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Diagnostic performance of knee ultrasonography for detecting degenerative changes of articular cartilage

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S U M M A R Y

Objective: To investigate the diagnostic performance of non-invasive knee ultrasonography (US) to detect degenerative changes of articular cartilage using arthroscopic grading as the gold standard.
Design: Forty adult patients referred to a knee arthroscopy because of knee pain were randomly selected for the study. Before the arthroscopy, knee US was performed and cartilage surfaces at medial and lateral femoral condyles as well as at intercondylar notch area (sulcus) were semi-quantitatively graded from US. Ultrasonographic grading was compared with the arthroscopic Noyes' grading for cartilage degeneration.
Results: Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic odds ratio for detecting arthroscopic cartilage changes in US varied between 52 and 83%, 50–100%, 88–100%, 24–46%, and 5.0–13.0, respectively, depending on the site. Correlation of severity of cartilage changes (grades) between US and arthroscopy varied from insignificant to significant depending on the site: at the sulcus area the correlation was highest ($r_s = 0.593$, $P < 0.001$), at the medial condyle also significant ($r_s = 0.465$, $P = 0.003$), and at the lateral condyle non-significant ($r_s = 0.262$, $P = 0.103$). The sum of cartilage grades in all three sites of the femoral cartilage between US and arthroscopy had the highest correlation ($r_s = 0.655$, $P < 0.001$).
Conclusions: Positive finding in US is a strong indicator of arthroscopic degenerative changes of cartilage, but negative finding does not rule out degenerative changes. Non-invasive knee US is a promising technique for screening of degenerative changes of articular cartilage, e.g., during osteoarthritis.

Introduction

Osteoarthritis (OA) is the most common joint disease, and causes joint pain, disability and health-care expenditure in an ageing society[1]. It has been estimated that about half of elderly people are suffering joint pain symptoms[2]. OA affects typically knee, hip, spine and hand joints[3]. Traditionally, OA has been characterized with progressive degeneration of the articular cartilage along with abnormal changes in the underlying subchondral bone.

Although there is not yet an effective cure for OA, sensitive and cost-effective diagnostic methods for OA at an early stage are important for proper treatment with lifestyle changes, physical therapy and medication. Furthermore, diagnostic sensitivity is needed in the development of new disease modifying drugs and in their subsequent clinical trials.

Non-invasive ultrasonography (US) of the joints offers non-invasive, fast, and inexpensive imaging method of OA[4]. If an acoustic window is available, such as in knee and metacarpophalangeal joints, significant portion of the articular surfaces can be clearly visualized, although access to some parts of weight bearing areas is limited. Recently there has been an increasing interest to use non-invasive US for diagnostics of OA-related changes in articular cartilage[5,6]. However, the technique still needs more clinical validation. Especially, there are no studies comparing non-invasive US with the current gold standard for diagnostics of degenerative changes in articular cartilage, i.e., arthroscopy.

In the present study, we aimed to clarify the diagnostic performance of non-invasive knee US to detect degenerative changes of

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articular cartilage using arthroscopic grading as the golden reference standard.

Methods

Study group

Forty patients (15 women and 25 men) with knee pain were recruited in the study. They underwent a knee arthroscopy in the Mikkeli Central Hospital, and were randomly selected for the study from the orthopaedic day-surgery patient list. The pre-diagnosis or other background information of the selected patients was not known before the selection. The mean age of patients was 52 years (range 37–73 years) and the mean body mass index (BMI) was 27.5 (range 24–35). Patients under 30 years of age were excluded from the study because of lower prevalence of OA in this age group. Altogether five patients were excluded from the study for the following reasons: two patients were under the age of 30 years, and in three others the orthopaedic surgeon cancelled the arthroscopy as unnecessary. All patients gave written informed consent and the study was approved by the ethics committee of the Mikkeli Central Hospital.

Ultrasound scanning and grading

US examination of the knee joint was conducted for each patient 1 h before the arthroscopy. The US equipment used was Esaote Technos with a 13 MHz linear probe (LA424) (Esaote Biomedica, Via Siffredi 58, 16153 Genova, Italy). The grey scale settings of the machine were kept constant for every patient and they were as follows: depth = 35 mm, gain = 145 dB, enhancement = 11, mechanical index = 0.9, soft tissue thermal index = 0.5, processing parameter = 8 and scan correlation parameter = 6. To ensure the constant performance of the US equipment and the used probe throughout the study, quality assurance measurements were conducted before the study. For grey scale imaging, a general purpose commercial CIRS Model 40 phantom (CIRS Inc., Norfolk, VA, USA) was used. In quality assurance measurements, the near-field resolution, axial resolution and lateral resolution of the system were <1.0 mm, <0.5 mm and <1.0 mm, respectively. The maximum penetration depth with this probe was 55.1 mm.

The sonographer (JMK), who has over 20 years experience in musculoskeletal sonography, was blinded to the history, clinical findings and imaging data of the patients. In the evaluation of degenerative changes in femoral articular cartilage, a patient was in supine position and a knee was fully flexed (120°, succeeded in every patient). First, the intercondylar notch area, including femoral condyles just above patellar bone (later called sulcus), was depicted. Subsequently, the cartilage in medial and lateral femoral condyles were fully scanned by sweeping the full surfaces of the cartilage from proximal to distal with the probe always in transverse position (Fig. 1). The ultrasound beam was kept perpendicular to the surface of femur all the time. The cartilage were subjectively evaluated as normal (grade 0) if they showed a monotonous anechoic band having a sharp hyperechoic anterior and posterior interfaces. Grade 1 degenerative changes (mild) were: loss of the normal sharpness of cartilage interfaces and/or increased echogenicity of the cartilage (one point for each observation site, thus maximum of three points if the findings were present in both condyles and in sulcus). Grade 2A degenerative changes (moderate) were: in addition to above changes, clear local thinning (less than 50%) of the cartilage was observed. Grade 2B degenerative changes were: local thinning of the cartilage more than 50% but less than 100% (two points at each observation site, maximum of six points). Grade 3 degenerative change (severe) was: 100% local loss of the cartilage tissue (three points, maximum of nine points). Scanning of one knee with documentation lasted about 10 min as a whole. Typical examples of different US cartilage grades are shown in Fig. 2.

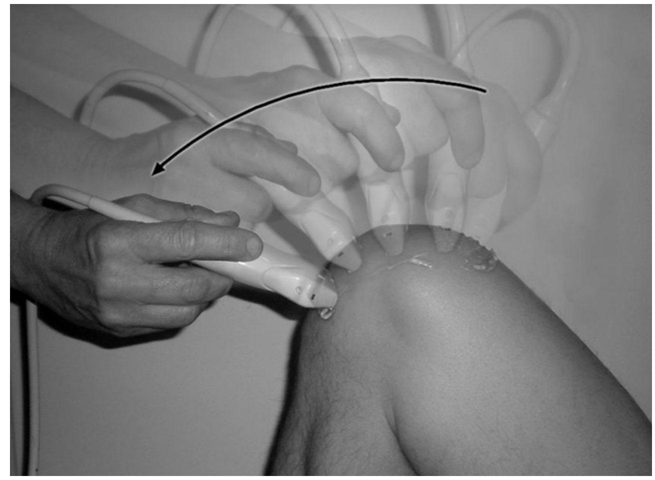

Fig. 1. The schematic presentation of the US scanning technique for detection of cartilage changes in the knee joint. Femoral medial, lateral, as well as intercondylar (sulcus) area are sweeped separately from proximal to distal.

Arthroscopy (gold standard)

After the US examination, arthroscopy of the knee was performed by an orthopaedic surgeon (PW, VW, IT, EK) who was blinded to the US findings and grade but not to the clinical history or other imaging findings of the patients. Cartilage surfaces of the medial and lateral femoral condyles, sulcus, as well as medial and lateral tibial plateaus were evaluated using the Noyes' grading scale[7]: grade 0 is normal; grade 1A represents mild softening or colour changes of the cartilage; grade 1B severe softening or colour changes; grade 2A partial cartilage defect of less than 50%; grade 2B partial cartilage defect more than 50% but less than 100%; grade 3A 100% defect of the cartilage with normal bone; and grade 3B is 100% defect with bone erosion.

Statistical analysis

Statistical analyses were conducted with SPSS software (ver. 17, SPSS Inc., Chicago, IL, USA) together with manual calculations. Sensitivity[8], specificity[8], positive predictive value[9], negative predictive value[9], positive likelihood ratio[10], negative likelihood ratio[10], and diagnostic odds ratio[11] were calculated by comparing US findings with arthroscopic findings separately in each site (medial condyle, lateral condyle, and sulcus area). Grade 0 was defined as normal (negative finding) in both US and arthroscopy, whereas grade ≥ 1 was defined as abnormal (positive finding). In the calculation of confidence intervals, we used the Score method with continuity correction as described by Newcombe (1998)[12].

In order to investigate the relation between the severity of grades between US and arthroscopy, Spearman's correlation analysis was applied. Spearman's analysis was chosen instead of Pearson since the semi-quantitative grading scales are not continuous. In all statistical analyses, $P < 0.05$ was considered as significant.

In addition to investigating US and arthroscopic findings separately in each site, the sum grade was also calculated by summing the grades from all three sites for US and arthroscopy. As a result, two sum grades for each patient were obtained, one grade for US and one

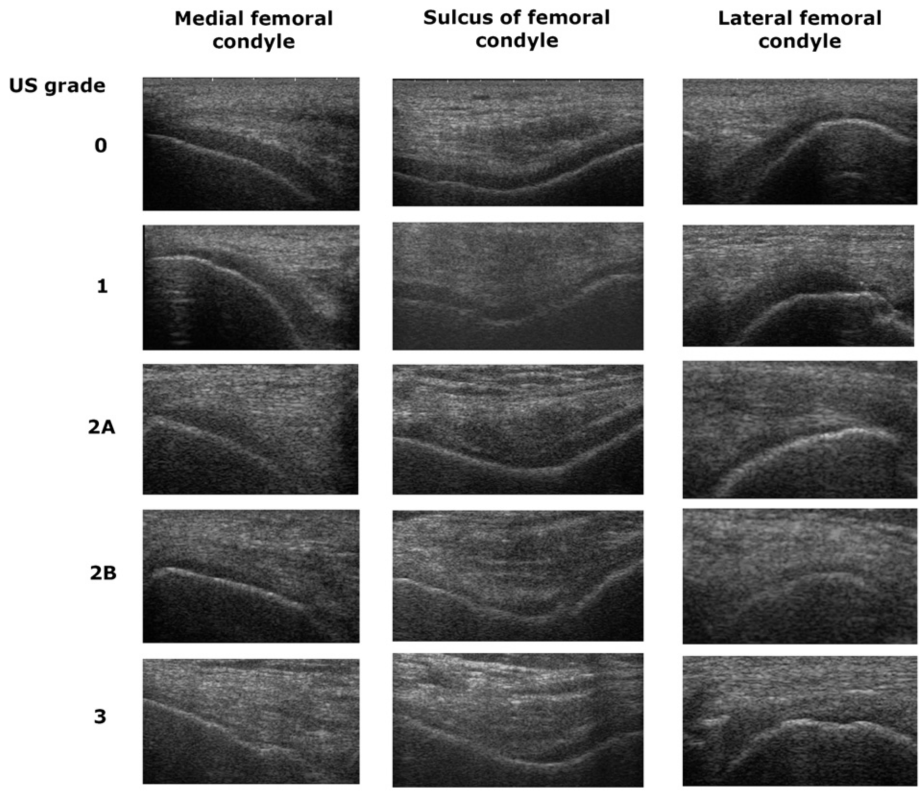

Fig. 2. Typical examples of different cartilage degenerative US grades (0, 1, 2A, 2B, 3) in the knee joint. For the definition of different grades, see the Methods.

for arthroscopy. These sum grades between US and arthroscopy, including cartilage changes from all three sites together, were then cross-correlated using the Spearman's analysis.

Results

Cross-tabulation of number of cases between US and arthroscopy with normal (negative) and abnormal (positive) findings in articular cartilage of femoral sulcus area, femoral medial condyle, and femoral lateral condyle is presented in the Table I. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio of US for detecting arthroscopic cartilage changes varied much depending on the site (Table II). The specificity was good in the femoral sulcus and lateral condyle, but not in the medial condyle. The sensitivity was good (83%) only in the medial femoral condyle. It is notable that the positive predictive value was strong in all sites being in the range of 88–100%. On the other hand, the negative predictive value remained low being in the range of 24–46%. The diagnostic odds ratio, a general indicator of test performance, of US varied between 5.0 and 13.0.

Correlation of severity of cartilage changes (grades) between US and arthroscopy varied from significant to insignificant depending on the site: at the sulcus area the correlation was highest [Fig. 3(A)], at the medial condyle it was also significant [Fig. 3(B)], but at the lateral condyle it remained low and non-significant [Fig. 3(C)]. The sum of grades from all three sites of the femoral cartilage between US and arthroscopy had the highest correlation [Fig. 3(D)].

Table I
Cross-tabulation of number of cases between US and arthroscopy with normal (negative) and abnormal (positive) findings in articular cartilage of femoral sulcus area, femoral medial condyle, and femoral lateral condyle. These data were used in the calculation of indicators of diagnostic performance

		Arthroscopy	
		Positive	Negative
Ultrasound	Positive	19	0
Sulcus area	Negative	16	5
Ultrasound	Positive	30	2
Medial condyle	Negative	6	2
Ultrasound	Positive	14	2
Lateral condyle	Negative	13	11

Discussion

For the first time, the diagnostic performance of non-invasive knee US to detect degenerative changes of articular cartilage, using arthroscopic grading as the reference, was reported. The results indicate that abnormal finding in knee US is a strong indicator of arthroscopic degenerative changes of cartilage. On the other hand, negative finding in US does not rule out arthroscopic degenerative changes. Furthermore, significant correlations of cartilage grades between US and arthroscopy suggest that US has a predictive value in detecting severity of cartilage degenerative changes at least at the femoral medial condyle and the sulcus area.

Lower and statistically insignificant correlation of cartilage grades between US and arthroscopy at the lateral condyle was probably a consequence of poorer accessibility of US for the lateral side because of the patellar shadow. Furthermore, our impression while analyzing the data was that in some cases the same cartilage pathology had been classified for different site in US and arthroscopy if it was located on the border of sulcus and condyle. Thus, the sonographer and arthroscopist might have meant the same lesion but have classified the lesions for different sites. For this reason, it was also important to evaluate the overall correlation of the sum of cartilage grades from all three sites, which was not affected by the

Table II
Indicators of diagnostic performance of US in femoral sulcus area, femoral medial condyle, and femoral lateral condyle

	Femoral sulcus area	Femoral medial condyle	Femoral lateral condyle
Sensitivity:	54.3% (36.9%–70.8%)	83.3% (66.5%–93.0%)	51.9% (32.4%–70.8%)
Specificity:	100.0% (46.3%–100.0%)	50.0% (9.2%–90.8%)	84.6% (53.6%–97.3%)
Positive predictive value:	100.0% (79.1%–100.0%)	93.8% (77.8%–98.9%)	87.5% (60.4%–97.8%)
Negative predictive value:	23.8% (9.1%–47.5%)	25.0% (4.5%–64.4%)	45.8% (26.2%–66.8%)
Positive likelihood ratio:	6.5* (0.4–93.9)	1.7 (0.6–4.5)	3.4 (0.9–12.7)
Negative likelihood ratio:	0.5* (0.3–0.7)	0.3 (0.1–1.1)	0.6 (0.4–0.9)
Diagnostic odds ratio:	13.0*	5.0	5.9

* Since there were zero false positives in femoral sulcus cartilage, a value of 0.5 was added to all observed counts in 2×2 table as suggested by Cox (1970)[22]. It should be noted that 0.5 was added only when calculating likelihood and odds ratios, since zero value does not affect calculations of sensitivity, specificity and predictive values.

possible misclassification. This correlation demonstrated to be the highest ($r_s = 0.655$). Consequently, non-invasive US of the knee has a significant predictive value for arthroscopic cartilage changes at femoral cartilage in general. However, in further studies, there should be also mapping or comparison of the specific cartilage lesions between the US scanning and other examination methods, e.g., magnetic resonance imaging (MRI) or arthroscopy, to verify that the same lesions are evaluated with different methods.

It would have been also interesting to calculate the indicators of diagnostic performance for the sum of cartilage grades from all three sites between US and arthroscopy. However, we were not able to do that because in the current patient material only one patient had completely normal arthroscopic findings in all three sites, and all the other patients had degenerative cartilage changes from mild to moderate at least in one site. Thus, more completely normal subjects would have been needed for the calculation of sensitivity and specificity values for the sum of cartilage grades. The determination of diagnostic performance of the US sum grade might be difficult also in the future since arthroscopy is an invasive procedure and planning of the study exposing non-symptomatic subjects, in which the completely normal findings could be expected in all areas of femoral cartilage, to any invasive procedure would not be ethically justified. However, the good correlation between the US sum grade and arthroscopy sum grade strongly suggests that US is capable to detect early OA changes in articular cartilage.

Currently, there is no generally accepted US grading scale for cartilage changes in knee OA. Therefore, we presented here a new US scoring method which was directly adopted from the Noyes' scoring system for arthroscopy[7]. This simple scoring method can be easily used to compare US scanning results with the arthroscopic findings. It is notable that we did not use quantification of the cartilage thickness in classification, because it has been shown earlier that that the thickness varies considerably both in healthy persons and in patients with OA[13–15]. Thus, the evaluation of the thinning of cartilage in each patient is based on the comparison of cartilage to adjacent areas of the same patient. The identification of an abnormal thinning using US is relatively easy with moderate and severe cartilage changes. However, as the US evaluation of thinning is based on comparison of cartilage to adjacent areas in the same patient, detection of early OA thinning is more difficult.

In this study, we did not observe any effect of BMI to the quality of the US imaging, although there were not very obese persons, i.e., BMI > 35, in this study. According to the experience of the authors there are no significant problems in the US scanning of the knee in very obese persons. In general, there are some other limitations related to external US of the knee joint. First, it is possible to scan only part of the femoral condyle cartilage because of the shadow of the patella. In the future, it is important to accurately clarify how much of the weight-bearing femoral cartilage, most commonly affected in knee OA, can be depicted with the external US modality. In this study, we chose transverse US scanning technique that

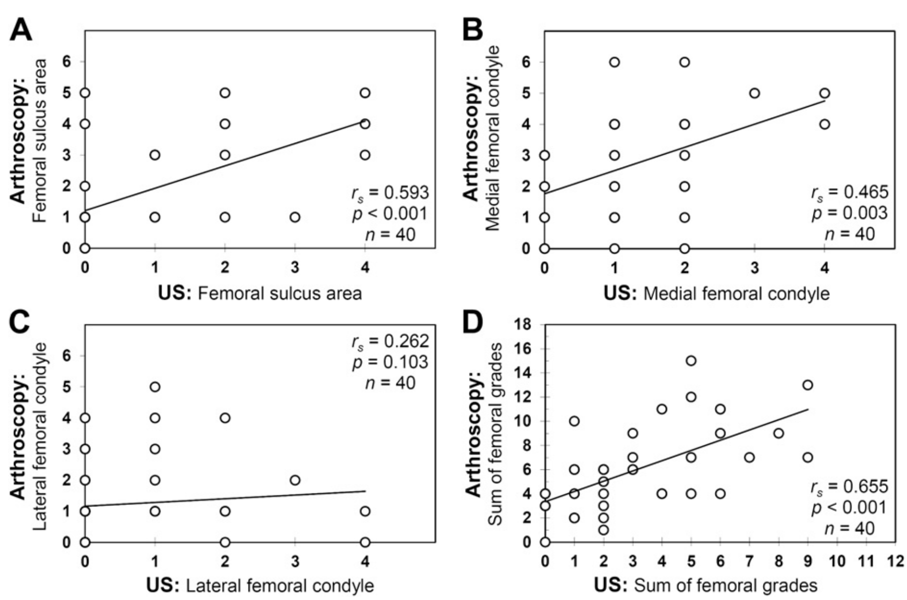

Fig. 3. Spearman's correlation graphs between US and arthroscopy cartilage grades. (A) Correlation in femoral sulcus area, (B) Correlation in femoral medial condyle, (C) Correlation in femoral lateral condyle, (D) Correlation between the sum of cartilage grades from all three sites of the femoral cartilage. In the figures, US grades 0, 1, 2A, 2B, and 3 are coded as 0, 1, 2, 3, and 4, respectively. Similarly, Noyes' arthroscopic grades 0, 1A, 1B, 2A, 2B, 3A, and 3B are coded as 0, 1, 2, 3, 4, 5, and 6, respectively.

proved to be the best approach according to the earlier investigations. However, further studies will show whether the longitudinal scanning of the knee joint cartilage could offer some extra benefit especially when depicting weight-bearing cartilage of the medial femoral condyle. Fusion imaging with modern US scanners together with anatomical MRI or computed tomography (CT) images might also offer a new way for these investigations.

As a second major limitation, external US has no access to the tibial plateau cartilage, although in the current patient population arthroscopic cartilage changes existed always together on the femoral and tibial sides. It should be also remembered that US has a limited role in the assessment of the menisci and subchondral bone, which have been shown to play a relevant role in the natural history of tibiofemoral OA.

Taken together, US grading still needs further validation, especially for early OA changes, before it can be recommended in routine clinical use. The new validation studies might include, e.g., quantitative MRI or histology as references. Furthermore, intra-observer and inter-observer reproducibilities should be investigated. It is also notable that with external US it is possible to evaluate joint effusion and synovitis, bony structures related to OA such as osteophytes and possibly also subchondral bone, and periarticular soft tissues like bursae and tendons[13–19]. The US grading of abnormal changes in those tissues in different stages of OA could be investigated and compared with reference techniques.

In the present study, the severity of knee pain was not asked from the patients. This was ignored because we wanted to confirm that the information of the pain level would not affect the grading results of US and arthroscopy. Since our aim was to relate between findings from two different diagnostic techniques, not to relate diagnostic findings with pain level, this is not a significant limitation of the present study.

Other general limitations of the study design are a relatively small study group and the use of a single observer in US grading. However, it is notable that the observer was blinded to patient anamnesis and their clinical, arthroscopy and radiographic findings.

In this study, we did not conduct any quantitative analysis of US imaging, e.g., mean grey-level values and grey-level variations inside region(s)-of-interest of cartilage or subchondral bone. It has been reported that ultrasound reflection intensity in the cartilage layer and in the subchondral bone, when measured directly on the cartilage surface, are sensitive for histological early OA changes both *in vitro* and *in vivo* during arthroscopy[20,21]. On the other hand, quantitative image analysis of non-invasive US of the knee joint, besides just measuring cartilage thickness, has not been reported. In principle, quantitative analysis might give more sensitive information of early OA than our semi-quantitative grading scale, which is subjective and dependent on the sonographist's experience. However, quantitative analysis of non-invasive external US has many challenges, e.g., attenuation effects of overlying soft tissues as well as different settings of the US equipment. Therefore, quantitative non-invasive external US requires detailed investigations, and could be a subject of completely new studies.

As a conclusion, the present study clearly demonstrates that positive finding in US is a strong indicator of arthroscopic degenerative changes of cartilage, but negative finding does not rule out degenerative changes. Since conventional ultrasound devices are widely available, diagnosis of early OA changes by US might improve current patient identification and treatment selection in the future. Thus, epidemiological studies as well as drug treatment follow up of OA might be possible with better performance than with the current, easily available diagnostic techniques. However, the limitations of US needs to be approved, and when the US finding is negative one must consider additional diagnostic modalities, e.g., MRI or arthroscopy, to verify the degenerative status of the articular surface.

Author contributions

SS: conception and design, analysis and interpretation of the data, statistical expertise, drafting of the article, and final approval of the article.

PW: collection of data (arthroscopic grading), critical revision of the article for important intellectual content, and final approval of the article.

VW: collection of data (arthroscopic grading), critical revision of the article for important intellectual content, and final approval of the article.

IT: collection of data (arthroscopic grading), critical revision of the article for important intellectual content, and final approval of the article.

EK: collection of data (arthroscopic grading), critical revision of the article for important intellectual content, and final approval of the article.

JA: collection of data (quality assurance measurements for US device), critical revision of the article for important intellectual content, and final approval of the article.

JMK: conception and design, collection of data (US scanning), analysis and interpretation of the data, drafting of the article, and final approval of the article.

Conflict of interest

None of the authors have any competing interests.

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