Ultrasonography of joints and correlation with function in Haemophilic Arthropathy - interim results of a clinical pilot trial (HämarthroSonoPilot)

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Aims and objectives

Sonography is well-used in routine clinical practice to examine joint bleedings in patients with severe bleeding disorders like Haemophilia A, Haemophilia B or severe forms of the von Willebrand's disease (espacially type 3). In Germany, about 4,000-5,000 patients living with severe or moderately severe haemophilia.

Joint damage from bleeding complications affect 90% of the patients with severe haemophilia and represent the vast majority of the complications of this disease. Ankle joints, knees and elbows are most commonly affected and good accessible by ultrasound examination. The haemophilic arthropathy (HA) is caused by recurrent haemorrhages in the joints. Even by prophylactic treatment with coagulation factor concentrates not every synovial haemorrhage can be prevented: Despite prophylaxis subclinical bleedings can occur, recurrent events lead to synovitis, following an increasing synovial hypertrophy with long-term failure load of joint-forming structures, particularly the knees and the ankles.

The 3D-motion-analysis helps to understand these processes by providing information about the forces and stresses acting on the joints during movement. But the 3D motion analysis does not provide information on the structural changes of hemophilic joints.

Conventional radiography is used to represent osseous destruction with progressive changes of hemophilic arthropathy. However, frequent follow-up of joint changes are hereby not recommended because of the radiation exposure. In addition, conventional radiography can not adequately present synovitis, small bruises or minor cartilage defects. The sensitivity to inflammation of the synovium, especially in the early stages of the disease, is very limited. In contrast, Magnetic resonance imaging (MRI) provides detailed information on all aspects of haemophilic joint changes such as effusion, synovial hypertrophy, bleeding and early osteochondral abnormalities, but it's expensive and not readily available.

Diagnostic Ultrasound is more sensitive than radiography in the detection of joint effusion and synovial changes. Compared with MRI, sonography provides a shorter examination time, lower costs and requires even in young patients, no sedation or anesthesia. However, the ultrasound has restrictions such as higher examiner dependence and only partially representability of many joints as osseous structures can't be penetrated by the diagnostic ultrasound.
Up to now some protocols for examination of the joints of haemophiliac patients with ultrasound were published to show signs of HA with effusion, synovitis, cartilage defects or subchondral bone damage. None of the so far published protocols was standardized and feasible enough to be used by the haemophilia treaters themself during routine examination in outpatient departments. In 2013 the first easy-to-learn standardized protocol and scoring system (HEAD-US) for scanning HA-joints with ultrasound was published by C. Martinoli. For the presentation of synovitis or effusions as a sign of activity and defects of the articular cartilage or subchondral bone as a sign of progression of HA standardized sonographic section planes are therefore now available.

Prior to this study no correlation of function and imaging of joints with HA was investigated. In this investigator-initiated-pilot-trial (supported bei Pfizer Deutschland GmbH, Germany and Baxter Deutschland GmbH, Germany) sonographic findings in HA are correlated with data from an ultrasonic motion-analysis of the knees and the results of an orthopedic examination for the first time worldwide.

**Images for this section:**

![Ultrasound image in case of Haemophilic Synovitis of the ankle](image)

*Fig. 1: Ultrasound image in case of Haemophilic Synovitis of the ankle*
Fig. 5: Haemophilic Arthropathy of the knees after joint bleedings
Methods and materials

First experiences were made in a group of 177 young German patients (3-51 years, median 15.3) with hemophilia A (75%), B (16%) or von Willebrand's disease (7%).

Standardized ultrasonography of the elbow, knee and ankle joints with a high-level-ultrasound machine (DEGUM class 3: Zonare z.one ultra) with a linear transducer (L14-5w) and simultaneously a clinical examination of the joints and a 3D-motion-analysis with an Ultrasound-Topometer of the knees were performed.

The Ultrasound-Topometer (developed at the University of Bonn, Germany) measures the time required for ultrasonic pulses from transmitters at defined points on the body of the patient (in motion) to four receivers, mounted in a rigid frame. The velocity of the ultrasonic wave and the length of the frame are known, therefore the exact location of limbs during the movement on a millimeter scale can be measured. A software program then calculates the angle, speed and acceleration. The calculated Motion-Score based on the magnitude of the deviation from the physiological, rhythmic movement, with higher values reflect a physiological movement with rolling instead of sliding movements.

Joint ultrasound characteristics were scored with the Score developed by C. Martinoli (HEAD-US). The scores and the results of the clinical orthopedic examination and the gait-analysis were correlated.

Images for this section:

Fig. 2: standard sonographic section planes for calculating the sonographic score (HEAD-US)
Fig. 3: clinical examination of trigger points

Fig. 4: 3D-motion-analysis (Ultrasound-Topometer)
### Disease Activity

#### Synovitis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophic Synovium</td>
<td>0</td>
</tr>
<tr>
<td>0. Absent/Minimal</td>
<td>1</td>
</tr>
<tr>
<td>1. Mild/Moderate</td>
<td>2</td>
</tr>
<tr>
<td>2. Severe</td>
<td></td>
</tr>
</tbody>
</table>

#### Disease Damage

**Articular Surfaces**

- **Cartilage**
  0. Normal
  1. Echotexture abnormalities, Focal partial/full-thickness loss of the articular cartilage involving <25% of the target surfaces
  2. Partial/full-thickness loss of the articular cartilage involving at least ≤50% of the target surface
  3. Partial/full-thickness loss of the articular cartilage involving >50% of the target surface
  4. Complete cartilage destruction or absent visualization of the articular cartilage on the target bony surface

- **Bone**
  0. Normal
  1. Mild irregularities of the subchondral bone with/without initial osteophytes around the joint
  2. Deranged subchondral bone with/without erosions and presence of prominent osteophytes around the joint

**Notes:**

- ELBOW: anterior aspect of the distal humeral epiphysis
- KNEE: femoral trochlea
- ANKLE: anterior aspect of the talar dome

**Fig. 6:** HEAD-US-Score (Haemophilia Early Arthropathia Detection with Ultrasonography)
Results

In patients with significant disease activity in the HEAD-US ultrasound score (activity \( \geq 1 \)) and clinical remarkable capsule pain and/or swelling also strikingly pathological sliding in motion analysis can be detected except some patients. In many patients with an abnormal sonographic score for the activity of haemophilic arthropathy (activity \( \geq 1 \)), no clear clinical joint pathology shows in the orthopedic examination, but in some patients without clinical signs in the examination a bad rolling-sliding ratio in the motion analysis attracts attention.

Except for central damage on the whole cartilage and bone defects of the joints are sonographically sufficiently well represented and quantified with the HEAD-US Score (by C. Martinoli) in patients with HA. Interestingly many joints (especially ankle joints) were sonographic affected by HA without any clinical signs. These findings are according to early published investigations in clinical not suspicious ankle joints with MRI (e.g. by Olivieri et al.).

In statistical data analysis a correlation between sonographic findings and clinical investigation of the ankle joints was seen. For the other investigated joints no good correlation between ultrasound and clinical investigations was found. These findings demonstrate, that the ultrasound and clinical investigations are independently useful in investigation of patients with early HA.

Because the results of the gait analysis are subjected especially in young patients disturbances such age-dependent coordination weakness perhaps a larger group of patients is needed to perform statistical analysis. These findings are according to new published investigations (see also the review article by Stephenson in Hemophilia 2013). But in age-independent analysis of our patients without sonographic findings (no synovitis, cartilage or bone defects) no correlation was found between coordination and gait analysis also.

In young patients from many different german haemophilia treatment centers (consistent treated with prophylaxis) compared to the results in the elderly patients (mostly treated with coagulation factors only on demand) significantly less damage to the articular cartilage and adjacent structures was shown.

Images for this section:
Fig. 7: results: percentage pathological sonographic findings of all examined hemophiliac joints
**Fig. 8:** percentage of joints with sonographic detection of damages in all examined patients
Conclusion

Diagnostic ultrasound is clinical used for imaging of effusion, bleeding, synovialitis, cartilage or bone damage in joints of haemophiliac patients. For the presentation of synovitis as a sign of activity and of defects of the articular cartilage and bone as a sign of progression of hemophiliacs arthropathy (HA), standardized section planes are now available (C. Martinoli).

This pilot trial in a cohort of 177 german haemophiliacs correlating a standardized sonographic diagnosis for detection of disease activity and joint function of a HA shows age-dependent promising results. Joint sonography shows some changes already before that stood out in the clinical examination.

Because of our findings it appears useful if haemophilia treaters in future learn and apply this method to control the therapy under close control and evaluation of joint changes. A good collection of joint changes is a good base for an optimal control of a modern individualized prophylaxis of haemophiliacs: The success of prophylactic factor substitution is with the ultrasound examination of the joints captured very well at any time.

Personal information

References


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