Residual hip dysplasia at 1 year after treatment for neonatal hip instability is not related to degenerative joint disease in young adulthood: a 21-year follow-up study including dGEMRIC

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Objective: Developmental dysplasia of the hip (DDH) is associated with an increased risk of early hip osteoarthritis (OA). We aimed to examine the outcome at the completion of growth in a cohort of children who had residual acetabular dysplasia at age 1 year following early treatment for neonatal instability of the hip (NIH).

Design: We examined 21 of 30 subjects who had been treated with the von Rosen splint neonatally for NIH and had residual acetabular dysplasia at age 1 year. Mean follow-up time was 21 years (range 17–24). Signs of OA and acetabular dysplasia were assessed by radiography. Cartilage quality was assessed by delayed Gadolinium Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC), a tool for molecular imaging of cartilage quality, at 1.5 T. Patient reported outcome (PRO) was assessed by the 12-item WOMAC score.

Results: No study participant had radiographic OA (defined as Kellgren–Lawrence grade ≥2) or minimum joint space width (JSW) ≤2 mm. The mean dGEMRIC index was 630 ms (95% CI: 600–666, range: 516–825) suggesting good cartilage quality. The mean 12-item WOMAC score was 1.2. Two of three radiographic measurements of DDH correlated positively to the dGEMRIC index.

Conclusions: Children treated neonatally for NIH have good hip function and no signs of cartilage degeneration at 21-year follow-up, despite residual dysplasia at age 1 year. Unexpectedly, radiographic signs of dysplasia were associated with better cartilage quality, as assessed with dGEMRIC. This may indicate cartilage adaptation to increased mechanical stress in mild hip dysplasia.

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pathology that eventually leads to osteoarthritis (OA). The technique is based on the principle that the negatively charged contrast agent Gd(DTPA)$^{2-}$ distributes in articular cartilage in an inverse relationship to the negatively charged glycosaminoglycan (GAG) after intravenous administration. GAG is essential for the biomechanical properties of the cartilage and decreases early in the OA disease process. Since Gd(DTPA)$^{2-}$ shortens the T$_1$ relaxation time of the MRI signal, a quantitative T$_1$ measurement within the cartilage provides a surrogate marker for cartilage GAG content. T$_1$ in the presence of Gd(DTPA)$^{2-}$ is often referred to as T$_1$Gd, and the dGEMRIC index is the mean T$_1$Gd in a chosen region of interest (ROI) within the cartilage. Hence, a high dGEMRIC index corresponds to higher GAG content and vice versa.

A low dGEMRIC index has been associated with failure of the Bernese periacetabular osteotomy in adult patients with DDH, presumably because it can differentiate the cases where the OA disease process has advanced too far from those where the cartilage composition is relatively normal. Furthermore, dGEMRIC is sensitive enough to show differences in cartilage composition between healthy subjects with different levels of physical activity, and has also been shown to correlate to both pain and the degree of acetabular dysplasia in DDH patients.

The purpose of this study was to examine the outcome after the completion of growth in subjects who had been treated neonatally with a von Rosen splint for NIH and still had residual acetabular dysplasia at age 1 year. Our hypothesis was that persistent dysplasia at the completion of growth would correlate to a low dGEMRIC index, possibly in combination with radiographic signs of OA and a worse patient reported outcome (PRO).

**Subjects and methods**

**Study participants**

All children who had been treated for NIH from 1987 to 1993 were identified from the pediatric hip register at our institute. The treatment protocol has previously been described in detail. In this study, only children with a positive Barlow or Ortolani sign neonatally were eligible for inclusion ($n = 131$). They were treated in the von Rosen splint for 6–12 weeks. Our follow-up protocol includes a radiographic examination at age 12 months. The acetabular index (AI) was measured according to Hilgenreiner, on digital AP pelvic radiography films. Subjects with an AI of $\geq 28^\circ$ in either hip at age 1 year were eligible for the study.

Thirty subjects had at least one hip with an AI $\geq 28^\circ$ at age 1 year. Of these, 29 could be contacted and 21 agreed to participate in the study. Eighteen of the 21 subjects were female. Mean age at treatment start was 1 day (range 0–4). Mean age at radiographic follow-up was 21 years (range 17–24). Mean age at clinical examination, answering the 12-item WOMAC and dGEMRIC examination was 21 years (range 18–24). Mean BMI was 24.7 (range: 18–53), the weight being measured on the day of the dGEMRIC examination.

**Radiography**

All patients had completed skeletal hip growth, i.e., had closed physes of the proximal femur and acetabulum. Radiographs were classified for OA according to Kellgren–Lawrence using AP pelvic and AP and lateral hip radiographs. The minimum joint space width (JSW) was measured according to Jacobi et al. Measurements assessing hip morphology were made on the AP pelvic radiographs, using three commonly used radiographic parameters of hip dysplasia: the center-edge angle of Wiberg (CE angle), the femoral head extrusion index (FHEI) and the acetabular angle of Sharp (Sharp angle).

Rotation of the pelvis in the axial plane was assessed by measuring the foramen obturator index (FOI) according to Tonnis. All FOI values were within 0.7–1.8 (range 0.74–1.42) which means that errors in measurements of the CE angle and Sharp angle due to rotation of the pelvis were within $\pm 2^\circ$.

**dGEMRIC**

Subjects received a double-dose (0.2 mmol/kg) intravenously of Gd(DTPA)$^{2-}$ (Magnevist, Schering AG, Berlin, Germany), followed by a 10 min timed walk. The walking time was based on a previously published methodological study on healthy volunteers and patients with hip dysplasia. dGEMRIC imaging was performed 60 min after the injection using a standard 1.5 T MRI system (MAGNETOM Avanto, Siemens AG, Erlangen, Germany), with two flexible Body Matrix coils positioned directly over the hips. Five turbo recovery images with different inversion times were used to calculate T$_1$ relaxation times. Repetition time (TR) was 1840 ms, echo time (TE) 15 ms, field-of-view (FoV) 140 $\times$ 140 mm$^2$, and imaging matrix 256 $\times$ 256. Inversion times (TI) were 1650, 650, 350, 150 and 50 ms. A 3 mm thick, central slice in the coronal plane of each hip was selected for T$_1$ mapping. Both hips were imaged in the same imaging session with the subject lying still in the MRI machine during the whole session. The ROI in each hip was drawn manually, including both the acetabular and the femoral cartilage of the weight-bearing region of the hip joint (Fig. 1). The dGEMRIC index of each hip was calculated as the mean T$_1$Gd of its ROI, excluding voxels with T$_1$Gd $>1300$ ms, according to standard protocol at our institution. dGEMRIC indices were then adjusted for BMI to correct for differences in distribution volume using the formula described by Tiderius et al. Two investigations were excluded due to motion artifacts, leaving 40 hips for dGEMRIC analysis. A standard clinical MRI scan of both hips was also performed in the same imaging session. The MRI scans were reviewed by a senior radiologist who was blinded with regards to all other outcomes of the study.
Clinical outcome

A clinical examination was performed, including the Trendelenburg test and measurement of passive hip range of motion, with the subject lying supine or prone (when measuring extension). Subjects answered questions about activity level and subjective hip problems, and the 12-item WOMAC questionnaire, which is a hip specific PRO measure with 12 items, where 0 points signifies no hip problems and 48 is the worst possible score.

No participant had contraindications to MRI or an elevated serum creatinine level. All subjects gave written informed consent and could withdraw freely at will.

The study was approved by the local institutional review board.

Software and statistics

Radiographs and MRI images were stored and viewed using IMPAX CS5000 (Agfa Healthcare NV, Mortsel, Belgium). Table I

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<th>FHEI (%)</th>
<th>Minimum JSW (mm)</th>
<th>Sharp Angle (°)</th>
<th>Kellgren–Lawrence grade</th>
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<th>Weight (kg)</th>
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* Numbers in parentheses denote age at radiography if differing from age at dGEMRIC and 12-item WOMAC.

dGEMRIC index excluded due to motion artifacts.

ROIs and calculations of dGEMRIC indices were performed using MedMap (Dept. of Medical Radiation Physics, Lund University, Malmö, Sweden). For comparison between groups, Student’s t-test was used in normally distributed samples (defined as Shapiro–Wilk W-statistic ≥ 0.95), and Mann–Whitney Rank Sum test in samples that failed normality testing (Shapiro–Wilk W-statistic < 0.95). Confidence intervals for proportions were calculated using binomial distribution. Confidence intervals for measurements on hips were calculated from the mean values of both hips from each subject, as these bilateral measurements were not considered to be independent. For analyses of relationships between variables measured bilaterally, the Mixed Effects Model was used to estimate the regression coefficient (β) with 95% CI. The residuals from the regression line in the Mixed Effects Model were tested for normality (Shapiro–Wilk W-statistic ≥ 0.95 to pass). P-values < 0.05 were considered statistically significant. Statistical analyses were performed using SigmaPlot 11.0 (Systat Software Inc., Richmond, CA, USA) and SPSS 21.0 (IBM Corp., Armonk, NY, USA).
Results

Radiography

The mean CE angle was 30° (95% CI: 28–32), the mean FHEI was 86% (83–88) and the mean Sharp angle was 41° (40–42). Individual values are listed in Table I. There was no statistically significant correlation between the CE angle and the dGEMRIC index ($P = 0.86$), $\beta = 0.25$ ($-2.6$–$3.2$) [Fig. 2(a)]. The FHEI correlated negatively to the dGEMRIC index ($P = 0.026$), $\beta = -4.6$ ($-8.7$ to $-0.6$) [Fig. 2(b)]. The Sharp angle correlated positively to the dGEMRIC index ($P = 0.011$), $\beta = 8.7$ (2.1–15) [Fig. 2(c)].

No subject had radiographic OA (defined as Kellgren–Lawrence grade $\geq 2$) or a minimum JSW $\leq 2$ mm (95% CI: 0–14%). There was no statistically significant correlation between the CE angle and the minimum JSW ($P = 0.47$). The FHEI correlated negatively to the minimum JSW ($P = 0.005$), $\beta = -0.04$ ($-0.07$ to $-0.01$). The Sharp angle correlated positively to the minimum JSW ($P = 0.023$), $\beta = 0.05$ (0.01–0.10). The minimum JSW did not correlate significantly to the dGEMRIC index ($P = 0.29$). In five hips (three subjects) there was a subtle possible osteophyte in the lateral aspect of the femoral head (Fig. 3). These five hips (shown as Kellgren–Lawrence 1 in Table I) did not differ significantly from the rest with regard to dGEMRIC index or any of the radiographic parameters (Table II).

There was no statistically significant correlation between the AI at age 1 year and any of the radiographic parameters at follow-up, including the dGEMRIC index.

dGEMRIC

The mean dGEMRIC index in the 40 investigated hips was 630 ms (95% CI: 600–666, range: 516–825). The results are listed in Table I. There was no statistically significant difference in the dGEMRIC index between neonatally stable and dislocated hips: 645 ms (95% CI: 603–688) and 625 ms (594–656) respectively ($P = 0.5$). Thirteen subjects had unilateral hip dysplasia (AI $\geq 28^\circ$) at age 1 year. In these subjects, the dGEMRIC index did not differ between the dysplastic and the contralateral hip at follow-up (paired $t$-test, $P = 0.97$) (Fig. 4).

All but one subject had a normal clinical MRI with no signs of labral tears or subchondral bone changes. Subject number 14 (Table I) demonstrated “very discrete subchondral sclerosis, labrae

![Fig. 2. Relations between radiographic parameters of hip dysplasia and cartilage quality assessed by dGEMRIC: a) the CE angle and the dGEMRIC index (a low CE angle consistent with hip dysplasia), b) the FHEI and the dGEMRIC index (a low FHEI consistent with hip dysplasia) and c) the Sharp angle and the dGEMRIC index (a high Sharp angle consistent with hip dysplasia). Each dot represents an individual hip.](image)
acetabuli that were not distinctly well-defined superolaterally and very discrete height reduction of the cartilage*.

Clinical outcome

No subject had a limp or a positive Trendelenburg sign. One subject had asymmetrical arcs of rotation (external/internal rotation: 60°/30° right, 40°/50° left). All other subjects had symmetrical (within 10°) range of motion. Mean values for hip range of motion were as follows: flexion: 126° (range 100–150), extension: 28° (15–45), abduction: 60° (35–85), adduction: 38° (25–50), external rotation: 52° (35–60) and internal rotation: 38° (20–50).

The mean 12-item WOMAC was 1.2 (95% CI: 0.02–2.5). There was one outlier scoring 11, marking 1 point on 11 separate items. The median score was 0.

Discussion

The main finding of this study is that patients with dysplastic hips at age 1 year after early treatment for NIH did not develop degenerative cartilage changes in early adulthood as shown by radiography and dGEMRIC. Still, some hips demonstrate radiographic OA (Tönnis 0–3)12. The hips with poor results had an average dGEMRIC index of 370 ms, with 9 of 10 hips having 500 ms in 9 of 20 subjects with radiographic DDH and hip dysplasia but no or minimal joint space narrowing (mean age 39 years) had 20–30% lower dGEMRIC index than the asymptomatic volunteers, with a mean dGEMRIC index of around 400 ms. In another study, Kim et al. found the same mean dGEMRIC index, 570 ms, in radiographically normal and asymptomatic hips with unilateral DDH, differentiating the healthy hips from their contralateral dysplastic counterparts14. Domayer et al. found dGEMRIC indices <500 ms in 9 of 20 subjects with radiographic DDH and hip symptoms25, although the mean dGEMRIC index in that cohort was 513 ms. In a study by Cunningham et al., the dGEMRIC index was the strongest predictor of early failure after a periacetabular osteotomy in adult DDH patients with various degrees of radiographic OA (Tönnis 0–3)12. The hips with poor results had an average dGEMRIC index of 370 ms, with 9 of 10 hips having <500 ms. Our study population consisted of 70% of the patients with the worst radiographic outcome at age 1 year of all cases treated early for NIH at our institution from 1987 through 1993. None of our subjects had a dGEMRIC index lower than 500 ms at follow-up in either hip. Despite that dGEMRIC is a highly sensitive method, it has several potential sources of error. As the contrast agent is water soluble, the distribution volume in the body is not directly proportional to body weight. This results in dosing bias in subjects with different BMI12. We have corrected for this confounder using the formula recommended by Tiderius et al.12. Cartilage thickness is another potential source of error in dGEMRIC. Due to slower diffusion of contrast agent into the deep regions of thicker cartilage, the dGEMRIC index can become falsely too long20. In this study the minimum JSW correlated negatively to the FHEI and positively to the Sharp angle. However, as the minimum JSW did not correlate to the dGEMRIC index, it seems unlikely that differences in cartilage thickness were responsible for the correlation between radiographic dysplasia and the dGEMRIC index. Another possible confounder is the subject’s weight. This results in dosing bias in subjects with different BMI12.

Table II

The five hips with a subtle possible osteophyte did not differ significantly from the rest with regard to the listed outcome variables

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* Mean (95% CI).
+ Median (interquartile range).

Fig. 3. A possible osteophyte on the lateral aspect of the femoral head in this case (arrow) was found in five hips (three subjects).
all individuals. The 10-min walk has been used at our institution for several years based on previously published data on asymptomatic subjects and patients with hip dysplasia.

A major problem with radiography in assessing OA is that radiographic changes appear late in the disease process, making radiography a suboptimal tool for evaluating the present type of study subjects. As expected, none of the subjects in this study had radiographic OA, defined as Kellgren–Lawrence grade II findings or higher. Neither did any subject have a minimum JSW of 2 mm or less, which is a radiographic finding associated with self-reported hip pain.

For evaluation of hip dysplasia in our skeletally mature subjects, three commonly used radiographic measures were chosen. The CE angle of Wiberg may be the most widely used measure of hip dysplasia in adults. CE angles below 20° are considered pathological and predict future OA development. We found a mean CE angle of 30° (29.9°), which is considered normal. Laborie et al. recently reported mean values around 31.5° (men: 32.1°, women: 31.0°), in a large reference population of healthy 19-year-old Norwegians. However, CE angles <28° have been shown to predict radiographic OA and THR at 20 year follow-up in a recent longitudinal cohort study on middle-aged women. We also assessed radiographic dysplasia both by measuring the FHEI according to Heyman and Herndon, again finding a mean value in the normal range. A third parameter of DDH, which is not affected by the position of the femoral head in the joint, but measures acetabular dysplasia, is isolated, is the Sharp angle. Ian Sharp himself considered values from 33° to 38° normal, and 39° to 42° “in the upper limit of normality”. The mean value in this cohort of 41° (40.8°) would thus be considered quite high, but it is almost identical with that reported in healthy 19-year-old women in Norway (40.7°). In a study on subjects undergoing closed reduction of hip dislocation at 1–46 months of age, age at reduction was the strongest predictor of radiographic outcome; reduction at an earlier age led to better results. Our subjects were all treated neonatally, but had not reached normal acetabular morphology at age 1 year. Unfortunately, we cannot evaluate the rate of acetabular remodeling due to lack of radiographic data between age 1 year and adulthood.

The 12-item WOMAC is a subset of questions from the widely used OA specific WOMAC PRO measure. The 12-item WOMAC shows internal construct validity and is able to discriminate between healthy controls, patients with a lesser degree of hip dysfunction and patients with established OA. Since we hypothesized that our study group would have no or only slight hip dysfunction, we chose the comparatively sensitive 12-item WOMAC to assess PRO. The subjects reported 12-item WOMAC scores on par with a previously published control population consisting of 200 subjects with no hip pain at a mean age of 32.6 years.

A higher AI at 1 year did not predict acetabular dysplasia at the completion of growth in this cohort. The finding that two of the three radiographic markers of dysplasia correlated to higher dGEMRIC indices (higher GAG content) is intriguing and somewhat surprising. Since acetabular dysplasia leads to higher joint contact pressures and is associated with a higher risk of developing OA in cohort studies of older subjects, we expected that hips with high Sharp angles or low CE angles and FHEI would have lower dGEMRIC indices. We hypothesize that the opposite finding could be explained by cartilage adaptation to increased mechanical demands in our “healthy” group of patients, where none had severe hip dysplasia and both PRO and dGEMRIC indices were considered normal. At this relatively young age (the mean age in our study was 21 years), it is possible that hip cartilage adapts, through increased GAG synthesis, to moderately increased mechanical stresses in the slightly dysplastic joint. Several clinical dGEMRIC studies of the knee, both on healthy volunteers with different levels of physical activity and middle-aged patients at increased risk of knee OA support the hypothesis of an adaptive capacity of human cartilage. A future follow-up, including dGEMRIC, may show if such adaptation is long-standing or if the increased mechanical demands on the joint ultimately lead to cartilage degeneration.

Children treated neonatally for NIH have good hip function and no signs of cartilage degeneration at 21-year follow-up, despite residual dysplasia at age 1 year. Radiographic signs of dysplasia were associated with better cartilage quality, as assessed with dGEMRIC. This finding may indicate adaptive properties of the cartilage to increased mechanical stress.

Author contributions

DW: study design, collection and analysis of data and writing of manuscript. CS: development of the software for T1Gd and dGEMRIC index calculation, and manuscript revision. LED and CJT: study design and critical revision of manuscript.

Conflict of interest

The authors declare no competing interests.

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