Impact of activity levels, age, and BMI on outcomes after the implantation of an aragonite-based scaffold for the treatment of knee chondral and osteochondral defects: analysis of an RCT at 4-year follow-up

Seth Lawrence Sherman[1], Peter Verdonk, Francesca De Caro, Elizaveta Kon[2]
[1]Orthopaedic Surgery, Stanford Medicine Outpatient Center, [2]Humanitas University

INTRODUCTION:
Chondral and osteochondral lesions in the knee joint are common and debilitating conditions. The avascular nature of articular cartilage prohibits primary healing of defects. To date, no gold standard treatment has been defined for these lesions; thus there is a need for novel treatment options to address this unmet need.
The aim of this study was to assess the results of a large, multicenter RCT comparing a novel cell-free aragonite-based scaffold to the standard of care (i.e. debridement/microfracture) for the treatment of chondral/osteochondral defects in knees with respect to patient activity levels. The clinical hypothesis was that the aragonite-based scaffold would be superior to surgical standard of care (SSOC) when measuring improvement in patient-reported outcomes.
METHODS:
251 patients were included: 167 patients in the scaffold group and 84 in the control. Patient reported outcomes were collected preoperatively, at 6 months postoperatively and annually up to 48 months after the treatment. The primary endpoint was the change from baseline to 48 months in the Knee Injury and Osteoarthritis Outcome Score (KOOS)–Overall Rating. Secondary endpoints included change from baseline in the Tegner Activity Scale, KOOS subscales (Pain, Symptoms, Activities of Daily Living, Sport/Recreation, Quality of Life), responder rate and treatment failure rate. Responder rate was defined as the percentage of patients achieving an increase in KOOS Overall Score of 30 points or more. Treatment failures were defined as any secondary invasive intervention, including intra-articular injection or any surgery in the treated joint. A repeated measures analysis using a mixed effects model with terms for group, visit, and group-by-visit interaction (Mixed Model for Repeated Measures, MMRM) was conducted to evaluate primary and secondary outcomes. Additional stratified and covariate analyses were conducted using MMRM. Outcomes for patients categorized as treatment failures were imputed using the baseline observation carried forward methodology. All enrolled subjects were followed for safety outcomes, i.e., knee replacements and osteotomies in the study knee.
RESULTS:
In the scaffold group, 22.6% (n=37) of patients had a BMI ≥30 kg/m^2, 79.9% (n=131) of patients had a pre-injury Tegner score ≤4 (activity level) and the mean age was 41.8 ±11.0 years. In the control group 32.5% (n=27) patients had a BMI ≥30 kg/m^2, 73.5% (n=61) of patients had a pre-injury Tegner score ≤4 (activity level), and the mean age was 45.9 ±11.0 years. Patients in the scaffold group achieved significantly better results in the KOOS overall score than controls across all BMI categories, age categories, and pre-injury activity levels up to the 48 months follow-up. Within the control group, patients aged 65 or more years did not show a significant increase in KOOS overall score at the 4-year follow-up compared to baseline. There were no statistically significant within-group differences or covariate-by-group interactions in outcomes based on BMI category, age category, or pre-injury activity level. Responders' rate and Failure rate were also significantly better in the scaffold group across all covariates. At the 48-month follow-up, 1.2% (n=2) of patients in the scaffold group and 9.5% (n=8) of patients in the control group had undergone a knee replacement or osteotomy (p=.003). Tegner scores for the scaffold group increased steadily from baseline to the 48-month follow-up (F-test for linear trend, p<.0001), while the control group showed a relatively small increase from baseline with a nonsignificant overall trend (p=.154). Patients in the scaffold group reported higher activity levels than the control group at all follow-up timepoints with a significant visit-by-group interaction (p < .0001).
DISCUSSION AND CONCLUSION:
The aragonite-based scaffold outperformed the control group at 48 months' evaluation. The analysis showed that BMI, age, and pre-injury activity did not significantly impact clinical outcomes for patients in the scaffold group and that outcomes for these patients were significantly better than their counterparts treated with debridement/microfracture.

Table 1 - Demographics and Baseline Characteristics

	Aragonite-based scaffold N=104	SSOC N=83	Aragonite-based scaffold minus SSOC Difference (%) or p-value	LB	UB
Demographics					
Gender, n (%)			2.8%	-10.2	15.4
Male	105 (64.0%)	51 (61.4%)			
Female	59 (36.0%)	32 (38.6%)			
Age, mean (SD)	41.8 (13.8)	45.9 (13.0)	-4.13%	-7.05	-1.21
Age Category, n (%)			0.541		
21 to <45 years (Young adulthood)	83 (56.7%)	41 (49.4%)			
45 to <65 years (Middle adulthood)	57 (39.0%)	40 (48.2%)			
≥ 65 years (Elderly)	6 (4.1%)	2 (2.4%)			
BMI, mean (SD)	29.4 (4.2)	27.9 (3.9)	-1.48%	-2.56	-0.40
BMI ≥ 30 kg/m², n (%)					
Yes	37 (22.6%)	27 (32.5%)			
No	127 (77.4%)	56 (67.5%)			
Lesion Characteristics					
Kellgren-Lawrence Grade, n (%)			18.7%	5.9	31.6
0 or 1	90 (54.9%)	39 (36.1%)			
2 or 3	74 (45.1%)	53 (63.9%)			
Lesion ≥ 4 cm², n (%)			9.3%	-4.8	22.5
Yes	96 (58.5%)	41 (49.4%)			
No	68 (41.5%)	42 (50.6%)			
Single vs Multiple Lesions, n (%)			-3.4%	-15.8	8.9
Single	137 (83.2%)	57 (68.7%)			
Multiple	57 (34.8%)	26 (31.3%)			
ICRS Grade (4B vs 3/4A), n (%)			39.3%	7.8	38.4
Grade 4B	43 (26.4%)	16 (19.3%)			
Grade 3/4A	101 (61.6%)	67 (80.7%)			
Baseline Functional Status					
KOOS – Overall Score, mean (SD)	41.2 (13.1)	41.7 (12.4)	-0.53	-3.95	2.89
Tegner Pre-Injury Score, mean (SD)	6.1 (1.9)	6.1 (2.0)	0.03	-0.46	0.54
Tegner Pre-Injury Activity Level, mean (SD)	2.5 (1.3)	2.4 (1.2)	0.08	-0.20	0.44
Pre-Injury Activity Level, n (%)			6.4	-4.2	17.7
Active (Tegner >4)	131 (79.0%)	61 (73.5%)			
Not Active (Tegner ≤4)	35 (21.1%)	22 (26.5%)			

Table 2: Mixed Model for Repeated Measures (MMRM) for KOOS Overall Score
Full Analysis Set[1]

	Aragonite-based scaffold			SSOC			Aragonite-based scaffold minus SSOC		
	Mean Change	95% CI	p-value[2]	Mean Change	95% CI	p-value[2]	Group difference in mean Change	95% CI	p-value[3]
BMI Category			0.056			0.407			0.626[4]
≥30 kg/m²	25.30	28.2 - 42.3	<.0001	16.5	8.1 - 25.0	0.0003	18.7	7.7 - 29.7	0.0009
<30 kg/m²	42.03	38.3 - 45.8	<.0001	21.6	16.0 - 27.3	<.0001	20.4	13.6 - 27.2	<.0001
Age Category			0.919			0.363			0.056[4]
21 to <45 years (Young adulthood)	40.75	36.5 - 45.2	<.0001	18.3	11.8 - 25.1	<.0001	22.3	14.3 - 30.3	<.0001
45 to <65 years (Middle adulthood)	40.19	34.9 - 45.4	<.0001	22.8	15.9 - 29.7	<.0001	17.4	8.7 - 26.0	0.0001
≥ 65 years (Elderly)	40.41	19.4 - 61.4	0.0002	1.4	-28.1 -31.0	0.9249	39.0	2.7 - 75.3	0.0352
Preinjury activity level (Tegner)			0.111			0.896			0.099[4]
Active (>4)	39.01	35.5 - 42.7	<.0001	20.3	14.7 - 25.8	<.0001	18.8	12.1 - 25.4	<.0001
Not Active (≤4)	46.29	38.9 - 53.7	<.0001	19.1	10.2 - 28.1	<.0001	27.2	15.6 - 38.7	<.0001

[1] **Baseline observation carried forward after treatment failure for 19 in scaffold group and 29 SSOC.**
[2] **p-value for within group comparison between subgroups at Month 48.**
[3] **p-value for within subgroup mean changes.**
[4] **Covariate by group interaction: 2-way interaction collapses over visit and tests whether the mean group difference over time varies by subgroup**