Influence Of Response Shift On Early Patient-Reported Outcomes Following Autologous Chondrocyte Implantation

By: **Jennifer S. Howard**, Carl G. Mattacola, David R. Mullineaux, Robert A. English, & Christian Lattermann

Abstract

Response shift is the phenomenon by which an individual's standards for evaluation change over time. The purpose of this study was to determine whether patients undergoing autologous chondrocyte implantation (ACI) experience response shift. Forty-eight patients undergoing ACI partici- pated. The "then-test" method was used to evaluate response shift in commonly used patient-reported outcome measures (PROMs)—the SF-36 Physical Component Scale (SF-36 PCS), WOMAC, IKDC, and Lysholm. Each PROM was completed pre- and 6 and 12 months post-surgery. At 6 and 12 months, an additional "then" version of each form was also completed. The "then" version was identical to the original except that patients were instructed to assess how they were prior to ACI. Traditional change, response shift adjusted change, and response shift magnitude were calculated at 6 and 12 months. T tests (p \ 0.05) were used to compare traditional change to response-shift-adjusted change, and response shift magnitude values to previously established minimal detectable change. There were no differences between traditional change and response-shift-adjusted change for any of the PROMs. The mean response shift magnitude value of the WOMAC at 6 months (15 ± 14, p = 0.047) was greater than the previously established minimal detectable change (10.9). The mean response shift magnitude value for the SF-36 PCS at 12 months (9.4 ± 6.8, p = 0.017) also exceeded the previously established minimal detectable change (6.6). There was no evidence of a group-level effect for response shift. These results support the validity of pre-test/post-test research designs in evaluating treat- ment effects. However, there is evidence that response shifts may occur on a patient-by-patient basis, and scores on the WOMAC and SF-36 in particular may be influenced by response shift.

Howard, J.S., Mattacola, C.G., Mullineaux, D.R. et al. Knee Surg Sports Traumatol Arthrosc (2014) 22: 2163. https://doi.org/10.1007/s00167-013-2654-1. Publisher version of record available at: https://link.springer.com/article/10.1007/s00167-013-2654-1

Influence of response shift on early patient-reported outcomes following autologous chondrocyte implantation

Jennifer S. Howard · Carl G. Mattacola · David R. Mullineaux · Robert A. English · Christian Lattermann

Abstract

Purpose Response shift is the phenomenon by which an individual's standards for evaluation change over time. The purpose of this study was to determine whether patients undergoing autologous chondrocyte implantation (ACI) experience response shift.

Methods Forty-eight patients undergoing ACI participated. The "then-test" method was used to evaluate response shift in commonly used patient-reported outcome measures (PROMs)—the SF-36 Physical Component Scale (SF-36 PCS), WOMAC, IKDC, and Lysholm. Each PROM was completed pre- and 6 and 12 months post-surgery. At 6 and 12 months, an additional "then" version of each form was also completed. The "then" version was identical to the original except that patients were instructed to assess how they were prior to ACI. Traditional change, response shift adjusted change, and response shift magnitude were calculated at 6 and 12 months. *T* tests ($p < 0.05$) were used to compare traditional change to response-shift-adjusted change, and response shift magnitude values to previously established minimal detectable change.

Results There were no differences between traditional change and response-shift-adjusted change for any of the PROMs. The mean response shift magnitude value of the WOMAC at 6 months (15 ± 14, $p = 0.047$) was greater than the previously established minimal detectable change (10.9). The mean response shift magnitude value for the SF-36 PCS at 12 months (9.4 ± 6.8, $p = 0.017$) also exceeded the previously established minimal detectable change (6.6).

Conclusions There was no evidence of a group-level effect for response shift. These results support the validity of pre-test/post-test research designs in evaluating treatment effects. However, there is evidence that response shifts may occur on a patient-by-patient basis, and scores on the WOMAC and SF-36 in particular may be influenced by response shift.

Level of evidence II.

Keywords Articular cartilage · Chondrocyte transplantation · Knee · Outcomes assessment · Response shift

J. S. Howard (✉)
Department of Rehabilitation Sciences, University of Kentucky, Lexington KY, Wethington Building, Room 206B, 900 South Limestone, Lexington, KY 40536-0200, USA
e-mail: J.S.Howard@uky.edu

J. S. Howard
Department of Orthopaedics and Sports Medicine, University of Kentucky, Lexington KY, Wethington Building, Room 206B, 900 South Limestone, Lexington, KY 40536-0200, USA

C. G. Mattacola
Division of Athletic Training, Department of Rehabilitation Sciences, University of Kentucky, Wethington Building, Room 210E, 900 South Limestone, Lexington, KY 40536, USA

D. R. Mullineaux
School of Sport and Exercise Science, College of Social Sciences, University of Lincoln, Brayford Pool, Lincoln, Lincolnshire LN6 7TS, UK

R. A. English
Division of Physical Therapy, Department of Rehabilitation Sciences, University of Kentucky, Room 204S Wethington Building, 900 South Limestone Street, Lexington, KY 40536, USA

C. Lattermann
Department of Orthopaedic Surgery and Sports Medicine, Center for Cartilage Repair and Restoration Medical Center, University of Kentucky, Kentucky Clinic K401, 740 South Limestone, Lexington, KY 40536, USA

Introduction

To assess function or health-related quality of life (HRQL), patients are often asked to evaluate their well-being using a self-report instrument to document patient-reported outcome measures (PROMs). However, PROMs may be influenced by response shift [44]. Response shift is the phenomenon by which an individual's self-evaluation of a construct changes due to a change in internal standards of measurement (recalibration), a change in values or priorities (reprioritization), or a personal redefinition of the target construct (reconceptualization) [48]. Response shift may interfere with the ability to accurately detect changes in patient's health. Response shift has been observed among terminal illness and chronic disease patients where physical health deteriorates, yet their self-reported HRQL remains stable [16, 34, 45, 47, 50, 53, 55]. It has been hypothesized that these changes may be a result of changing values, standards, and priorities [44]. Additionally, response shift has been previously observed among knee arthroplasty and microfracture patients [1, 37, 38, 57].

While early results for autologous chondrocyte implantation (ACI) [5] outcomes are promising, the existing literature primarily reports outcomes using PROMs [4, 6–9, 11–14, 17, 23–25, 27, 31–33, 36, 41, 52, 56]. Although PROMs are used frequently in the orthopaedic literature, the traditional pre–post-test research designs used may be influenced by response shift phenomenon. In particular, the extended preparation and rehabilitation required for ACI, combined with the inherent expectations associated with surgery, may make patients prone to response shift [39]. If the PROMs frequently used to evaluate ACI outcomes are subject to a response shift, then reported outcomes may under- or over-estimate the effectiveness of existing articular cartilage treatments, calling into question the validity of much of the existing ACI outcomes literature.

The purpose of this study was to determine whether patients undergoing ACI experience response shift. The International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, the Western Ontario and McMaster Osteoarthritis Index (WOMAC), and the medical outcomes study 36-item short-form health survey Physical Component Scale (SF-36 PCS) rely heavily on subjective evaluations of function and pain levels, which may be influenced by response shift. Therefore, it was hypothesized that these common ACI outcome instruments would demonstrate the evidence of a response shift. In contrast, the Lysholm Knee Scale (Lysholm) focuses on the capacity to perform specific tasks rather than the ease or pain associated with task performance; therefore, it was hypothesized that Lysholm scores would not be influenced by response shift.

Materials and methods

Patients were prospectively recruited from an active cartilage centre within a public university affiliated sports medicine clinic. Inclusion criteria were the following: planned ACI surgery to the knee, willingness to participate, and no uncorrectable contraindications to ACI such as extensive degenerative joint disease, insufficient meniscus, or unstable knee. There were no exclusions based on the limb malalignment if the malalignment was corrected prior to or at the time of surgery via high tibial osteotomy or tibial tubercle transfer. Patients undergoing concomitant meniscal transplant were excluded. A total of 56 consecutive patients who met eligibility requirements were approached to participate in this study (Fig. 1). The final participating enrolment for this study was 48 patients (29 males, 19 females, 35.1 ± 8.0 yrs, 180.7 ± 31.7 cm, 92.4 ± 20.3 kg). Among these patients, 24 underwent ACI to the patellofemoral joint with a tibial tubercle transfer, 2 underwent ACI to the lateral femoral condyle, and the remaining 22 underwent ACI to the femoral condyle, of which 4 also had a concomitant high tibial osteotomy. The mean number of defects treated per patient was 1.5 ± 0.6 with an average treatment area of 8.7 ± 6.9 cm^2 (range 1.9–39.0 cm^2) as measured intraoperatively. All participants signed a university-approved institutional review board consent form.

Surgical procedures and rehabilitation

All patients underwent a two-step ACI procedure performed by the same surgeon (XX). During the first procedure, a limited chondroplasty was performed and the lesion was evaluated arthroscopically. At this time, a biopsy was obtained from the intercondylar notch (100–200 mg cartilage). This sample was sent to a commercial laboratory where it was cultured and expanded (Carticel, Genzyme Corp., Cambridge, MA). In a second surgical procedure, chondrocyte implantation was performed using a formal arthrotomy. First, the defect or defects were prepared using a curette to debride down to the subchondral plate with stable edges. A type I/III collagen membrane (Geistlich Bio-Gide$^{(R)}$, Geistlich Pharma North America Inc., Princeton, New Jersey) was shaped to match the defect. Sutures and fibrin glue (Tisseel, Baxter Healthcare Corp., Deerfield, IL) were used to adhere the membrane over the defect to form a water-tight seal. The chondrocytes in suspension were then injected beneath the membrane into the defect through a small portal remaining at the edge of the collagen membrane. The portal was then closed and sealed with sutures and additional fibrin glue.

All patients followed standardized rehabilitation protocols following surgery [26]. All patients were braced in full

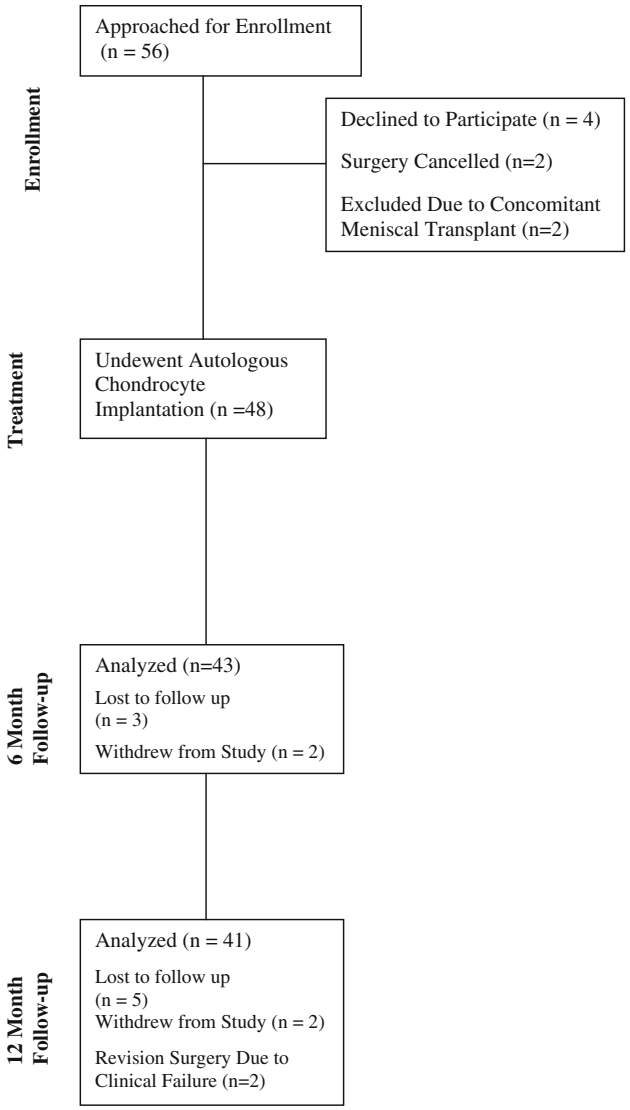

Fig. 1 Study enrolment and follow-up

extension and were non-weight bearing for 2 weeks postoperatively. Toe-touch weight bearing was permitted from 2 to 4 weeks with partial weight bearing from 4 to 6 weeks and progression to full weight bearing between weeks 6 and 12. Continuous passive motion was prescribed for all patients for 6–8 h per day for 6 weeks. For defects in the tibiofemoral joint, knee braces were gradually unlocked between 2 and 4 weeks as quadriceps control was gained. For defects to the patellofemoral joint, knees were braced in full extension for weight bearing through 4 weeks postoperative and then were gradually unlocked as quadriceps control was gained between weeks 4 and 6. Once good quadriceps control was gained, all patients were transitioned to a hinged knee sleeve. All patients were recommended to abstain from high-intensity cutting or pivoting activity until at least 12 months post-ACI.

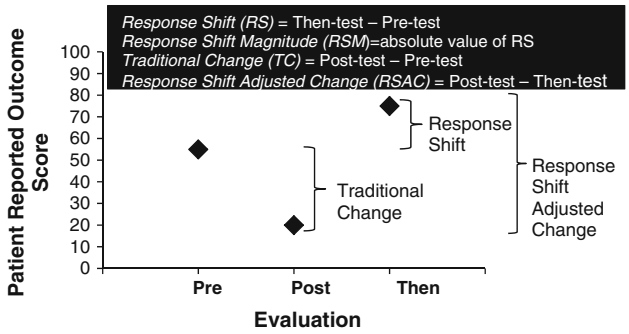

Fig. 2 Then-test method for assessing response shift. For the then-test method, patients are requested to complete an outcome instrument three times. First pre-treatment (pre-test), again at a specified post-treatment time point (post-test), and at that same post-treatment time point, they also complete a then-test on which they are asked to retrospectively rate how they were at the pre-treatment time point. From these three scores, response shift, response shift magnitude, traditional change, and response-shift-adjusted change can then be calculated. In the present study, post and then evaluations were completed at 6 and 12 months postoperatively

Outcome measures

Patient-reported outcomes

The PROMs used in this study were the SF-36 PCS [29, 30, 54], the WOMAC [3], the IKDC [21], and the Lysholm [49]. Reliability among cartilage patients has been previously evaluated for each of these instruments [3, 21, 22, 28, 29, 40]. A researcher independent of the treating physician reviewed each instrument with the patients and was available to answer any questions they may have had. All PROMs were completed prior to implantation and at 6 and 12 months post-surgery.

Assessment of response shift

One of the most common statistical approaches for measuring response shift is the then-test method (Fig. 2) [18, 19]. This approach is identical to a traditional pre-test/post-test method with the exception that subjects complete an additional "then-test" assessment at the same session as their post-test assessment. For the then-test, subjects are instructed to assess how they were at the time of the pre-test, prior to the intervention. The rationale for this design is that by completing the then-test and the post-test at the same time, subjects will provide responses utilizing the same frame of reference and calibration standards for both. In a pre-/post-design, traditional change (TC) is the difference between post-test and pre-test scores and is the only variable of interest. With the then-test method, response shift is calculated as the difference between the then-test and the pre-test and the response-shift-adjusted

change (RSAC) is considered to be the difference between the post-test and the then-test.

Statistical analysis

Apriori power analysis using previously published 12-month response shift values in orthopaedic knee patients [37] (with PROM standard deviation values that were comparable to those previously observed in our own internal cartilage and ligament patient registry) demonstrated a need to enrol 35 patients to achieve sufficient power (0.80) to detect a response shift with $\alpha = 0.05$.

Main outcome measures

The dependent variables of response shift, response shift magnitude, TC, and RSAC were calculated for the IKDC, Lysholm, SF-36 PCS, and WOMAC from pre-operation to 6 and 12 months post-ACI as described in Fig. 2.

Group-level effect

To investigate the occurrence of a group-level response shift, paired *t* tests were used to compare then-test with pre-test scores and to compare TC with RSAC for each PROM. Significant *t* test results ($p < 0.05$) would support the occurrence of a group-level effect with a consistent response shift occurring across patients.

Individual-level effect

To investigate the occurrence of an individual-level (patient-by-patient) effect for response shift, response shift magnitude was calculated as the absolute value of the response shift for each PROM. One-sample *t* tests were used to compare the response shift magnitude with previously established minimal detectable changes (MDCs) for each PROM instrument ($p < 0.05$). The MDC at 6- and 12-month follow-up has been previously established among patients post-ACI for the IKDC (15.6 points at 6 months; 13.7 points at 12 months), WOMAC (10.9, 15.3), and SF-36 PCS (8.3, 6.6) [15]. For the Lysholm scale, an MDC of 14 was calculated from previously published reliability and ICC values among patients awaiting surgery for chondral defects [2, 22].

Results

Study enrolment and follow-up is presented in Fig. 1. Main outcome measures are reported in Table 1. No group-level effect for response shift was observed. There were no differences between pre-test and then-test scores for any of the PROMs evaluated. There were also no differences between RSAC and TC, and none of the mean response shift values exceeded previously established MDC values.

Individual-level analysis

Response shift magnitude values were used to determine the number of subjects that experienced a response shift beyond the MDC at the 6- and 12-month time points for each PROM instrument. At 6 months, it was observed that there was a response shift beyond the MDC for 17 patients assessed via the IKDC, 16 patients for the SF-36 PCS, 15 patients for the Lysholm, and 23 patients for the WOMAC. At the 12-month time point, 10 patients for the IKDC, 23 patients for the SF-36 PCS, 17 patients for the Lysholm, and 14 patients for the WOMAC experienced response shifts that exceeded the MDC. Overall, 13 patients at 6 months and 7 patients at 12 months demonstrated the evidence of a response shift on at least 3 of the four instruments utilized. The only PROMs to show a significant response shift at an individual level across patients were the total WOMAC score at 6 months and the SF-36 PCS at 12 months. The mean response shift magnitude value for the WOMAC at 6 months was 15 ± 14, which was significantly greater than the MDC over 6 months of 10.9 established by Greco et al. [15] ($p = 0.047$). The mean response shift magnitude value for the SF-36 PCS (9.4 ± 6.8) at 12 months also exceeded the previously established MDC (6.6) [15] over a 12-month follow-up ($p = 0.017$).

Discussion

The key finding of the present study was that traditional pre–post-test methods for evaluating PROMs appear valid for assessing group-level treatment effects following ACI. No group-level effects for response shift were observed. These results fail to support the hypothesis that response shift would be evident for the IKDC, SF-36 PCS, and WOMAC, but the results do support the hypothesis that no response shift would be observed for the Lysholm.

A significant difference between pre-test and then-test scores for the WOMAC [37, 38] and the SF-36 PCS [37] has been previously reported at 6 and 12 months following knee arthroplasty. Similarly, a response shift was reported using the Lysholm scale among patients with a median of 34 months following knee microfracture [1]. Upon initial review, our failure to observe a group-level response shift is in disagreement with the previous work [1, 37, 38] in orthopaedic knee patients. However, upon further examination, the values observed in the present study are very similar to those reported elsewhere. In the present study,

Table 1 Main outcome variables for response shift among autologous chondrocyte implantation patients

Measure	IKDC		Lysholm		SF-36 PCS		WOMAC	
	Mean (95 % CI)	*p* values*	Mean (95 % CI)	*p* values	Mean (95 % CI)	*p* values	Mean (95 % CI)	*p* values
Pre-test	38.1 (34.5, 41.6)		46 (41, 51)		37.5 (35.0, 40.0)		33 (29, 38)	
Post-test 6 months	51.1 (45.6, 56.6)		62 (55, 69)		43.5 (40.7, 46.3)		22 (17, 28)	
Post-test 12 months	56.2 (46.5, 65.9)		65 (58, 73)		43.8 (40.1, 47.4)		20 (14, 27)	
Then-test at 6 months	39.9 (33.9, 45.8)	n.s.	41 (36, 47)	n.s.	38.7 (35.5, 41.8)	n.s.	36 (39, 44)	n.s
Then-test at 12 months	39.4 (33.5, 45.2)	n.s.	43 (37, 48)	n.s.	39.3 (36.1, 42.5)	n.s.	35 (29, 41)	n.s
Response shift at 6 months	1.4 (−4.4, 7.2)		−5 (−11, 1)		1.0 (−2.2, 4.2)		5 (−2, 11)	
Response shift at 12 months	0.0 (−6.3, 6.4)		−4 (−10, 1)		1.4 (−2.3, 5.1)		2 (−3, 8)	
Response shift magnitude at 6 months	13.65 (9.7, 17.6)	n.s.	15 (11, 19)	n.s.	8.3 (6.3, 10.2)	n.s.	15† (11, 20)	0.047
Response shift magnitude at 12 months	13.64 (10.0, 17.3)	n.s.	14 (10, 17)	n.s.	9.4† (7.2, 11.5)	0.017	13 (9, 16)	n.s.
Traditional change at 6 months	13.3 (8.1, 18.4)		16 (11, 22)		6.3 (3.5, 9.0)		−10 (−15, −6)	
Traditional change at 12 months	17.6 (12.1, 23.1)		19 (13, 25)		5.9 (3.4, 8.5)		−13 (−17, −8)	
Response-shift-adjusted change at 6 months	11.7 (3.3, 20.0)	n.s.	21 (14, 28)	n.s.	4.9 (0.6, 9.2)	n.s.	−15 (−23, −6)	n.s.
Response-shift-adjusted change at 12 months	17.3 (8.1, 26.4)	n.s.	24 (16, 31)	n.s.	4.5 (0.6, 8.4)	n.s.	−15 (−21, −9)	n.s.
Minimal detectable change at 6 months	15.6 [11]		14 [16]		8.3 [11]		10.9 [11]	
Minimal detectable change at 12 months	13.7 [11]		14 [16]		6.6 [11]		15.3 [11]	

* Comparisons made for each instrument at both 6 and 12 months: then-tests to pre-tests; response shift magnitude to minimal detectable change; traditional change to response-shift-adjusted change; n.s. [non-significant ($p > 0.05$)]

† $p < .05$

Response shift = then-test − pre-test

Response shift magnitude = absolute value of response shift

Traditional change = post-test − pre-test

Response shift adjusted change = post-test − then-test

mean RS values of -5 ± 19 and -4 ± 18 for the Lysholm were observed compared to a median RS of -7 by Balain et al. [1] Similarly, we observed mean RS values of 5 ± 20 and 2 ± 17 for the WOMAC and 1.0 ± 10.4 and 1.4 ± 11.6 for the SF-36 PCS, compared with previously reported mean WOMAC RS values of 3.8 ± 19.5, 5.5 ± 16.9, and 6.7 ± 15.5 and SF-36 PCS values of -1.7 ± 8.1 and -3.2 ± 7.9 [37, 38]. In all cases, the mean or median differences between then-test and pre-test scores were less than the previously established MDC scores for each instrument, and standard deviations or reported ranges were quite high. However, the larger sample sizes in the previous studies, ranging from 53 [1] to 234 [37], resulted in statistically significant RS values, leading the authors to conclude that a response shift had occurred.

By examining actual mean RS values and standard deviations, it can be concluded that the group effect for response shift observed in previous studies was no more clinically meaningful than those observed in the present study. This conclusion was reiterated by the previous authors who conceded that although a statistically significant response shift had occurred, adjusting for the response shift did not change clinical conclusions regarding treatment efficacy [1, 37, 38]. Based on the present study and previous reports, a slight group effect for response shift may occur among postoperative orthopaedic knee patients; however, this response shift is not substantial enough on a group level to invalidate the use of traditional pre–post-outcomes assessment methods.

In comparing response shift magnitude values with previously established MDC values for articular cartilage patients, a statistically significant response shift was observed on an individual level for the WOMAC at 6 months ($p = 0.047$) and the SF-36 PCS at 12 months ($p = 0.017$). Although the WOMAC and SF-36 PCS scores did not demonstrate a group-level effect for response shift, the mean response shift magnitude observed on WOMAC and SF-36 PCS scores did exceed MDC values—meaning individual patients did exhibit a response shift. However, some patients' then-test scores recalibrated positively (then-test $>$ pre-test), while others shifted negatively (then-test $<$ pre-test) as a result mean response shift values were not statistically significant, but WOMAC and SF-36 response shift magnitude values were significant. However, response shift magnitude values suggest that WOMAC and SF-36 PCS scores are susceptible to response shift on the individual patient level. If WOMAC and/or SF-36 PCS scores are being used to track treatment progress of an individual patient, response shift should be taken into consideration.

Additional analyses using MDC values suggested that some individual patients may experience a clinically relevant response shift across PROM instruments with 13 patients at 6 months and 7 patients at 12 months observed to have response shift magnitude values exceeding MDC values on at least 3 out of 4 PROMs. The direction of the response shift is important on a group level to evaluate the influence of response shift on interpretation of overall treatment effects across patients. However, because it is clear that patients may experience either a positive or negative response shift, averaging RS values across patients may obscure the occurrence of a true, albeit non-uniform, response shift.

Question structure may contribute to the WOMAC and SF-36 PCS being more influenced by response shift than the IKDC or Lysholm. The versions of the WOMAC and the SF-36 included in this study rely heavily on 5- or 6-item Likert-like response choices. For example, WOMAC response choices include "none", "mild", "moderate", "severe", or "extreme". This type of scale can be highly subjective and may be prone to scale recalibration and situational interpretation [35]. Depending on the patient's prior experiences, mild and moderate may have different meanings over time as the patient has more information and new experiences for comparison. While other PROM instruments contain some similarly structured questions, the WOMAC and SF-36 provide significantly less context from which the patient is asked to answer the questions. In contrast, the IKDC and the Lysholm provide the patient with reference criteria creating meaningful standards around which one can anchor his or her internal scale. For example, the IKDC asks "What is the highest level of activity you are able to perform without significant giving way in your knee?" and in addition to providing response choices such as "very strenuous" or "strenuous" examples of each level of activity are provided, such as "very strenuous activities like jumping or pivoting as in basketball or soccer". By placing the dysfunction of giving way in the participation context of soccer or basketball, the instrument is cueing the patient to a specific sample of relevant experiences or activities from which to evaluate his or her own function. By providing scale anchors and directing the patient towards a specific sample of experiences, the IKDC and Lysholm appear to reduce the risk of significant variation in scale and conceptualization between and within patients over time.

Personal and environmental factors may explain why among cartilage patients response shift seems to be an individual and not a group phenomenon. Unlike a terminal disease, which will likely impact every aspect of life, the impact of physical limitations secondary to knee surgery vary from person to person depending on factors such as employment status, pre-injury activity level, social support, and preoperative expectations. These contextual factors have previously been referred to as "antecedents" in Spranger and Schwartz's model of response shift and

HRQL [48]. This model of response shift stresses the importance of variables such as personality, sociodemographics, access to care, physical environment, expectations, and spiritual identity on health outcomes. All of these factors may vary from person to person, further explaining the great variability observed and why evidence of a response shift may exist on an individual level, but not on the group level. Awareness of this individual response shift may be highly relevant to clinicians as they try to reconcile changes in patient-reported health (or lack thereof) with observations of changes in physical health and performance [20]. Clinicians may strongly benefit by having an awareness of what factors may make an individual prone to a response shift and how those factors can be utilized to provide the individual with the highest possible self-perceived HRQL.

By asking patients to recall their level of function 6–12 months prior, the then-test method may be prone to recall bias [42]. However, the then-test method has been demonstrated as having convergent validity with more complicated methods of evaluating response shift including structural equation modelling and analysis of covariance, which require much larger samples sizes than were available in this investigation [42, 51]. Additional research has demonstrated that recall bias alone was unable to explain changes in then-test scores observed among multiple sclerosis patients or human immunodeficiency virus/acquired immune disease syndrome patients, and at least a portion of observed changes could be attributed to response shift [43, 46]. Finally, the use of the then-test method allowed for direct comparison to previous investigations of response shift in orthopaedic knee patients.

Additionally, it is cautioned that the conclusions drawn from this study must be limited to the patient population and time points investigated. The study population included ACI patients undergoing a variety of concomitant procedures. While this patient sample may seem heterogeneous relative to those reported commonly in the literature for ACI, we believe including complex patients in our sample actually increases the generalizability of our findings to true ACI populations treated in clinical practice [10]. Similarly, we only examined response shift within the first year following ACI and cannot draw conclusions concerning the effect of response shift on longer-term outcomes.

Conclusions

These results support the validity of traditional pre-test/post-test research designs in evaluating short-term treatment effects following cartilage repair. However, there is evidence that response shift may occur on an individual level on a patient-by-patient basis, and short-term scores on the WOMAC and SF-36 PCS in particular may be influenced by response shift. On a clinical level, recognizing the occurrence of a response shift may be key in evaluating short-term treatment progress for individual patients. This is particularly true for treatments such as ACI where physicians depend heavily on patient self-report and appraisal of progress because tools for diagnostic evaluation are limited and not always feasible or cost-effective.

Acknowledgments This publication was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant UL1TR000117. Additionally, this work was supported by a grant from the University of Kentucky COM Physician Scientist Clinical Scholar Award, the American Orthopaedic Society for Sports Medicine (AOSSM) Career Development Award, and the National Institute of Health (NIH) (1K23AR060275-01A1). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Conflict of interest The authors declare that they have no conflict of interest regarding funding of the presented research.

References

1. Balain B, Ennis O, Kanes G, Singhal R, Roberts SN, Rees D, Kuiper JH (2009) Response shift in self-reported functional scores after knee microfracture for full thickness cartilage lesions. Osteoarthr Cartil 17(8):1009–1013
2. Beaton DE (2000) Understanding the relevance of measured change through studies of responsiveness. Spine 25(24):3192–3199
3. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW (1988) Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 15(12):1833–1840
4. Bentley G, Biant LC, Carrington RWJ, Akmal M, Goldberg A, Williams AM, Skinner JA, Pringle J (2003) A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. J Bone Joint Surg Br 85(2):223–230
5. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L (1994) Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med 331(14):889–895
6. Brittberg M, Tallheden T, Sjogren-Jansson E, Lindahl A, Peterson L (2001) Autologous chondrocytes used for articular cartilage repair: an update. Clin Orthop Relat Res 391:S337–S348
7. Browne JE, Anderson AF, Arciero R, Mandelbaum B, Moseley Jr JB, Micheli LJ, Fu F, Erggelet C (2005) Clinical outcome of autologous chondrocyte implantation at 5 years in US subjects. Clin Orthop Relat Res 436:237–245
8. Dhollander AAM, Verdonk PCM, Lambrecht S, Verdonk R, Elewaut D, Verbruggen G, Almqvist KF (2012) Short-term outcome of the second generation characterized chondrocyte implantation for the treatment of cartilage lesions in the knee. Knee Surg Sports Traumatol Arthrosc 20(6):1118–1127
9. Ebert JR, Robertson WB, Lloyd DG, Zheng MH, Wood DJ, Ackland T (2008) Traditional vs accelerated approaches to post-

operative rehabilitation following matrix-induced autologous chondrocyte implantation (MACI): comparison of clinical, biomechanical and radiographic outcomes. Osteoarthr Cartil 16(10):1131–1140
10. Engen CN, Engebretsen L, Årøen A (2010) Knee cartilage defect patients enrolled in randomized controlled trials are not representative of patients in orthopedic practice. Cartilage 1(4):312–319
11. Farr J (2007) Autologous chondrocyte implantation improves patellofemoral cartilage treatment outcomes. Clin Orthop Relat Res 463:187–194
12. Ferruzzi A, Buda R, Faldini C, Vannini F, Di Caprio F, Luciani D, Giannini S (2008) Autologous chondrocyte implantation in the knee joint: open compared with arthroscopic technique. Comparison at a minimum follow-up of 5 years. J Bone Joint Surg Am 90(Suppl 4):90–101
13. Filardo G, Kon E, Di Martino A, Patella S, Altadonna G, Balboni F, Bragonzoni L, Visani A, Marcacci M (2012) Second-generation arthroscopic autologous chondrocyte implantation for the treatment of degenerative cartilage lesions. Knee Surg Sports Traumatol Arthrosc 20(9):1704–1713
14. Filardo G, Vannini F, Marcacci M, Andriolo L, Ferruzzi A, Giannini S, Kon E (2013) Matrix-assisted autologous chondrocyte transplantation for cartilage regeneration in osteoarthritic knees. Am J Sports Med 41(1):95–100
15. Greco NJ, Anderson AF, Mann BJ, Cole BJ, Farr J, Nissen CW, Irrgang JJ (2010) Responsiveness of the international knee documentation committee subjective knee Form in comparison to the Western Ontario and McMaster Universities Osteoarthritis Index, modified Cincinnati knee rating system, and short form 36 in patients with focal articular cartilage defects. Am J Sports Med 38(5):891–902
16. Hagedoorn M, Sneeuw KCA, Aaronson NK (2002) Changes in physical functioning and quality of life in patients with cancer: response shift and relative evaluation of one's condition. J Clin Epidemiol 55(2):176–183
17. Harris JD, Siston RA, Pan X, Flanigan DC (2010) Autologous chondrocyte implantation: a systematic review. J Bone Joint Surg Am 92(12):2220–2233
18. Howard GS (1979) Internal invalidity in pretest-posttest self-report evaluations and a re-evaluation of retrospective pretests. App Psych Meas 3(1):1–23
19. Howard GS, Schmeck RR, Bray JH (1979) Internal invalidity in studies employing self-report instruments: a suggested remedy. J Educ Meas 16(2):129–135
20. Howard JS, Mattacola CG, Howell DM, Lattermann C (2011) Response shift theory: an application for health related quality of life in rehabilitation research and practice. J Allied Health 40(1):31–38
21. Irrgang JJ, Anderson AF, Boland AL, Harner CD, Kurosaka M, Neyret P, Richmond JC, Shelborne KD (2001) Development and validation of the international knee documentation committee subjective knee form. Am J Sports Med 29(5):600–613
22. Kocher MS, Steadman JR, Briggs KK, Sterett WI, Hawkins RJ (2004) Reliability, validity, and responsiveness of the Lysholm Knee Scale for various chondral disorders of the knee. J Bone Joint Surg Am 86A(6):1139–1145
23. Kon E, Gobbi A, Filardo G, Delcogliano M, Zaffagnini S, Marcacci M (2009) Arthroscopic second-generation autologous chondrocyte implantation compared with microfracture for chondral lesions of the knee: prospective nonrandomized study at 5 years. Am J Sports Med 37(1):33–41
24. Kreuz PC, Müller S, von Keudell A, Tischer T, Kaps C, Niemeyer P, Erggelet C (2013) Influence of sex on the outcome of autologous chondrocyte implantation in chondral defects of the knee. Am J Sports Med. doi:10.1177/0363546513489262
25. Kreuz PC, Steinwachs M, Erggelet C, Lahm A, Krause S, Ossendorf C, Meier D, Ghanem N, Uhl M (2007) Importance of sports in cartilage regeneration after autologous chondrocyte implantation: a prospective study with a 3-year follow-up. Am J Sports Med 35(8):1262–1268
26. Lattermann C (2011) UK Center for Cartilage Repair and Restoration University of Kentucky. http://ukhealthcare.uky.edu/rehab-protocol/#.UGuk55jAcdc
27. Mandelbaum B, Browne JE, Fu F, Micheli LJ, Moseley Jr JB, Erggelet C, Anderson AF (2007) Treatment outcomes of autologous chondrocyte implantation for full-thickness articular cartilage defects of the trochlea. Am J Sports Med 35(6):915–921
28. Marx RG, Jones EC, Allen AA, Altchek DW, O'Brien SJ, Rodeo SA, Williams RJ, Warren RF, Wickiewicz TL (2001) Reliability, validity, and responsiveness of four knee outcome scales for athletic patients. J Bone Joint Surg Am 83(10):1459
29. McHorney CA, Ware Jr JE, Lu JF, Sherbourne CD (1994) The MOS 36-item short-form health survey (SF-36): iII. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care 32(1):40–66
30. McHorney CA, Ware Jr JE, Raczek AE (1993) The MOS 36-item short-form health survey (SF-36): iI. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 31(3):247–263
31. Micheli LJ, Moseley JB, Anderson AF, Browne JE, Erggelet C, Arciero R, Fu FH, Mandelbaum BR (2006) Articular cartilage defects of the distal femur in children and adolescents: treatment with autologous chondrocyte implantation. J Pediatr Orthop 26(4):455–460
32. Mithöfer K, Minas T, Peterson L, Yeon H, Micheli LJ (2005) Functional outcome of knee articular cartilage repair in adolescent athletes. Am J Sports Med 33(8):1147–1153
33. Mithöfer K, Peterson L, Mandelbaum BR, Minas T (2005) Articular cartilage repair in soccer players with autologous chondrocyte transplantation: functional outcome and return to competition. Am J Sports Med 33(11):1639–1646
34. Nagl M, Farin E (2012) Response shift in quality of life assessment in patients with chronic back pain and chronic ischaemic heart disease. Disabil Rehabil 34(8):671–680
35. Ogden J, Lo J (2012) How meaningful are data from Likert scales? An evaluation of how ratings are made and the role of the response shift in the socially disadvantaged. Journal of Health Psychology 17(3):350–361
36. Pestka JM, Bode G, Salzmann G, Südkamp NP, Niemeyer P (2012) Clinical outcome of autologous chondrocyte implantation for failed microfracture treatment of full-thickness cartilage defects of the knee joint. Am J Sports Med 40(2):325–331. doi:10.1177/0363546511425651
37. Razmjou H, Schwartz CE, Yee A, Finkelstein JA (2009) Traditional assessment of health outcome following total knee arthroplasty was confounded by response shift phenomenon. J Clin Epidemiol 62(1):91–96
38. Razmjou H, Yee A, Ford M, Finkelstein JA (2006) Response shift in outcome assessment in patients undergoing total knee arthroplasty. J Bone Jt Surg Am 88(12):2590–2595
39. Reinold MM, Wilk KE, Macrina LC, Dugas JR, Cain EL (2006) Current concepts in the rehabilitation following articular cartilage repair procedures in the knee. J Orthop Sports Phys Ther 36(10):774–794
40. Roos EM, Klassbo M, Lohmander LS (1999) WOMAC osteoarthritis index. Reliability, validity, and responsiveness in patients with arthroscopically assessed osteoarthritis. Western Ontario and MacMaster Universities. Scand J Rheumatol 28(4):210–215
41. Rosenberger RE, Gomoll AH, Bryant T, Minas T (2008) Repair of large chondral defects of the knee with autologous chondrocyte

implantation in patients 45 years or older. Am J Sports Med 36(12):2336–2344
42. Schmitt NW, Pulakos ED, Lieblein A (1984) Comparison of three techniques to assess group-level beta and gamma change. App Psychol Meas 8(3):249–260
43. Schwartz C, Rapkin B (2012) Understanding appraisal processes underlying the thentest: a mixed methods investigation. Qual Life Res 21(3):381–388
44. Schwartz CE, Sprangers MA (1999) Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research. Soc Sci Med 48(11):1531–1548
45. Schwartz CE, Sprangers MAG (2002) An introduction to quality of life assessment in oncology: the value of measuring patient-reported outcomes. Am J Manag Care 8(18 Suppl):S550–S559
46. Schwartz CE, Sprangers MAG, Carey A, Reed G (2004) Exploring response shift in longitudinal data. Psychol Health 19(1):51–69
47. Sprangers MA, Schwartz CE (1999) The challenge of response shift for quality-of-life-based clinical oncology research. Ann Oncol 10(7):747–749
48. Sprangers MA, Schwartz CE (1999) Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 48(11):1507–1515
49. Tegner Y, Lysholm J (1985) Rating systems in the evaluation of knee ligament injuries. Clin Orthop Relat Res 198:42–49
50. Tierney DK, Facione N, Padilla G, Dodd M (2007) Response shift: a theoretical exploration of quality of life following hematopoietic cell transplantation. Cancer Nurs 30(2):125–138
51. Visser M, Oort F, Sprangers M (2005) Methods to detect response shift in quality of life data: a convergent validity study. Qual Life Res 14(3):629–639
52. Viste A, Piperno M, Desmarchelier R, Grosclaude S, Moyen B, Fessy MH (2012) Autologous chondrocyte implantation for traumatic full-thickness cartilage defects of the knee in 14 patients: 6-year functional outcomes. Orthop Traumatol Surg Res 98(7):737–743
53. Wagner JA (2005) Response shift and glycemic control in children with diabetes. Health Qual Life Outcomes 3:38
54. Ware Jr JE, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. conceptual framework and item selection. Med Care 30(6):473–483
55. Westerman MJ, The A-M, Sprangers MAG, Groen HJM, van der Wal G, Hak T (2007) Small-cell lung cancer patients are just 'a little bit' tired: response shift and self-presentation in the measurement of fatigue. Qual Life Res 16(5):853–861
56. Zaslav K, Cole B, Brewster R, DeBerardino T, Farr J, Fowler P, Nissen C (2009) A prospective study of autologous chondrocyte implantation in patients with failed prior treatment for articular cartilage defect of the knee: results of the study of the treatment of articular repair (STAR) clinical trial. Am J Sports Med 37(1):42–55
57. Zhang X-H, Li S-C, Xie F, Lo N–N, Yang K-Y, Yeo S-J, Fong K-Y, Thumboo J (2012) An exploratory study of response shift in health-related quality of life and utility assessment among patients with osteoarthritis undergoing total knee replacement surgery in a tertiary hospital in Singapore. Value Health 15(1 Suppl):S72–S78