Purpose: There is a high unmet medical need for disease modifying drugs in OA that have an effect on joint structure. Fibroblast growth factor 18 (FGF18) promotes chondrocyte proliferation and stabilizes an anabolic chondrocyte phenotype. Data from a proof-of-concept trial in knee OA demonstrated that sprifermin (rhFGF18) increased total cartilage volume and thickness. This effect seemed to be more pronounced in the lateral compartment, raising the question of the distribution of the effect on cartilage change on different knee subregions. Here we use a location-independent analysis method, to identify whether sprifermin modifies the magnitude of (subregional) cartilage loss compared with placebo, independent of the location where it occurs in individual joints.
Methods: Study participants (n=168; ≥40-year-old; 69% female) had symptomatic and radiographic femorotibial OA (KLG2 or 3), and were not confined to medial disease. Sprifermin (10, 30, or 100μg) or placebo were injected once weekly for 3 weeks after randomization, and at 13 weeks. 1.5mm coronal SPGR MRIs were acquired at baseline and 13, 26 and 52 weeks. Medial (MFTC) and lateral femorotibial cartilage (LFTC) was segmented by 7 readers, with blinding to acquisition order and treatment (Chondrometrics GmbH). Cartilage thickness (changes) were computed in each of 16 femorotibial subregions (5 medial and 5 lateral tibial, 3 medial and 3 lateral femoral).The location-independent magnitude of subregional thickness changes (in mm) was calculated using ordered values (OV), individually assigning the magnitude of cartilage loss in the subregion with the greatest loss to OV1, the one with the second greatest loss to OV2, and so forth, and the one with the smallest loss/greatest increase to OV16). In the current analysis, results of the 100μg cohort (n=63) vs. matching placebo (n=21) were compared using t-tests.
Results: Total femorotibial cartilage thickness loss at 52 weeks was less in sprifermin treated than in placebo treated knees, with effects being significant in LFTC (p=0.03) but not MFTC (p=0.16) (Table 1). Significant treatment effects ($p<0.05$) were detected in 2/16 subregions (minimal p-value =0.006 in the external lateral femur), and in 10/16 OVs (minimal p=0.004 in OV12). The 10 OVs included some in which cartilage loss was observed (OV4-8) and some in which cartilage thickening was observed in the placebo group (OV11-15).
Conclusions: This location-independent analysis shows that sprifermin can modify the magnitude of cartilage loss in subregions with low OVs, where (individual) mechanical challenges may be greater and drug effects may be more important clinically. The OV approach also has the advantage that no single region must be defined a priori as structural endpoint, which is challenging given spatial inter-subject heterogeneity of (subregional) cartilage loss in OA, particularly in cohorts without predefined (medial or lateral) involvement. The results further show that OVs are more effective and informative in revealing structural treatment effects than region-based analysis, and that sprifermin not only increases cartilage thickness (in regions where no loss is observed), but actually reduces cartilage loss (in regions where cartilage loss is observed with placebo).

Table 1
Cartilage thickness change (mm) in sprifermin treated vs. placebo knees

	Placebo Mean ± SD change	100μg dose Mean ± SD change	Difference Effect-Size	p value
MFTC	-0.07 ± 0.18	0.00 ± 0.16	0.43	0.1603
LFTC	-0.04 ± 0.19	0.04 ± 0.12	0.58	0.0323
SR^{max}	-0.03 ± 0.11	0.04 ± 0.09	0.78	0.0055
OV1	-0.22 ± 0.16	-0.18 ± 0.15	0.25	0.3529
OV2	-0.15 ± 0.12	-0.12 ± 0.12	0.25	0.3500
OV3	-0.12 ± 0.09	-0.09 ± 0.09	0.39	0.1571
OV4	-0.10 ± 0.08	-0.05 ± 0.07	0.64	0.0198
OV5	-0.08 ± 0.07	-0.04 ± 0.06	0.73	0.0094
OV6	-0.07 ± 0.06	-0.02 ± 0.06	0.79	0.0057
OV7	-0.05 ± 0.06	-0.01 ± 0.06	0.69	0.0132
OV8	-0.03 ± 0.06	0.01 ± 0.05	0.62	0.0244
OV9	-0.01 ± 0.06	0.02 ± 0.05	0.50	0.0708
OV10	0.01 ± 0.06	0.03 ± 0.05	0.49	0.0739
OV11	0.02 ± 0.06	0.05 ± 0.05	0.64	0.0210
OV12	0.03 ± 0.07	0.06 ± 0.04	0.80	0.0044
OV13	0.04 ± 0.06	0.08 ± 0.05	0.78	0.0065
OV14	0.07 ± 0.07	0.10 ± 0.05	0.64	0.0232
OV15	0.09 ± 0.07	0.13 ± 0.06	0.60	0.0305
OV16	0.15 ± 0.10	0.18 ± 0.07	0.35	0.2124

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MALALIGNMENT; A POSSIBLE TARGET FOR PREVENTION OF INCIDENT KNEE OA IN MIDDLE-AGED OVERWEIGHT AND OBESE WOMEN

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Purpose: The present study evaluates the effects of malalignment and its interaction with BMI on the onset of clinical and radiographic knee osteoarthritis (OA) over a 2.5 year follow-up period in a high risk group of middle-aged overweight and obese women.
Methods: Data of the PROOF study (ISRCTN 42823086) were used. In total, 407 women between 50 and 60 years, with a BMI ≥ 27 kg/m2, and without clinical and radiological knee OA at baseline were included in this study. Both knees of all 351 women (86%) with baseline knee alignment data and the primary outcome available were selected. At baseline, body weight and height were measured and standardized semi-flexed PA radiographs of both knees were taken according to the MTP protocol. All subjects filled in a questionnaire with questions on knee complaints and number of days with knee pain. All measurements were repeated after 2.5 years of follow-up. Minimal joint space width (medial and lateral), K&L grade and anatomical knee alignment angle were digitally assessed on all radiographs. Varus alignment was defined as an anatomical angle 184°. The predefined primary outcome measure was the incidence of knee OA, defined as onset of K&L ≥ 2 or the onset of clinical knee OA (according to the ACR criteria), or joint space narrowing (JSN) ≥ 1.0 mm in the medial or lateral compartment. Using Generalized Estimated Equations, which takes into account the correlation between knees within subjects, effects of varus and valgus alignment on the primary outcome and on the items separately were evaluated, with neutrally aligned knees serving as reference. The interaction between malalignment and baseline BMI was also studied, by adding BMI and the interaction term with malalignment to the analysis. If a significant interaction was found, overweight (BMI < 30 kg/m2) and obese subjects (BMI ≥ 30 kg/m2) were analysed separately. All analyses were adjusted for K&L grade at baseline and the randomized groups of the interventions of the PROOF study.
Results: Varus alignment was found in 40% and valgus alignment in 13% of all knees. Baseline characteristics are presented in Table 1. Overall, only varus alignment had a significant effect on the incidence of K&L ≥ 2 (9% vs. 3% in neutral knees. OR 2.8, 95% CI 1.3 - 5.9). For the primary outcome and for medial JSN a significant interaction between malalignment and baseline BMI was found ($p < 0.01$). In obese subjects, varus alignment had a significant effect on the primary outcome (22% vs. 13% in neutral knees. OR 1.8, 95% CI 1.1 - 3.1) and on medial JSN (9% vs. 4% in neutral knees. OR 2.6, 95% CI 1.1 - 6.3). These associations were not found in non-obese subjects.
Conclusions: In women at high risk for developing knee OA, varus aligned knees had a significant increased risk for the development of radiographic knee OA. Within obese women, varus aligned knees also had a significantly increased risk for incidence of knee OA according to the primary outcome and for joint space narrowing in the medial compartment. Since varus alignment is a potentially modifiable factor, results from the present study suggest that varus alignment might be a target for the prevention of knee OA in middle-aged overweight and obese women.

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DOES CARTILAGE THICKNESS CHANGE DIFFER BETWEEN ACL DEFICIENT KNEES WITH AND WITHOUT RECONSTRUCTION SURGERY

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Purpose: An ACL tear is a common knee injury, involving a serious trauma and a subsequent period of chronic alterations in joint biomechanics. The risk of developing incident knee OA after an ACL tear is known to be highly elevated although the driving mechanisms are not known. In this study, we tested the hypothesis that treatment of the initial injury influenced change in femorotibial cartilage thickness over the first five years after injury. We thus explored femorotibial cartilage thickness changes during the first 2 years (BL→Y2) and during a subsequent three-year period (Y2→Y5) after an acute ACL tear.