	Senolt et al.[11]	Control vs. K/L 4	0.785	-0.239	1.810	0.133	
Control vs. K/L 4	Wakitani[12]	Control vs. K/L 4	4.723	3.290	6.156	0.000	
Control vs. K/L 4			1.398	0.472	2.325	0.003	

sCOMP lower   sCOMP higher

Fig. 4. A Forest plot depicting the calculated ESs of sCOMP exist when comparing patients with differing radiographic knee OA severities compared to controls. Each of the diamonds represents the overall ES for each of the comparisons made for each (K/L) classification.

(ES = 0.41, CI: 0.25−0.60), demonstrating small groups significantly influenced the overall effect for each subgroup. However, if we were to remove the comparisons with <10 subjects per group, no comparisons would be available for the K/L-1 severity.

Discussion

To be a useful biomarker for the diagnosis of pre-radiographic knee OA, the biomarker must have a strong correlation with the disease, thereby having levels that are distinguishable between patients with and without the condition[4,15,16]. Based on the results of this systematic review, we concluded that sCOMP is consistently elevated in patients with radiographic knee OA compared to healthy controls (Fig. 2). Furthermore, higher levels of sCOMP are associated with a trend toward greater radiographic OA severity when compared to controls, as indicated by the ESs (Fig. 3). Further
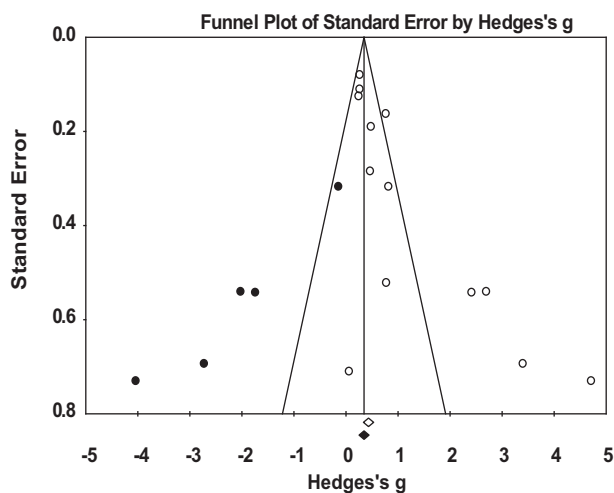

Fig. 5. A funnel plot of standard error by Hedges's g using Duval and Tweedie's Trim and Fill method to assess publication bias of the comparisons used to determine if differences in sCOMP levels exist when comparing differing knee OA severities when compared to healthy controls.

investigation is warranted to determine if this marker can be utilized to assess the presence of pre-radiographic OA, and in evaluating OA interventions in order to delay permanent joint degradation.

Study quality assessment

The mean quality index assessment for these studies was 59%. Three[4,14,23] of the studies were considered high quality, one was considered moderate quality[3] and three of the studies[11,12,33] were considered low quality. For the studies that were considered low quality, a majority of the criteria examining external and internal bias were either unable to be determined or not represented in the manuscript. These criteria included subject recruitment and representation of the population being sampled, blinding of investigators, appropriateness of statistical tests used and validity and reliability of the measurement tools used. Also, missing were criteria that were specific to internal validity. For example, a majority of the internal validity (confounding) criteria were not represented in most manuscripts considered moderate and low quality. These criteria addressed whether subjects were recruited from the same population, during the same period of time and if there was adequate adjustment for confounding in the analyses.

K/L classification and assessment

As part of the inclusion criteria, the K/L classification for knee OA must have been included and reported. This classification system was chosen because it is the most commonly used radiological classification system used to grade OA[29]. Two studies reviewed did not report the number of radiologists used to determine K/L classification[12,33]. Senolt et al.[11] reported the use of two radiologists for the review of subject radiographs and K/L classification assignment. One of the studies reported using a blinded rheumatologist to assign K/L classifications[3]. Cibere et al.[14] reported two blinded investigators with good interrater reliability (ICC = 0.79) read the radiographs and independently classified the patients. Consensus was reached between readers if they disagreed on K/L classification for the patients[14]. Finally, two studies reported the use of a single radiologist assessing the radiographs for K/L classification

Group by
Subgroup within study

Group by / Subgroup within study	Study name Subgroup within study	Hedges's g	Lower limit	Upper limit	p-Value
large	Clark et al 2 large [4]	0.255	0.007	0.503	0.044
large	Clark et al.4 large [4]	0.492	0.118	0.867	0.010
large	Jordan et al.2 large [23]	0.275	0.116	0.433	0.001
large	Jordan et al.3 large [23]	0.274	0.056	0.493	0.014
large	Jordan et al.4 large [23]	0.777	0.456	1.098	0.000
large	Senolt et al.2 large [11]	0.476	-0.084	1.036	0.096
large	Senolt et al.3 large	0.828	0.204	1.453	0.009
large		0.408	0.251	0.566	0.000
small	Senolt et al.1 small [11]	0.070	-1.323	1.464	0.921
small	Senolt et al.4 small [11]	0.785	-0.239	1.810	0.133
small	Wakitani 1 small [12]	2.708	1.646	3.769	0.000
small	Wakitani 2 small [12]	2.426	1.360	3.491	0.000
small	Wakitani 3 small [12]	4.723	3.290	6.156	0.000
small	Wakitani 4 small [12]	3.410	2.049	4.772	0.000
small		2.332	1.087	3.577	0.000

Hedges's g and 95% CI — scale: −4.00, −2.00, 0.00, 2.00, 4.00
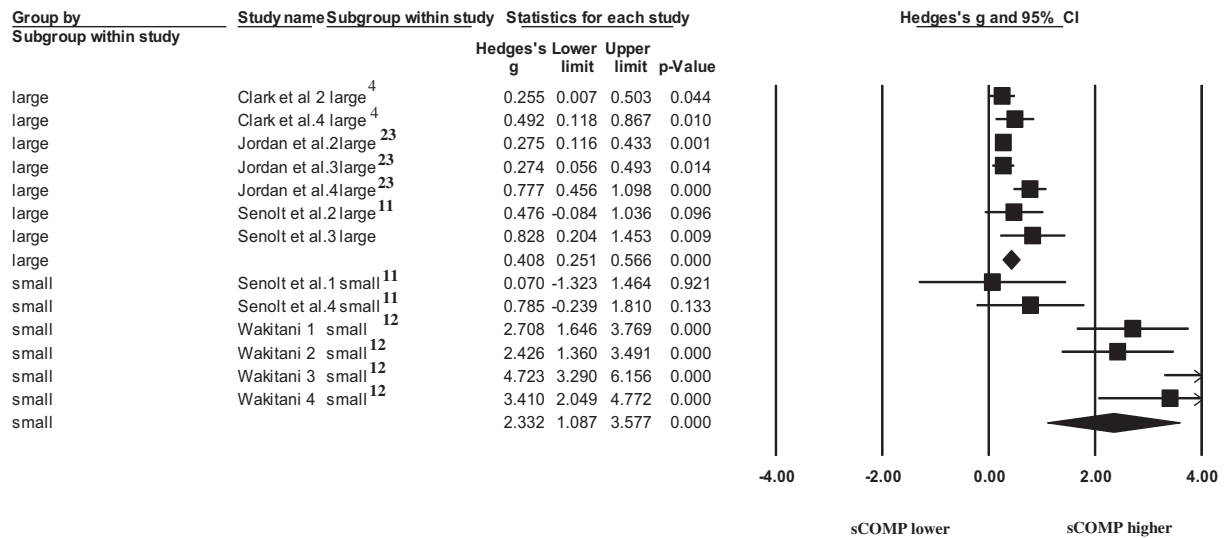
sCOMP lower   sCOMP higher

Fig. 6. A Forest plot depicting the calculated ESs for large groups ($n > 10$) and small groups ($n < 10$) used to answer the second question.

assignment and reported the inter- and intrarater reliability[4,23]. It is important to report the number of individuals that are involved in reviewing radiographs, as this information will allow the readers to understand that bias was adequately controlled for. Also, reporting the inter- and intrarater reliability allows for interpretation of the generalizability of these measures among different clinicians.

Only three studies used in this review provided definitions for each of the K/L classifications used to assess OA severity[3,4,23]. A recent review of K/L classifications used in current published research, specifically in reference to a grade of 2, reported grade 2 definitions are different throughout the reported literature[29]. Therefore it is essential the K/L grades be defined in each of the studies[35]. Knowing which definition the authors used to identify K/L-2 subjects will allow better comparisons to be made across the studies.

Serum COMP ELISAs and associated coefficients of variation (CV)

It has been previously reported that certain ELISAs are more appropriate for detecting human sCOMP than others[36]. For the purposes of this systematic review we did not exclude studies based on the ELISA used to detect human sCOMP levels. Therefore, multiple ELISAs were used to detect human sCOMP for the studies that were included in our review (Table II). Three studies used an ELISA manufactured by AnaMar Medical[3,14,33], three studies[4,11,23] used an in house ELISA as previously reported by Vilim *et al.*[37], and one study used an ELISA manufactured by Kamiya Biomedical Company[12]. The study using the Kamiya Biomedical Company ELISA[12] did have the largest calculated ES. However, the authors cannot conclude whether or not this ELISA was more sensitive than the others used in this review. It must be noted that Jordan *et al.*[23] and Clark *et al.*[4] did report modifications to the Vilim *et al.*[37] ELISA protocol in that an alkaline phosphatase-conjugated avidin was used rather than the previously reported peroxidase.

Previous research reported a weak correlation ($R^2 = 0.210$) between the AnaMar Medical ELISA and the in house ELISA reported by Vilim *et al.*[36,37] for measuring sCOMP levels in the same subjects[36]. For the purposes of this review, readers must be aware that there are differences in detecting sCOMP levels for each of the different ELISA manufactures. The only way to ascertain which ELISA kit is the best at detecting sCOMP levels can only be accomplished by comparing each technique with serum samples from the same subjects, which cannot be done using the available data for this meta-analysis. One advantage of the data contained within this systematic review and meta-analysis is that the ESs provide a unit-less measure of the magnitude of change between groups which allow standardization for comparison between studies.

Table II
ELISA manufacture information and associated CVs for each of the studies

Study	ELISA manufacture information	Type of ELISA	Specific antibodies used	Interassay CV	Intraassay CV
Cibere *et al.*[14]	AnaMar Medical, Lund, Sweden	Sandwich	Two monoclonal antibodies (not specified)	<5%	<5%
Clark *et al.*[4]	In house method*	Competitive	Monoclonal antibody 17-C10	Not reported	Not reported
Fernandes *et al.*[3]	Anamar Medical, Uppsala, Sweden	Sandwich	Two monoclonal antibodies (not specified)	Not reported	Not reported
Jordan *et al.*[23]	In house method*	Sandwich	Monoclonal antibodies 16-F12 and 17-C10	9.7% for "normal" controls 8.7% for "high" controls	5.8% for "normal" controls 6.6% for "high" controls
Mundermann *et al.*[33]	AnaMar Medical AB, Lund, Sweden	Sandwich	Mouse monoclonal antibodies (not specified)	<1.9%	<2.7%
Senolt *et al.*[11]	In house method*	Sandwich	Monoclonal antibodies 17-C10 and 16-F12	Not reported	Not reported
Wakitani *et al.*[12]	Kamiya Biomedical Company, Seattle, WA.	Sandwich	Not specified	Not reported	Not reported

* The same in house method was used for each of these studies, and the information regarding this method can be found in Vilim V, Voburka Z, Vytasek R, Senolt L, Tchetverikoc I, Kraus VB, *et al.* Monoclonal antibodies to human cartilage oligomeric matrix protein: epitope mapping and characterization of sandwich ELISA. *Clin Chim Acta* 2003;328:59−69. However, it must be noted that Clark *et al.*[4] and Jordan *et al.*[23] reported slight modifications to the in house method used for their studies.

CVs are reported in order to determine the assay variability, and the interassay and intraassay CVs are most commonly reported[38]. Four studies did not report the inter- or intraassay CVs for the ELISAs used to determine human sCOMP[3,4,11,12]. Three studies did report inter- and intraassay CVs; with Mundermann *et al.*[33] reporting the lowest CVs (<1.9% for interassay, <2.7% for intraassay). Table II reports the inter- and intraassay CVs for each of the studies used in this systematic review and meta-analysis. The acceptable range of reportable CVs are often laboratory specific, therefore it is important that this information be presented in order to ascertain the variability of the reported sCOMP levels in each of the ELISAs performed.

Sensitivity analysis and publication bias assessments

We conducted two separate sensitivity analyses. For the first question, the lowest pooled ES was interpreted as weak (ES = 0.37, CI: 0.18−0.60). For the second analysis, the lowest pooled ES was interpreted as strong (ES = 0.78, CI: 0.50−1.01). Based on these findings, we concluded that our reported results were stable, and that no individual study substantially influenced the overall pooled effects calculated for either meta-analysis.

For the second question, we performed a sensitivity analysis investigating the effects of the small groups ($n < 10$) on the overall effects for each of the subgroups (Fig. 6). The results of this sensitivity analysis revealed the small groups have a much larger overall effect (ES = 2.33, CI: 1.1−3.6) compared to the large groups (ES = 0.41, CI: 0.25−0.60). However, the smaller groups also demonstrated greater imprecision, indicating potentially inflated results of the smaller groups which will directly influence the overall effect.

We also assessed publication bias using the Orwin's Fail-Safe N[25] and Duval and Tweedie's Trim and Fill method[24]. Although the initial funnel plot indicated there was a possibility of publication bias for each of our questions (Figs. 3 and 5), our secondary publication bias analysis indicated that more than 20 studies for the first question and 44 studies for the second question, with non-significant results, would need to be included in the analysis in order to make the pooled results become trivial and nullify our overall effects.

Limitations

This review is not without limitations. First, it must be noted that only studies using the K/L classification scale for OA were included. This classification system was chosen as it is a common classification system used to grade OA[29]. There are other systems for classifying OA; however, we chose to use only the K/L classification scale in order to ensure consistent comparisons across studies.

Second, a recent meta-epidemiological study associated with randomized control trials for OA treatment determined smaller studies ($n < 100$) can have a deleterious effect on the interpretation of the overall meta-analysis results[34]. For the purposes of our meta-analysis, we considered a group small if they contained <10 subjects. For question 2, we had six groups that were considered small. In order to determine whether or not these groups had a harmful effect on the overall ESs for each subgroup, we conducted a secondary analysis of small vs large comparisons (Fig. 6). Based on this analysis, we determined that the small group comparisons may inflate the overall ESs. Therefore caution is necessary when interpreting our results for the K/L-1 comparison as this subgroup only had nine subjects. In addition, it was not possible to determine if several of the studies were prospective or retrospective in nature. Inclusion of this information in the future will allow more accurate synthesis of the available data.

Conclusions

The usefulness of sCOMP as a diagnostic biomarker for identification of knee OA prior to the occurrence of permanent joint degradation is contingent upon the sensitivity to detect differences in patients with and without the disease and between differing severities of the disease[4,15,16]. For both questions posed in this review, level C evidence is currently available in the literature. This recommendation was reached based on consistent level 4 studies or extrapolations from level 2 studies[32]. To strengthen this recommendation, future rigorous prospective investigations should be conducted. However, based on the available reported data, our results indicate sCOMP is elevated in patients with diagnosed knee OA compared to controls (Fig. 2). Furthermore, clear trends were identified based on disease severity with larger ESs for K/L-3 and K/L-4 comparisons when compared to K/L-2 comparisons (Fig. 4).

Author contributions

All authors made substantial contributions to all three sections: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of the data, (2) the drafting of the article or revising it critically for important intellectual content and, (3) final approval of the version submitted.

Conflict of interest

There are no competing interests to disclose for any of the authors on this manuscript.

Supplementary material

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.joca.2011.09.005.

References

1. Garnero P, Delmas PD. Biomarkers in osteoarthritis. Curr Opin Rheumatol 2003;15:641−6.
2. Tseng S, Reddi AH, Di Cesare PE. Cartilage oligomeric matrix protein (COMP): a biomarker of arthritis. Biomark Insights 2009;4:33−44.
3. Fernandes FA, Pucinelli MLC, da Silva NP, Feldman D. Serum cartilage oligomeric matrix protein (COMP) levels in knee osteoarthritis in a Brazilian population: clinical and radiological correlation. Scand J Rheumatol 2007;36(3):211−5.
4. Clark AG, Jordan JM, Vilim V, Renner JB, Dragomir AD, Luta G, et al. Serum cartilage oligomeric matrix protein reflects osteoarthritis presence and severity: the Johnston County Osteoarthritis Project. Arthritis Rheum 1999;42(11):2356−64.
5. Palmieri-Smith RM, Thomas AC. A neuromuscular mechanism of posttraumatic osteoarthritis associated with ACL injury. Exerc Sport Sci Rev 2009;37(3):147−53.
6. Vilim V, Vytasek R, Olejarova M, Machacek S, Gatterova J, Prochazka B, et al. Serum cartilage oligomeric matrix protein reflects the presence of clinically diagnosed synovitis in patients with knee osteoarthritis. Osteoarthritis Cartilage 2001;9(7):612−8.
7. Andersson MLE, Thorstensson CA, Roos EM, Petersson IF, Heinegayrd D, Saxne T. Serum levels of cartilage oligomeric matrix protein (COMP) increase temporarily after physical

exercise in patients with knee osteoarthritis. BMC 2006;7(98): doi: 10.1186/1471-2474-7-98.

8. Bruyere O, Collette JC, Ethgen O. Biochemical markers of bone and cartilage remodeling in prediction of longterm progression of knee osteoarthritis. J Rheumatol 2002;30: 1043−50.

9. Garnero P, Piperno M, Gineyts E, Christgau S, Delmas PD, Vignon E. Cross sectional evaluation of biochemical markers of bone, cartilage, and synovial tissue metabolism in patients with knee osteoarthritis: relations with disease activity and joint damage. Ann Rheum Dis 2001;60(6):619−26.

10. Wislowska M, Jablonska B. Serum cartilage oligomeric matrix protein (COMP) in rheumatoid arthritis and knee osteoarthritis. Clin Rheumatol 2005;2:278−84.

11. Senolt L, Braun M, Olejarova M, Forejtova S, Gatterova J, Pavelka K. Increased pentosidine, an advanced glycation end product, in serum and synovial fluid from patients with knee osteoarthritis and its relation with cartilage oligomeric matrix protein. Ann Rheum Dis 2005;64(6):886−90.

12. Wakitani S, Nawata M, Kawaguchi A, Okabe T, Takaoka K, Tsuchiya T, et al. Serum keratan sulfate is a promising marker of early articular cartilage breakdown. Rheumatology 2007; 46(11):1652−6.

13. Pavelka K, Forejtova S, Olejarova M, Gatterova J, Senolt L, Spacek P, et al. Hyaluronic acid levels may have predictive value for the progression of knee osteoarthritis. Osteoarthritis Cartilage 2004;12(4):277−83.

14. Cibere J, Zhang H, Garnero P, Poole AR, Lobanok T, Saxne T, et al. Association of biomarkers with pre-radiographically defined and radiographically defined knee osteoarthritis in a population-based study. Arthritis Rheum 2009;60(5): 1372−80.

15. Bauer DC, Hunter DJ, Abramson SB, Attur M, Corr M, Felson D, et al. Classification of osteoarthritis biomarkers: a proposed approach. Osteoarthritis Cartilage 2006;14(8):723−7.

16. Otterness IG, Swindell AC, Zimmerer RO, Poole AR, Ionescu M, Weiner E. An analysis of 14 molecular markers for monitoring osteoarthritis: segregation of the markers into clusters and distinguishing osteoarthritis at baseline. Osteoarthritis Cartilage 2000;8(3):180−5.

17. Hedbom E, Antonsson P, Hjerpe A, Aeschlimann D, Paulsson M, Rosa-Pimentel E, et al. Cartilage matrix proteins. An acidic oligomeric protein (COMP) detected only in cartilage. J Biol Chem 1992;267(9):6132−6.

18. Muller G, Michel A, Altenburg E. COMP (cartilage oligomeric matrix protein) is synthesized in ligament, tendon, meniscus, and articular cartilage. Connect Tissue Res 1998;39(4): 233−44.

19. Neidhart M, Hauser N, Paulsson M, DiCesare PE, Michel BA, Hauselmann HJ. Small fragments of cartilage oligomeric matrix protein in synovial fluid and serum as markers for cartilage degradation. Br J Rheumatol 1997;36(11):1151−60.

20. DiCesare P, Hauser N, Lehman D, Pasumarti S, Paulsson M. Cartilage oligomeric matrix protein (COMP) is an abundant component of tendon. FEBS Lett 1994;354(2):237−40.

21. Recklies AD, Baillargeon L, White C. Regulation of cartilage oligomeric matrix protein synthesis in human synovial cells and articular chondrocytes. Arthritis Rheum 1998;41(6): 997−1006.

22. Bleasel JF, Poole AR, Heinegard D, Saxne T, Holderbaum D, Ionescu M, et al. Changes in serum cartilage marker levels indicate altered cartilage metabolism in families with the osteoarthritis-related type II collagen gene COL2A1 mutation. Arthritis Rheum 1999;42(1):39−45.

23. Jordan JM, Luta G, Stabler M, Renner JB, Dragomir AD, Vilim V, et al. Ethnic and sex differences in serum levels of cartilage oligomeric matrix protein: the Johnston County Osteoarthritis Project. Arthritis Rheum 2003;48(3):675−81.

24. Borenstein M, Hedges L, Higgins J, Rothstein H. Introduction to Meta-analysis. West Sussex, UK: John Wiley & Sons, Ltd.; 2009.

25. Orwin RG. A Fail-Safe N for effect size in meta-analysis. J Educ Stat 1983;8(2):157−9.

26. Munn J, Sullivan SJ, Schneiders AG. Evidence of sensorimotor deficits in functional ankle instability: a systematic review with meta-analysis. J Sci Sports Med 2010;13(1):2−12.

27. Downs S, Black N. The feasibility of creating a check list for the assessment of methodological quality of both randomised and non-randomised trials. J Epidemiol Community Health 1998; 52(6):377−84.

28. Dragomir AD, Kraus VB, Renner JB, Luta G, Clark A, Vilim V, et al. Serum cartilage oligomeric matrix protein and clinical signs and symptoms of potential pre-radiographic hip and knee pathology. Osteoarthritis Cartilage 2002;10(9):687−91.

29. Schiphof D, Boers M, Bierma-Zeinstra SMA. Differences in descriptions of Kellgren and Lawrence grades of knee osteoarthritis. Ann Rheum Dis 2008;67:1034−6.

30. Hedges LV, Olkin I. Statistical Methods for Meta-analysis. Academic Press Inc; 1985.

31. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd edn. Hillsdale, NJ: Lawrence Erlbuam Assoc.; 1988.

32. Centre for Evidence Based Medicine. Levels of evidence and grades of recommendation [cited 2010 May 15]; Available from: http://www.cebm.net/index.aspx?o=1025; 1988.

33. Mundermann A, King KB, Smith RL, Andriacchi TP. Change in serum COMP concentration due to ambulatory load is not related to knee OA status. J Orthop Res 2009;27(11):1408−13.

34. Nuesch E, Trelle S, Reichenbach S, Rutjes A, Tschannen B, Altman D, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. BMJ 2010;341:c3515: doi: 10.1136/bmj.c3515.

35. Oiestad BE, Engebretsen L, Storheim K, Risberg MA. Knee osteoarthritis after anterior cruciate ligament injury: a systematic review. Am J Sports Med 2009;37(7):1434−43.

36. Stabler T, Fang F, Jordan J, Vilim V, Kraus VB. A comparison of methods for measuring cartilage oligomeric matrix protein (COMP) in human subjects with knee OA. Osteoarthritis Cartilage 2007;15(Suppl C). C81−C82.

37. Vilim V, Voburka Z, Vytasek R, Senolt L, Tchetverikov I, Kraus VB, et al. Monoclonal antibodies to human cartilage oligomeric matrix protein: epitope mapping and characterization of sandwich ELISA. Clin Chim Acta 2003;328:59−69.

38. Reed GF, Lynn F, Meade BD. Use of coefficient of variation in assessing variability of quantitative assays. Clin Diagn Lab Immunol 2002;9(6):1235−9.