Effect of total joint replacement in hip osteoarthritis on serum COMP and its correlation with mechanical-functional parameters of gait analysis

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SUMMARY

Objective: To study the effect of total hip replacement (THR) on serum cartilage oligomeric matrix protein concentration (sCOMP) and its correlation with joint loading during gait in patients with unilateral hip osteoarthritis.
Design: In this prospective multimodal (clinical, biomechanical, biochemical) study blood samples from 15 patients were taken before and up to three times after THR (7 days, 3 months and 1 year), each after a resting period of at least 30 min, for analysis of sCOMP. Gait analysis was performed before and 1 year after THR to determine hip and knee joint moments.
Results: Seven days after THR, sCOMP decreased significantly compared to the preoperative measurement ($p < 0.001$). Three months and 1 year postoperatively, sCOMP reverted to concentrations in the range of the preoperative value. One year postoperatively, a linear correlation between sCOMP and the maximum hip flexion moment was indicated in the first half of the stance phase on the unaffected side ($r = -0.736$, $p = 0.024$). No further correlations could be determined.
Conclusions: Surprisingly, the removal of a joint affected by osteoarthritis did not have a sustained effect on sCOMP. Both before and after THR there was no scientifically substantiated correlation between sCOMP and joint moments from gait analysis. Consequently, the examination of sCOMP is not useful to detect altered joint loads that may influence degenerative changes of adjacent joints after THR.
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1. Introduction

Osteoarthritis (OA) is one of the leading causes of joint pain and chronic disability worldwide [1]. Patients with unilateral hip OA adopt characteristic gait patterns to reduce pain. Gait analysis has been used for decades to quantify these biomechanical abnormalities. Typical gait patterns of patients with hip OA include modified spatio-temporal gait parameters like reduced gait speed compared to healthy controls [2]. Kinetic gait parameters are also altered and patients present higher knee and hip joint loading in the non-affected limb compared to the affected limb before total hip replacement (THR) [3–6]. Pathological joint loading during gait is a potential risk factor for initiation of OA and enhances its progression [7]. In particular, peak external knee adduction moments (KAM) are associated with initiation and progression of OA [7, 8]. Moreover, several studies revealed that gait modifications in patients

with hip OA result in abnormal loading on other joints of the lower extremities. As an example, patients flex their trunk more to the affected side in order to relieve pain [9,10]. The line of action of the ground reaction force shifts laterally as a result of increased lateral trunk displacement and therefore also has an influence on knee joint loading on the side of the affected hip [11,12]. A shift of the knee joint load from the medial to the lateral compartment could be shown in the affected limb in patients with unilateral hip OA [13]. Even after THR abnormal kinetics of the hip and knee have been discovered [6,14–16].

Irreversible joint damages are often already manifested at the time of first diagnosis using traditional radiographic measures. Besides the established, elaborated gait analysis, other methods might be useful to detect OA before irreversible joint cartilage damage occurs, to improve disease staging and to predict the course of disease [17,18]. Currently, extracellular matrix components that are released from articular

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cartilage, subchondral bone and synovial tissue, are used as biomarkers and monitored to quantify joint remodeling and disease progression. They are partially metabolized by the joint tissue and released as intact proteins or as fragments into biological fluids where they can be detected and quantified [18–21]. Biomarkers can be classified into one or more of the following categories by using the "BIPED" classification: burden of disease, investigative, prognostic, efficacy of intervention and diagnostic [22]. For instance, the non-collagenous, non-proteoglycan pentameric glycoprotein cartilage oligomeric matrix protein (COMP), also known as thrombospondin 5, can especially be found in the extracellular matrix of articular cartilage [18,19,23–25]. It is mainly produced by chondrocytes and an important component in the organization of the collagenous cartilage matrix [23,25]. In addition, COMP has also been identified in other tissues such as ligaments, meniscus and vascular smooth muscle, but the respective contribution of these sources to overall sCOMP in the circulation is not known so far [26]. The release of the biomarker COMP is mechanosensitive and, therefore, elevated serum levels were detected with increased joint load, for example during walking and running even in healthy adults [27–30]. COMP is also related to cartilage degradation during OA [18–20,24,31]. The serum COMP concentration (sCOMP) increases with the number of affected joints as well as with the severity of OA [19]. On the other side, decreasing sCOMP was found in response to immobilization. Again, even healthy individuals show significantly decreased sCOMP after extended bed rest [32,33]. However, the time course of sCOMP after total joint replacement has never been analyzed systematically. Only Sharif et al. [34] discovered incidentally altered sCOMP after total knee replacement. It is therefore important to further investigate the influence of an artificial joint on sCOMP before and after THR.

Biomechanical changes using instrumented gait analysis and biochemical markers in body fluids such as COMP can be used to evaluate patients with OA in the research setting [35]. However, a correlation between gait pattern and sCOMP has not been investigated so far. Until now, only gait patterns of healthy volunteers were correlated with sCOMP [36–38]. Herger et al. [36], Denning et al. [37] and Firner et al. [38] found that with rising joint load sCOMP increases more strongly as a basis for investigating the relevance of the dose-response relationship between ambulatory load magnitude and load-induced changes in biomarkers involved in joint cartilage metabolism for the initiation and progression of articular cartilage disease such as OA. We are not aware of any study that analyzes the correlation of sCOMP and gait pattern in patients with unilateral hip OA. Therefore, the purpose of the present study was to identify and to compare these appropriate biomechanical and biochemical outcome measures before and after THR. This should create conditions to establish an approach that will allow screening of high-risk patients and an earlier diagnosis of OA than currently possible with traditional radiographic measures. Therefore, sCOMP was compared with already established biomechanical joint loading data from gait analysis. We hypothesized that (1) sCOMP would sustainably decrease after removal of the affected hip joint. In addition, we hypothesized that (2) before THR higher sCOMP would directly correlate with lower dynamic hip and knee joint loading of the affected limb since the load on this side is kept low by compensatory mechanisms [3–6]. Consequently, joint loading of the non-affected side would positively correlate with sCOMP before THR. Finally, we hypothesized that (3) after removal of the affected hip joint, sCOMP would correlate with joint loading of the ipsilateral knee and contralateral hip and knee joint.

2. Methods

2.1. Participants

Fifteen patients diagnosed only with unilateral symptomatic hip OA, validated by conventional anterior/posterior and lateral pelvic radiographs (7 females, 8 males, age = 58.1 ± 8.8 years, height = 1.74 ± 0.08 m, weight = 80.3 ± 16.2 kg, body mass index (BMI) = $26.3 \pm$ 4.5 kg/m^2), from our university hospital voluntarily participated in the study (Table 1). All patients reported pain for the ipsilateral hip whereas the contralateral hip was free from any symptoms at the preoperative time point. At the time of all follow-up measurements all patients were pain-free. The period of prospective examination began before surgery and ended approximately 1 year after initial THR. Patients were included if THR was indicated, Kellgren-Lawrence-Score [39] was ≥ 2 and both standing and walking without assistive device was possible. Exclusion criteria were previous orthopedic surgery of lower extremities, earlier joint infection or inflammatory arthritis, OA of lower limb joints (except the affected hip joint), chronic or neuromuscular diseases and injury of lower extremities.

Prior to first examination, all participants gave informed consent. The study was accepted by the local medical ethics committee of the Goethe University Frankfurt in Germany (No. 497/15) and conducted in accordance with the Declaration of Helsinki. This is a prospective multimodal (clinical, biomechanical, biochemical) study with level of evidence II.

2.2. Gait analysis

In nine patients the gait pattern was analyzed within 1 week before THR ($t_0 = 3.2 \pm 1.8$ days) and about 1 year postoperatively ($t_3 = 52.5 \pm 2.0$ weeks) because five failed due to postoperative lack of interest and one did not meet the quality standards for gait analysis (a more detailed explanation can be found below). To collect spatio-temporal and kinematic data at 200 Hz an 8-camera MX T10 Vicon motion capture system (VICON Motion Systems, Oxford, UK) was used. Simultaneously, ground reaction forces were acquired at 1.000 Hz with two AMTI force plates (Advanced Mechanical Technology, Inc., Watertown, MA), localized in the mid of a 15 m long level walkway. A lower body protocol (called MA) was used as an aid for better reliability and accuracy when analyzing gait data [40]. In addition to the standardized Plug-in-Gait marker set [41], reflective markers were brought on the medial malleolus, medial femoral condyle and greater trochanter to ascertain joint centers of rotation for ankle, knee and hip. The hip joint center was calculated with a standardized geometrical prediction method using regression equations [42] which is frequently used in this field [43]. Patients were asked to walk barefoot in freely chosen gait velocity along the walkway.

After the analysis, 3D marker trajectories were reconstructed and missing frames filled by using the Vicon-Nexus software version 2.5 (Vicon Motion Systems, Oxford, UK). A Woltring filter was applied to spline smooth the data [44]. Altogether, five trials were examined for each subject and the mean value was taken for further analysis. Good quality of the marker trajectories and precise foot-force plate-contact were prerequisites for use of the trial. To exclude the potential effect of cross-talk - meaning that one joint rotation (e.g. flexion in the sagittal plane) is construed as another (e.g. adduction in the frontal plane) because of axis malalignment of the marker set - and in keeping with physiological and clinical standards, only patients having a knee varus/valgus ROM during gait $\leq 10°$ were included [45].

Means and standard deviations were calculated by a custom-made algorithm in Matlab R2018b (The MathWorks, Inc., Natick, MA). Moreover, using an inverse dynamic approach, external joint moments (normalized to body weight) were calculated from force plate data and

Table 1
Anthropometric parameters of patients (mean with standard deviation in parenthesis).

Characteristic	Patients, t_0 (n = 15)	Patients, t_3 (n = 10)
Gender, female/male	7/8	6/4
Age (years)	58.1 (8.8)	59.3 (10.5)
Height (m)	1.74 (0.08)	1.73 (0.06)
Body mass (kg)	80.3 (16.2)	82.3 (19.1)
Body mass index (kg/m^2)	26.3 (4.5)	27.3 (5.1)

t_0 – 6.2 ± 10.2 days before total hip replacement; t_3 – 52.4 ± 1.9 weeks after total hip replacement.

mathematically derived joint centers. Hip and knee joint moments in the frontal and sagittal plane were analyzed in this study on the basis of clinical relevance [13,14,46]. The graphs of the KAM and external hip adduction moment (HAM) show a characteristic "m" or "double hump" wave form. Consequently, the following external joint moments in the frontal plane were defined as primary outcomes in the present study: First and second peak of KAM and HAM in first and second half of stance phase. In addition, the impulse of KAM and HAM (area under the curve) [36] was calculated. Regarding the sagittal plane, peak flexion moment in the first half of stance phase and peak extension moment in the second half of stance phase for the knee and hip joint were determined. All gait parameters were normalized to 100% stance phase, which is defined as the time between the moment of heel-strike (first ground contact) and toe off (last ground contact).

2.3. Blood samples and COMP analysis

After a resting time for at least 30 min to minimize the influence of previous activity [27,47], venous blood samples were taken at the following four time points: t_0 within 1 week (6.2 ± 10.2 days) before THR, t_1 7 days (7.0 ± 0.5 days) postoperative, t_2 3 months (14.0 ± 1.8 weeks) postoperative and t_3 about 1 year (52.4 ± 1.9 weeks) postoperative. Blood samples from 15 patients were collected for the first three time points. Only ten patients completed the study with blood sampling at t_3 because five failed due to lack of interest. Blood samples at the times t_0 and t_3 were taken after 30 min rest on the same day before gait analyses to avoid the influence of joint load and fatigue.

Serum was analyzed for COMP concentration as follows. After clotting for at least 15 min in the serum tube, samples were centrifuged for 10 min at $2670 \times g$ and stored aliquoted in Eppendorf tubes at $-80\ °C$ until further analysis. All samples were diluted 1:50 and analyzed in duplicates for each participant on the same assay plate to avoid inter-assay variation [32] using a commercial enzyme-linked immunosorbent assay (Human COMP ELISA kit, BioVendor, Brno, Czech Republic). The mean value for each patient at each time point was used for further exploration. Absolute sCOMP was used for statistical analysis. Relative sCOMP between two time points t and t' was calculated as (sCOMP(t')-sCOMP(t))/sCOMP(t)*100.

2.4. Statistical analysis

Statistical data analysis was performed with SPSS Version 25 (IBM Corporation, New York, NY, USA). The Shapiro-Wilk-test as well as the coefficient of skewness and kurtosis were used to confirm normal distribution of the analyzed parameters. To show time related effects of absolute sCOMP, one-way repeated measures analysis of variance (ANOVA) was used. In case of a significant main effect, post hoc pairwise comparisons (Bonferroni) were performed (hypothesis 1). The significance level was set at $p \le 0.05$.

Pearson product-moment correlation analyses (coefficient r) were performed to identify linear relationships between absolute sCOMP and joint moments (knee and hip) during gait in the affected and non-affected limb both pre- (hypothesis 2) and postoperative (hypothesis 3). Correlation values below 0.30 were interpreted as low, between 0.30 and 0.65 as medium and correlations above 0.65 as high [48].

3. Results

COMP data of all participating patients were normally distributed at all time points. Absolute sCOMP for each time point is summarized in Table 2. The course of sCOMP after THR for ten patients, normalized to baseline concentration before THR (t_0), is illustrated in Fig. 1. Additionally, the absolute sCOMP for each of these ten patients at all sampling time points is shown in Fig. 2. Within 7 days after THR (t_1) sCOMP decreased on average by 32.23%. Three months (t_2) and 1 year (t_3) after surgery the mean sCOMP went back to the range of baseline

Table 2

Serum COMP concentrations (mean with standard deviation in parenthesis) before and 3 time points after total hip replacement ($n = 15$ patients at t_0, t_1, t_2; $n = 10$ patients at t_3).

Time points	Absolute sCOMP (ng/ml)	95% confidence interval	
		Lower limit	Upper limit
t_0	718.96 (135.77)	643.77	794.15
t_1	477.28 (147.27)	395.73	558.84
t_2	732.92 (237.54)	601.37	864.47
t_3	754.88 (255.07)	572.41	937.34

sCOMP – serum cartilage oligomeric matrix protein concentration; THR – total hip replacement; t_0 – 6.2 ± 10.2 days before THR; t_1 – 7.0 ± 0.5 days after THR; t_2 – 14.0 ± 1.7 weeks after THR; t_3 – 52.4 ± 1.9 weeks after THR.
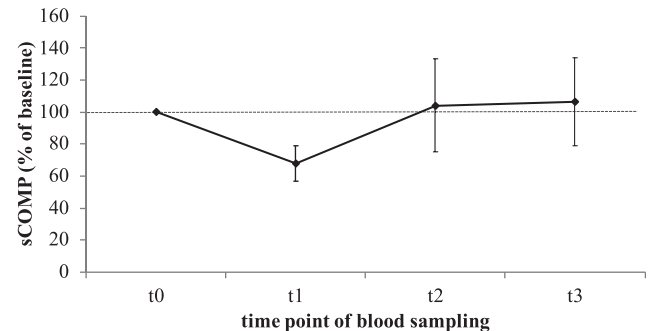

Fig. 1. Relative sCOMP (mean with standard deviation) up to one year after total hip replacement (THR) normalized to sCOMP at baseline (before THR, $n = 10$ patients). sCOMP – serum cartilage oligomeric matrix protein concentration; t_0 – 7.1 ± 12.4 days before THR; t_1 – 7.0 ± 0.7 days after THR; t_2 – 14.0 ± 2.1 weeks after THR; t_3 – 52.4 ± 1.9 weeks after THR; $sCOMP_{t0/t0} = 100\%$; $sCOMP_{t1/t0} = 67.77 \pm 11.14\%$; $sCOMP_{t2/t0} = 104.08 \pm 29.03\%$; $sCOMP_{t3/t0} = 106.55 \pm 27.40\%$.
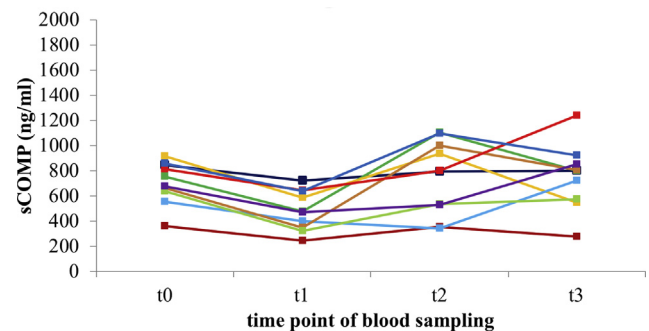

Fig. 2. Absolute sCOMP for each patient up to one year after total hip replacement ($n = 10$ patients). sCOMP – serum cartilage oligomeric matrix protein; THR – total hip replacement; t_0 – 7.1 ± 12.4 days before THR; t_1 – 7.0 ± 0.7 days after THR; t_2 – 14.0 ± 2.1 weeks after THR; t_3 – 52.4 ± 1.9 weeks after THR; minimal $sCOMP_{t0} = 361.94$ ng/ml; maximal $sCOMP_{t0} = 914.73$ ng/ml.

concentration (104.08 $\pm$ 29.03% and 106.55 $\pm$ 27.40% normalized to baseline concentration). ANOVA showed a significant time related effect of absolute sCOMP ($p = 0.001$). Pairwise comparisons of mean absolute sCOMP indicated a significant difference between time point t_0 before and t_1 after THR ($p < 0.001$; Table 3). Measured concentrations at t_2 and t_3 were also significantly higher than sCOMP at t_1 ($p = 0.049$ and $p = 0.011$). Pairwise comparisons between t_0, t_2 and t_3 did not result in significant differences.

Correlations between absolute sCOMP and biomechanical parameters measured by gait analysis are shown in Table 4. All kinetic gait parameters of interest were normally distributed. Pearson product-moment correlation analyses between absolute sCOMP and joint moments at t_0

Table 3
Pairwise comparisons (Bonferroni) between concentrations of absolute sCOMP ($n = 10$ patients).

	p-Value	Mean difference	95% confidence interval	
			Lower limit	Upper limit
sCOMP (t_0)/				
sCOMP (t_1)	<0.001*	222.93	135.29	310.57
sCOMP (t_2)	1.000	−41.00	−253.39	171.38
sCOMP (t_3)	1.000	−46.93	−269.82	175.97
sCOMP (t_1)/				
sCOMP (t_2)	0.049*	−263.93	−526.57	−1.29
sCOMP (t_3)	0.011*	−269.86	−479.58	−60.14
sCOMP (t_2)/				
sCOMP (t_3)	1.000	−5.92	−314.73	302.89

sCOMP – serum cartilage oligomeric matrix protein concentration; THR – total hip replacement; $t_0 - 7.1 \pm 12.4$ days before THR; $t_1 - 7.0 \pm 0.7$ days after THR; $t_2 - 14.0 \pm 2.1$ weeks after THR; $t_3 - 52.4 \pm 1.9$ weeks after THR; *Significant difference.

before THR demonstrated neither a significant correlation for the affected nor for the non-affected side. Even after THR at t_3 no linear correlations for the affected side were found, however a trend towards negative correlation between sCOMP(t_3) and the maximum hip flexion moment in the first half of the stance phase could be observed ($r = -0.652$, $p = 0.057$). Regarding the non-affected side at t_3 after THR, a significant negative correlation was demonstrated between sCOMP(t_3) and the maximum hip flexion moment in the first half of the stance phase ($r = -0.736$, $p = 0.024$).

4. Discussion

The purpose of the present longitudinal study was to examine for the first time the effect of THR on sCOMP in patients with unilateral hip OA. Secondly, sCOMP was compared with biomechanical joint loading using instrumented gait analysis before and after THR. The removal of a joint affected by OA did not have a sustained influence on sCOMP. After a drop of sCOMP 7 days postoperatively, sCOMP increased 3 months after THR back to the range of baseline concentration and remained at this level up

to 1 year after surgery. Preoperatively, sCOMP did not depend on changes in joint moments caused by gait alterations. An unexpected negative correlation between sCOMP and maximum hip flexion moment of the unaffected side after THR was detected. Rather, other factors seem to have an influence on the release of COMP from cartilage.

We observed a significantly decreased sCOMP 7 days after THR, analyzed using an ELISA. These results partially confirmed our first hypothesis that sCOMP would permanently decrease after removal of the arthritic hip joint, since in OA COMP originates mainly from the affected joint and is mechanically released into the serum [20,31]. However, contrary to our hypothesis, 3 months and 1 year after THR we observed sCOMP in the range of baseline concentrations before THR. In order to explain this result, the relevant influences on the release of COMP are pointed out in the following. A certain basal level of sCOMP can be detected in healthy individuals. The majority of COMP is in its intact form and released as a result of normal loading of and extrusion from cartilage tissue [21]. Increased sCOMP in patients with OA has been described in several studies with the explanation that additional COMP is released in response to cartilage damage [18–20,24,31]. As mentioned above, COMP is then released as both intact as well as fragmented protein [20,21]. Further degradation might occur in the serum. Since the antibodies used in different assays might target different parts of the COMP molecule, a comparison of absolute sCOMP is generally difficult. Further, different commercially available assays [19,20,31] report results in units [31] that cannot be converted like mg/l and U/l. Addison et al. [49] demonstrated a correlation of sCOMP with the total-body bone scintigraphy in patients with symptomatic OA. This means that sCOMP is related to total-body burden of OA. Clark et al. [19] described a dependence of sCOMP on the size and number of affected joints and severity of disease. If one refers these results to our study, sCOMP would have to decrease permanently after removal of the large affected hip joint in patients with unilateral hip OA.

The results of the present study suggest that there are further influences on the release of COMP from the extracellular cartilage matrix. Liphardt et al. [32,33] who investigated sCOMP in bed rest studies could detect a reduced sCOMP due to immobilization and thus lacking mechanical loading of the tissue. The decrease in sCOMP observed in our study 7 days after surgery may indicate that limited mobility and reduced

Table 4
Pearson correlation coefficients (r) and p-Values (in parenthesis) for absolute sCOMP and kinetic gait parameters during the stance phase of gait ($n = 9$ patients).

	Preoperative		Postoperative	
	Affected side	Non-affected side	Affected side	Non-affected side
Knee moments – sagittal plane				
Max. flexion first half of stance	0.395	0.490	−0.003	−0.386
	(0.293)	(0.181)	(0.994)	(0.305)
Max. extension second half of stance	0.041	0.008	0.263	0.034
	(0.917)	(0.984)	(0.495)	(0.931)
Knee moments – frontal plane				
Max. adduction first half of stance (1st KAM)	−0.285	−0.087	−0.254	0.050
	(0.458)	(0.824)	(0.509)	(0.898)
Max. adduction second half of stance (2nd KAM)	−0.272	0.072	−0.148	0.259
	(0.479)	(0.854)	(0.704)	(0.501)
Adduction impulse (AUC)	−0.252	−0.059	−0.137	0.176
	(0.514)	(0.880)	(0.726)	(0.651)
Hip moments – sagittal plane				
Max. flexion first half of stance	−0.276	0.065	−0.652	−0.736
	(0.472)	(0.868)	(0.057)[+]	(0.024)*
Max. extension second half of stance	−0.249	−0.305	−0.332	−0.174
	(0.518)	(0.425)	(0.382)	(0.655)
Hip moments – frontal plane				
Max. adduction first half of stance (1st HAM)	0.091	0.301	0.195	−0.058
	(0.815)	(0.431)	(0.614)	(0.883)
Max. adduction second half of stance (2nd HAM)	0.087	0.300	0.017	0.272
	(0.823)	(0.433)	(0.965)	(0.479)
Adduction impulse (AUC)	0.034	0.286	0.152	0.317
	(0.930)	(0.455)	(0.697)	(0.407)

sCOMP – serum cartilage oligomeric matrix protein concentration; AUC – area under the curve; flexion – positive values; extension – negative values; adduction – positive values; abduction – negative values; *Significant correlation; [+]Trend towards a linear correlation.

mechanical loading during the first days after THR. COMP is not only released by cartilage damage in OA, but to some extent also by increased but physiological joint load during walking and running, as the release of COMP is mechanosensitive [27–30]. For our results, this could mean that patients 3 months and 1 year after surgery are more mobile than 7 days postoperative because they are free from symptoms and pain. The increased mobility 3 months and 1 year postoperatively compared to the preoperative time compensates for the expected permanent decrease of sCOMP after removal of the arthritic hip. Thus, the same level of pre-operative concentrations and those 3 months and 1 year postoperatively can be explained. Sharif and colleagues [34] reported increased sCOMP 3 months after total knee replacement (TKR), persisting for up to 12 months. This is in contrast to our study, even though we also did not detect a decrease or a difference in sCOMP 3 and 12 months post-operatively compared to the baseline measurement. The discrepancy between both studies could be explained as follows: First, Sharif and colleagues [34] examined patients with knee OA after TKR, in contrast to our study which examined patients with unilateral hip OA after THR. The contribution of COMP from the respective joint cartilage to the measured sCOMP is generally not known and may therefore be different for knee and hip joint. Second, in our study, blood samples were taken after a resting time of at least 30 min to minimize the influence of previous activity. Sharif and colleagues [34] did not specify a standardized resting period before blood samples were taken. This could be a reason for the postoperative increase in sCOMP in the study of Sharif and colleagues [34], because patients were free from symptoms and pain and therefore more mobile. Third, blood samples were only taken 3 months post-operatively and not after 7 days as in our study. These differences between both studies make it difficult to compare the results. In summary, the results show that sCOMP depended not only on OA but also on ac-tivity before blood sampling. In order to reduce the short-term impact of activity and immobilization on sCOMP in the present study design, pa-tients rested at least 30 min before blood sampling [27,47]. Obviously, a restricted movement over 7 days after THR has a greater impact on the release of COMP into the serum than a resting time of 30 min immedi-ately before blood sampling. On the other hand, the influence of fatigue after previous defined activity, which has not been taken into account in the present study, may have an influence on the COMP analysis and gait parameters. This aspect was outside the scope of this research and should therefore be considered in the design of future studies.

We could not find a significant correlation between sCOMP and joint moments during gait before THR. Therefore, the second hypothesis that a higher sCOMP before THR would directly correlate with a lower dy-namic hip and knee joint loading of the affected side and with a higher dynamic hip and knee joint loading of the non-affected was refuted. Herger et al. [36] and Denning et al. [37] were able to demonstrate a load-induced increase in sCOMP in healthy volunteers. According to their results, the already described increased joint load on the unaf-fected joint before THR [3–6] should lead preoperatively to increased sCOMP. Firner et al. [38] investigated the effect of increased external knee flexion moments on sCOMP in healthy volunteers. The participants ran on a treadmill with a passive and then with active knee orthoses. No significant differences were found between external knee flexion mo-ments and sCOMP. Consequently, our study confirmed these results as sCOMP did not correlate with hip and knee joint moments in patients affected by OA.

With respect to our third hypothesis, 1 year after THR a significant correlation between sCOMP and maximum hip flexion moment for the non-affected side could be observed in the first half of the stance phase. One year after THR, COMP can no longer be released from the artificial hip joint. The measured sCOMP must have been released either from the remaining articular cartilage with unknown OA status or other tissues that contain COMP [26]. Increased production or degradation of COMP in cartilage may be the reason for a release into the blood serum [34]. This underlines the potential of COMP as a prognostic marker, as the degradation of articular cartilage begins before the onset of pain and

radiological changes occur [17,18,35]. However, the gait pattern 1 year after THR is still altered and can therefore also influence sCOMP. Pre-vious research described increased joint load of the non-affected side after THR [6,14–16]. Consequently, increased joint loading would result in a load-induced release of COMP into serum as previously described for healthy volunteers [36,37]. However, we were only able to observe a negative correlation. Therefore, our results provide no scientific evidence for a load-induced release of COMP in patients with unilateral hip OA treated with a THR.

The results of the present study should be interpreted carefully and in light of its limitations. First, we examined a small number of patients. However, we collected sufficient data at different time points to obtain obvious and significant differences in sCOMP. In addition, the increase of sCOMP 3 months after THR to baseline concentration was confirmed by a fourth measurement 1 year after THR in ten patients. To avoid inter-assay variation of sCOMP, samples were analyzed for each patient on the same plate. Second, due to the surprising course of sCOMP after THR, it would be interesting to know whether COMP is released as an intact protein or in form of specific fragments into the serum [20,21]. Third, although we adhered to a resting time of at least 30 min before each blood sampling, the interpretation of our results regarding OA is limited by the load dependence of sCOMP at the time of the first follow-up after THR. The use of a step counter during study participation would be a possibility to measure the long-term mobility of the participants in order to better incorporate this into the interpretation of sCOMP. Fourth, it would have been interesting to analyze COMP not only in serum but also in synovial fluid and collect blood samples at other times to find out exactly when sCOMP increases. This was not possible in our study for clinical-practical and ethical reasons and warrants further investigation. Fifth, the use of medication as well as the type and extent of physiotherapy were not documented during the study period.

In conclusion, the present longitudinal study was the first that analyzed the effect of THR on sCOMP at different postoperative time points. We were able to show that sCOMP initial decreased after THR and then increased again to the preoperative baseline concentration after THR. Our results indicate that the release of COMP is primarily influ-enced by mobility and that the removal of a hip joint affected by OA does not have a sustained influence on sCOMP. Due to the absence of sub-stantiated correlation between sCOMP and biomechanical joint loading using instrumented gait analysis, the examination of COMP is not useful to detect altered joint loads during gait that may influence degenerative changes of adjacent joints after THR. Future studies are necessary to better understand the initial decrease in sCOMP immediately after THR and the subsequent and persistent increase to the preoperative level 1 year after THR. In particular, a potential OA progression in other joints could influence sCOMP within the one year follow up time. It is impor-tant to use the aforementioned approaches to improve study design to determine whether COMP is a suitable prognostic marker for degenera-tion of articular cartilage in patients with OA. The aim could be the screening of high-risk patients and an earlier diagnosis of OA. This makes it possible to develop more effective and specific therapeutic approaches for the treatment of patients before irreversible damage to articular cartilage occurs.

Author contributions

Role of the funding source

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

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