



# The role of orthopaedic surgery in haemophilia: current rationale, indications and results

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- The musculoskeletal problems of haemophilic patients begin in infancy when minor injuries lead to haemarthroses and haematomas.
- Early continuous haematological primary prophylaxis by means of the intravenous infusion of the deficient coagulation factor (ideally from cradle to grave) is of paramount importance because the immature skeleton is very sensitive to the complications of haemophilia: severe structural deficiencies may develop quickly.
- If primary haematological prophylaxis is not feasible due to expense or lack of venous access, joint bleeding will occur. Then, the orthopaedic surgeon must aggressively treat haemarthrosis (joint aspiration under factor coverage) to prevent progression to synovitis (that will require early radiosynovectomy or arthroscopic synovectomy), recurrent joint bleeds, and ultimately end-stage osteoarthritis (haemophilic arthropathy).
- Between the second and fourth decades, many haemophilic patients develop articular destruction. At this stage the main possible treatments include arthroscopic joint debridement (knee, ankle), articular fusion (ankle) and total joint arthroplasty (knee, hip, ankle, elbow).

**Keywords:** haemophilia; haemophilic arthropathy; orthopaedic surgery

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## Introduction

The clinical severity of haemophilia is usually related to the plasma level of factor VIII or factor IX. Patients are classified as having mild, moderate or severe haemophilia depending on the level of the deficient factor, which can be > 5% of normal in mild cases and < 1% of normal in severe haemophilia. This is reflected in the frequency and causes of bleeding. Whereas a patient with mild haemophilia will bleed rarely, usually only after significant trauma or surgery, those with severe haemophilia may

have several episodes per month, and typically bleed spontaneously as a result of minimal trauma or activities of daily living.<sup>1</sup>

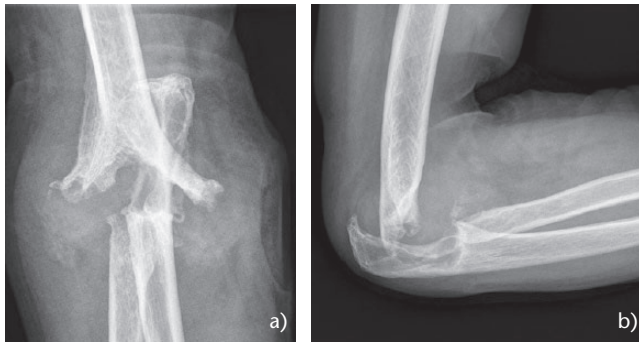
About 90% of bleeding episodes in haemophilic patients occur within the musculoskeletal system and, of these, 80% occur within the joints (mainly elbows, knees and ankles). Planning and undertaking elective orthopaedic surgery in haemophilic patients is most effective with the involvement of an experienced multidisciplinary team (MDT) at a specialized haemophilia treatment centre.<sup>2</sup> The team at least requires a haematologist, whose function is to control haemostasis, an orthopaedic surgeon, a physical medicine and rehabilitation physician, and a physiotherapist. At all stages the patient should be informed to ensure that their expectations and functional goals are realistic and can be accomplished. The planning phase should ensure that surgery proceeds without complication, but the surgical team should be ready to handle unanticipated problems. Postoperative rehabilitation should begin soon after surgery, with attention paid to treatment of haemostasis and pain. Surgery in patients with inhibitor requires even more careful preparation.<sup>2</sup>

## Bleeds within the joints

The vast majority of bleeding episodes in haemophilic patients occur within the joints (haemarthrosis). Of these haemorrhages, the knees, elbows and ankles account for almost 80%. The patient's initial perception of an acute haemarthrosis often starts as an aura or a tingling sensation in the joint. The involved articulation is usually held in flexion, swollen (fluid content on palpation), and active and passive motion is painful and very restricted.<sup>3</sup>

## Pathogenesis

With the early intravenous provision of the missing coagulation factor, haemorrhages can be controlled and conservative orthopaedic management can usually terminate the episode without any long-term complications. Should the haemorrhage persist or a re-bleed occur, intra-articular



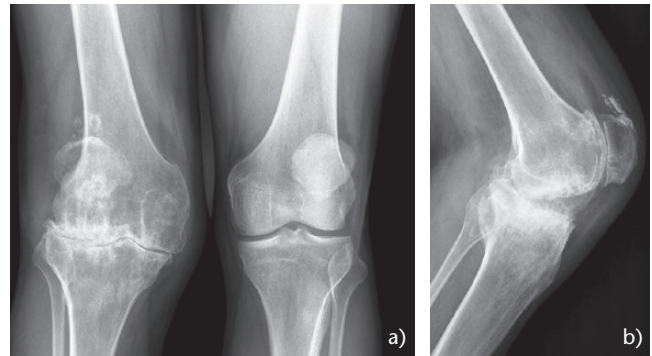
**Fig. 1** Elbow haemophilic arthropathy: (a) anteroposterior radiograph; (b) lateral view.

blood causes apoptosis of the chondrocytes. At the same time the synovial membrane tries to reabsorb blood and begins to hypertrophy when there is too much blood in the joint. Then a vicious cycle of chronic synovitis develops, leading to joint destruction and classical haemophilic arthropathy.<sup>4</sup> The hypertrophic synovium is characterized by villous formation, marked increased vascularity (neoangiogenesis), and the chronic presence of inflammatory cells. In children, synovitis causes hypertrophy of the epiphyseal growth plates. Bone hypertrophy may lead to leg-length discrepancies, angular deformities and alterations of contour in the developing skeleton.<sup>5</sup> If the synovitis is not controlled, further cartilage damage will follow. The synoviocytes disintegrate and release lysosomal enzymes, which not only destroy articular cartilage but also further inflame the synovium. The haemosiderin staining of the synovium and cartilage bears testimony to the destructive elements of proteolytic enzymes. Symptoms of chronic arthropathy typically develop by the second or third decade. As the joint cartilage progressively degrades, deterioration in joint function occurs (limited and painful movements) (Figs. 1, 2 and 3).<sup>3</sup>

### Haematological prophylaxis

Continuous prophylactic intravenous clotting factor replacement has been reported to slow the natural course of haemophilic arthropathy. Many authors have stated that continuous haematological prophylaxis from two to 18 years prevented the development of haemophilic arthropathy if the concentration of the patient's deficient factor was prevented from falling below 1% to 3% of normal. This can be achieved with the intravenous infusion of 25 to 40 U/kg factor VIII three times weekly in patients with haemophilia A and 25 to 40 U/kg factor IX twice weekly in patients with haemophilia B.<sup>6,7</sup>

The most feared and clinically significant complication of factor replacement is the development of alloantibodies (inhibitors) directed against the exogenous factor VIII



**Fig. 2** Haemophilic arthropathy of the knee joint: (a) anteroposterior view; (b) lateral radiograph.

molecules which inhibit the function of the replacement factor VIII.<sup>8</sup> Inhibitors to factor VIII occur in about one-third of those with severe haemophilia A, typically within the first 20 exposures to exogenous factor VIII early in the first 2–3 years of life when venous access is a challenge.<sup>9</sup> The development of inhibitors to factor VIII results in a significant increase in the likelihood of morbidity due to uncontrollable bleeding.<sup>10</sup>

A new drug called Emicizumab has been developed for the treatment of patients with haemophilia A. Emicizumab-kywh (ACE910) is a recombinant, humanized, asymmetric bispecific antibody that functions to bring activated factor IXa and zymogen factor X into an adequate steric conformation to mediate the activation of factor X to factor Xa thereby mimicking the cofactor function of factor VIIIa.<sup>11</sup> Once-weekly subcutaneous injection of Emicizumab at three dose levels has been demonstrated to be efficacious as prophylaxis to prevent bleeding in most haemophilia A patients with inhibitors to factor VIII. Moreover, in more than two-thirds of patients without inhibitors to factor VIII, prevention of bleeding has been demonstrated. The mean annual treated bleeding rates were diminished in patients with as well as those without an inhibitor to factor VIII. The main advantage of Emicizumab is subcutaneous administration and efficacy irrespective of the presence of inhibitors. Emicizumab could conceivably represent a new era in the management of patients with haemophilia A.<sup>12</sup>

### Treatment of haemarthroses

Haemarthrosis must be aggressively treated to prevent chondrocyte apoptosis and progression to synovitis, recurrent joint bleeds and ultimately end-stage osteoarthritis. These joint bleeds need the following: deficient factor intravenous replacement to 50%; joint aspiration to debulk the joint blood and alleviate associated pain (Fig. 4); short-term immobilization for 48 hours; and



**Fig. 3** Bilateral ankle haemophilic arthropathy: (a) anteroposterior radiograph of both ankles; (b) lateral view of the left ankle; (c) lateral radiograph of the right ankle.

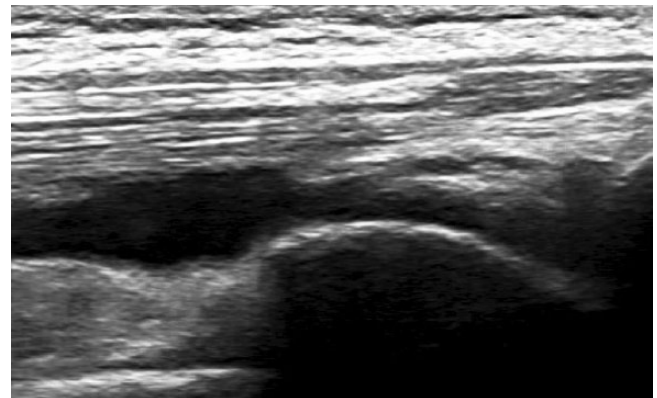


**Fig. 4** Joint aspiration in acute haemophilic haemarthrosis.

deficient factor replacement every 2–3 days (prophylaxis regimen) until the joint is fully rehabilitated and there is no evidence of residual blood and/or associated synovitis.<sup>13</sup> In this respect, point-of-care ultrasonography (POC-US) is essential (Fig. 5).<sup>14,15</sup> Chronic synovitis will require a synovectomy: radiosynovectomy (RS) or arthroscopic synovectomy (AS).<sup>16</sup>

### Treatment of synovitis

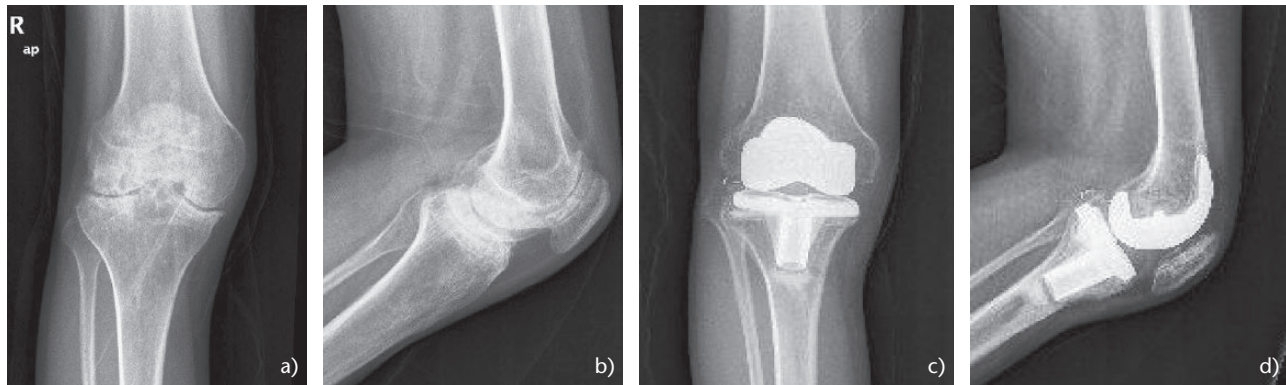
If left untreated, synovitis followed by degenerative changes within the joint will occur and a stiff or painful joint will result. Many authors have previously defined the role of RS, a common therapeutic procedure for chronic haemophilic synovitis. For the treatment of chronic haemophilic synovitis, RS should always be indicated as the first procedure. It is an easy procedure with a number of satisfactory results.<sup>16</sup> With RS with Yttrium-90,



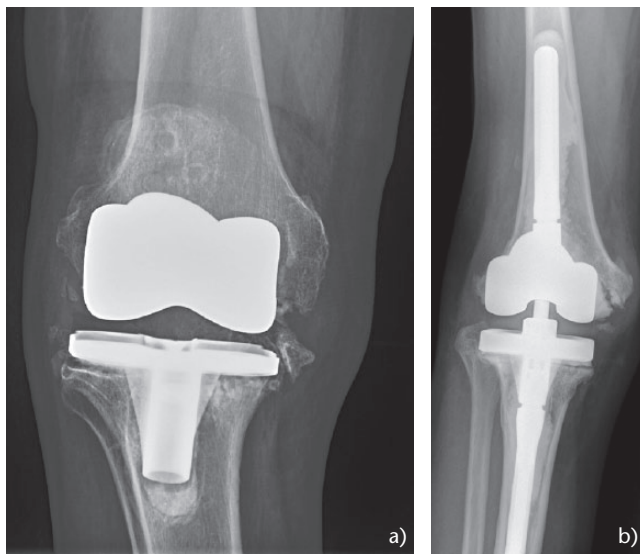
**Fig. 5** Ultrasonography (US) of acute haemarthrosis.

Phosphorus-32 or Rhenium-186 there is an expected 75% to 85% success rate. The indication for RS is the presence of synovitis (confirmed clinically and by POC-US) causing two or more haemarthroses in a particular joint over the last six months despite adequate haematological prophylaxis.<sup>16</sup> It is important to emphasize that no more than three RSs should be repeated within an approximate six-month window in order not to exceed the maximum annual recommended dose of radioactive materials (1 milisievert-mSv/year). It does not mean that RS can be repeated many times in the life of the haemophilic patients if needed, provided that the safety level of 1 mSv/year is always respected. If after three procedures, RS fails, an AS is indicated.<sup>16</sup> Arthroscopic synovectomy generally achieves similar results to RS; however, as AS is a surgical procedure under general anaesthesia (recommended in haemophilic patients), it can be accompanied by a certain number of complications common to surgical procedures.

Both RS and AS are procedures for synovial destruction used in a number of haemophilia centres for the management of chronic haemophilic synovitis. Taking into



**Fig. 6** Total knee replacement (TKR) in a patient with inhibitor: (a) anteroposterior preoperative radiograph; (b) lateral preoperative view; (c) anteroposterior postoperative radiograph; (d) lateral postoperative view. The result was excellent.



**Fig. 7** Aseptic loosening of a primary total knee replacement 18 years after implantation that required revision arthroplasty with a CCK (constrained condylar knee) implant: (a) anteroposterior preoperative view; (b) anteroposterior postoperative radiograph. The result was excellent.

account the risk of infection after surgical procedures in human-immunodeficiency-virus-positive patients, RS is recommended first. RS is also of particular interest in patients with inhibitors, who otherwise are difficult to treat from the haematological point view (by means of aPCCs [activated prothrombin complex concentrates] and/or rFVIIa [recombinant activated FVII]). The reported rate of complications after RS is 1%.<sup>16</sup>

### Treatment of arthropathy

The orthopaedic complications of haemophilia are patient-specific and treatment protocols often need to be altered to suit the individual.

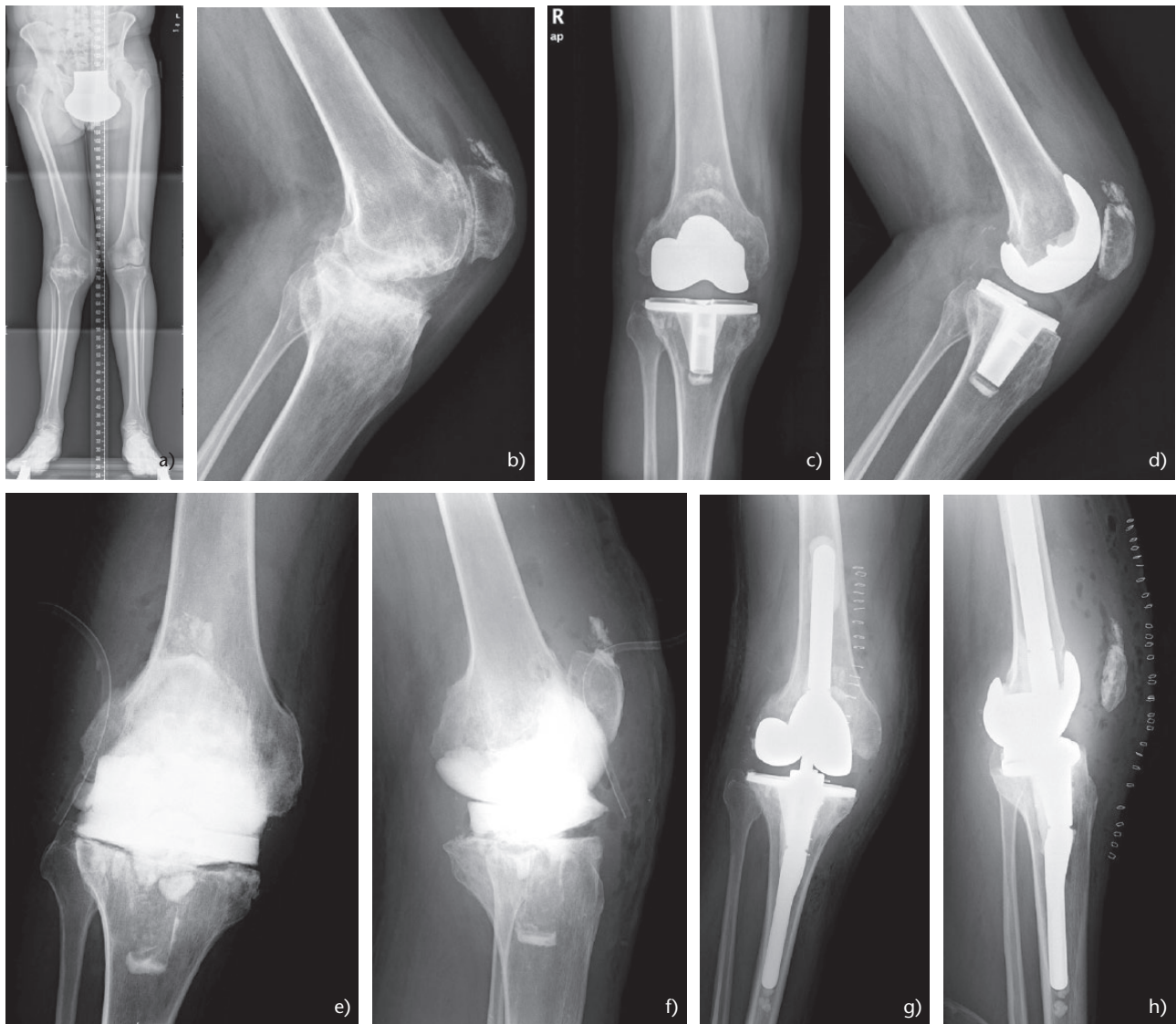
### Elbow arthropathy

Excision of the radial head and partial open synovectomy is a consistently reliable operation that appears to prolong the functional life of the elbow joint. With proper selection it dramatically reduces the rate of haemarthroses, improves forearm rotation by 20° to 60°, decreases pain, improves function and does not cause a problem with elbow instability.<sup>17,18</sup> In some cases of valgus deformity, ulnar nerve involvement may occur. In this case, surgical ulnar nerve release should be indicated.<sup>3</sup> The scant data regarding results of total elbow replacement (TER) for haemophilic arthropathy are limited to small case series and case reports. Research has found that, while pain alleviation and patient satisfaction are promising, variable results with significant complications and infection rates may discourage routine use of TER for haemophilic arthropathy of the elbow.<sup>19</sup> The rate of reported complications is between 12.5% and 85%.<sup>20–23</sup> The rate of reported revisions is between 12.5% and 37.5%.<sup>24,25</sup>

### Knee arthropathy

Arthroscopic debridement should be considered in the young haemophilic patient to avoid or delay total knee replacement (TKR). The operation may give the patient years of life without pain.<sup>26</sup> The most commonly used procedure in advanced knee haemophilic arthropathy is TKR (Figs. 6 and 7). However, the high risk of infection (7% on average) is a concern (Fig. 8).<sup>27–30</sup> Reported results of primary TKR in haemophilia are satisfactory.<sup>27–31</sup> It is paramount today to use a multimodal blood-loss prevention approach (MBLPA) including intra-articular tranexamic acid (TXA) in primary and revision TKR for patients with haemophilia.

In a reported study, an MBLPA-TXA in TKR for haemophilic patients was effective, with a zero transfusion rate (compared with 40% in the non-MBLPA-TXA group).<sup>32</sup> The MBLPA-TXA group had less postoperative blood loss



**Fig. 8** Two-stage revision total knee replacement (TKR) in a periprosthetic infection: (a) anteroposterior view of the knee before TKR; (b) lateral radiograph of the knee prior to TKR; (c) anteroposterior view of the knee after TKR; (d) lateral view of the knee after TKR; (e) articulated spacer implanted in the first stage of the two-stage revision arthroplasty performed (anteroposterior view); (f) lateral radiograph of the articulated spacer; (g) anteroposterior view of the revised implant (constrained condylar knee [CCK] design) after the second stage of the two-stage revision arthroplasty; (h) lateral radiograph of the revised implant (CCK design) after the second stage of the two-stage revision arthroplasty. The result was excellent.

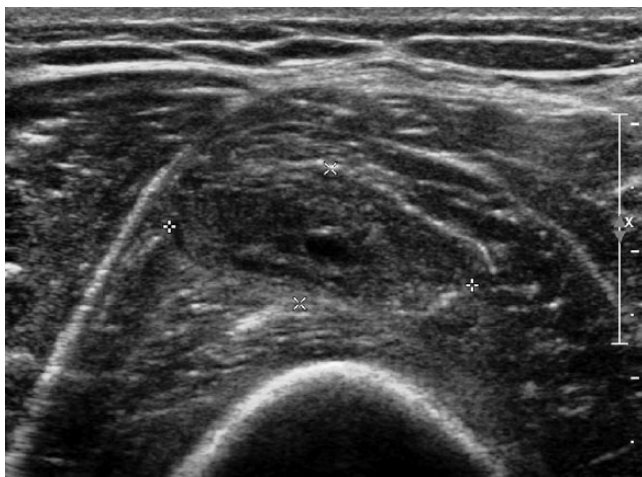
than the non-MBLPA-TXA group. The MBLPA-TXA group included the following: (a) tourniquet with 100 mmHg above systolic pressure, released after skin closure; (b) surgical blood-saving protocol, including: femoral canal obturation with bone graft and intra-articular infiltration of posterior capsule, medial and lateral capsule, and ligaments, before closure, of 80 cc saline with adrenalin 300 mcg, morphic chloride 10 mg, tobramycin 100 mg, beta-methasone sodium phosphate 6 mg, betamethasone acetate 6 mg, and ropivacaine 200 mg; (c) an intra-articular injection of a combination of TXA (25 mL, 2500 mg) and sodium chloride (10 mL, 18 mg).<sup>32</sup>

In the non-MBLPA-TXA group, the standard procedure was used, without any particular blood-saving technique (tourniquet with 350 mmHg, released before skin closure for electrocoagulation of bleeding; no limits or treatment to preoperative haemoglobin; no femoral canal obturation, 24–48 hour vacuum drain, opened with skin closure, no intra-articular infiltration; and no TXA administration).<sup>32</sup>

The reported rate of survival after TKR at ten years is between 83% and 92%.<sup>23,33–35</sup> Late periprosthetic infections are a major concern, and precautions aiming to avoid haematogenous spread of infections during factor



**Fig. 9** Pseudoaneurysm after primary total knee replacement (TKR) with a constrained condylar knee (CCK) design due to severe varus deformity and muscular atrophy: (a) anteroposterior view of the knee before TKR; (b) lateral radiograph prior to TKR; (c) severe postoperative haemarthroses five days after surgery was treated with joint aspiration; (d) angiogram demonstrated the existence of an arterial pseudoaneurysm (arrow); (e) arterial embolization (arrow) solved the problem.



**Fig. 10** Ultrasonography (US) of a muscle haematoma.

concentrate infusions should be strongly encouraged. Pseudoaneurysms after TKR may occur (Fig. 9). In haemophilia, the most common cause of a haemarthrosis following TKR is the development of a pseudoaneurysm.<sup>36-40</sup> This complication is due to unrecognized injury of the peri-articular vessels. Failure to diagnose and treat it may lead to subsequent recurrence of bleeding. Following aspiration of the haemarthrosis via arthrocentesis the existence of a pseudoaneurysm must be suspected. A CT angiogram and a digital subtraction arteriography must be performed to confirm the diagnosis. An arterial embolization of the pseudoaneurysm must then be performed immediately using a helical microcoil.<sup>38</sup>

#### Ankle arthropathy

The surgical management of the haemophilic ankle must include arthroscopic ankle debridement (in the initial stages of cartilage degeneration), and ankle distraction, ankle arthrodesis or total ankle replacement (TAR) (in late stages of cartilage degeneration).<sup>41</sup>

While patients with severe haemophilic arthropathy of the ankle are likely to improve in terms of pain and range of motion after TAR, there is insufficient information to routinely advise its use. Complication and infection rates are concerning, and the absence of survival analysis information makes it hard to quantify the profit to the patient in light of the dangers and resources implicated in the procedure.<sup>41</sup> A study found a total rate of intraoperative and postoperative complications of 33%.<sup>42</sup> In other reports the predicted implant survival of TAR was 94% at 5, 85% at 10 and 70% at 15 years, respectively.<sup>43</sup>

A common deformity associated with tibiotalar and subtalar arthropathy is fixed plantar flexion, that can be alleviated by means of the surgical lengthening of the Achilles tendon associated to a posterior open capsulotomy.<sup>41</sup>

Anterior osteophytes of the distal tibia and talus sometimes cause pain due to impingement. In these cases, open or arthroscopic removal of such osteophytes should be indicated.<sup>41</sup>

#### Intra-muscular bleeds

In the majority of cases, bleeds within the muscles are caused by trauma. They are very often associated with direct trauma and the pathology becomes quite evident due to the swelling; pain, local warmth and bruising that typically appear in the overlying skin. The vast majority of these muscle bleeds resolve spontaneously with adequate factor coverage, leaving no functional loss. It is, however, necessary to examine the patient carefully to ensure that there is no danger to vascular elements and no neural compromise. Diagnostic US (Fig. 10) and/or CT scan (Fig. 11) are paramount to confirm diagnosis.<sup>14,15</sup>

Compartment syndromes (Volkmann's contracture of the hand and foot) have been reported as a result of such bleeding incidences within the closed compartments of the forearm and leg.<sup>44</sup> Compartment syndromes (forearm, leg) are surgical emergencies.



**Fig. 11** Computerized tomography (CT) scan showing an iliopsoas haematoma (arrow).

The most common and most serious of muscle bleeds occur in the iliopsoas muscle. Right lower-quadrant abdominal pain has mimicked the symptomatology of an acute appendicitis. Compression of the femoral nerve may present as an area of reduced sensation in the anterior aspect of the thigh. Attempts to extend the hip joint cause severe pain and force the patient into hyperlordosis of the lumbar spine. As it is difficult clinically to differentiate between a bleed into the iliopsoas muscle and an intra-articular haemorrhage into the hip joint, one must rely on objective testing. US and/or CT scan are able to differentiate between the largely extended joint capsule with intra-articular haemorrhage and the bleed that is situated within the muscle fibres (Fig. 11). The iliopsoas muscle haematoma takes a long time to improve even under haematological prophylaxis, and then flexion contracture of the hip joint may persist for weeks. Secondary haemorrhages into the same area are common and hence, prophylactic factor replacement must be continued. Whereas coxhaemarthrosis is a problem requiring days of extra treatment, an iliopsoas haematoma may require weeks until full resolution is achieved (to be confirmed with US and/or CT scan).<sup>3</sup>

### Haemophilic pseudotumours

The pseudotumour is basically an encapsulated haematoma. A thick fibrous capsule surrounds a haematoma in varying degrees of organization; calcification and ossification may be seen within it. The management of the patient with a haemophilic pseudotumour is complex and with a high rate of potential complications. There are a number of therapeutic alternatives for this dangerous condition: embolization, radiation, percutaneous management, surgical removal and exeresis and filling of the dead cavity.<sup>45</sup>

Proximal pseudotumours occur in the proximal skeleton, especially around the femur and pelvis. They appear to originate in the soft tissue, erode bone secondarily from outside, and develop slowly over many years. An iliopsoas muscle haematoma may develop a pelvic pseudotumour. Proximal pseudotumours occur in adults and do not respond to conservative treatment. Large proximal pseudotumours in adults should be removed surgically as soon as they are diagnosed. Distal pseudotumours occurring distal to the wrist and ankle appear to be secondary to intraosseous haemorrhage, and develop rapidly. They are seen mainly in children and adolescents.<sup>45</sup>

Distal pseudotumours should be treated primarily with long-term factor replacement and immobilization. In children, surgical removal or even amputation is indicated when conservative treatment fails to prevent progression. Percutaneous evacuation should be considered in inoperable advanced pseudotumours. Evacuation is carried out with a large trocar under image intensifier control; the cavity is filled with different quantities of fibrin seal or cancellous bone, depending on the size of the pseudotumour.<sup>46</sup>

It is hoped that with the advent of widespread maintenance therapy, pseudotumours will be less common in the future. It is important that they are diagnosed early, and prevention of muscular haematomas is key to reducing their incidence. Untreated, proximal pseudotumours will ultimately destroy soft tissues, erode bone and may produce neurovascular complications. Surgical excision is the treatment of choice but, like all orthopaedic procedures in haemophilic patients, should only be carried out in major haemophilia centres by a multidisciplinary surgical team.

### Fractures

In haemophilic patients fractures can occur anywhere in the long bones but are more prevalent near the joints or in the diaphysis of the long bone. The lower limb bones, especially the femur, are the most common sites for fractures. Fracture haematomas tend to be large in volume and may be the cause of acute compartment syndrome.<sup>47</sup>

Poor musculature, osteoporosis, and haemophilic changes in the bone may predispose haemophilic patients to risk of fractures. In patients with haemophilia the fracture can occur after a trivial trauma, especially if associated factors of haemophilic arthropathy, muscle wasting, and osteoporosis render the bone more fragile and prone to fracture.<sup>48</sup>

The goal of modern fracture treatment must be to obtain an optimal outcome with the patient's return to full activity as soon as possible. Today, internal fixation is indicated in most displaced fractures in the adult, whereas external fixation remains the best choice for initial

stabilization with severe soft tissue injuries. If a fracture is correctly treated in a haemophilic patient it will progress to consolidation in a similar time frame to those occurring in the general population.<sup>47</sup>

## Conclusions

Haemophilia left untreated or treated on demand (only when a haemarthrosis occurs) destroys the joints at a very young age. Primary haematological prophylaxis, currently the gold standard for the management of haemophilia, is not completely efficacious. Moreover, it is only available for 25% to 30% of patients worldwide. Advances in haematology, combined with advances in orthopaedic surgery, have made it possible to ameliorate the musculoskeletal complications of haemophilia through orthopaedic surgical procedures. These procedures are safe, even in the most complex cases, such as patients with inhibitor. The risk of bleeding in surgical procedures is higher for patients with haemophilia than for the general population and there is also a greater risk of infection. Both these factors augment the risk of a poor result. Whatever the surgical technique, appropriate surgical haemostasis must be achieved by intravenous infusion of concentrate of the deficient factor (factor VIII or factor IX), at the correct doses (ideally for 10–14 days). In patients with inhibitor, haemostasis can be achieved with the intravenous infusion of aPCCs and/or rFVIIa. Surgical orthopaedic procedures that are usually needed by haemophilic patients include joint aspiration, synovectomy (radiosynovectomy or arthroscopic synovectomy), arthroscopic joint debridement (ankle, knee), Achilles tendon lengthening, removal of ankle osteophytes (open or arthroscopic), arthrodesis of the ankle, TKR, TAR, TER, total hip replacement (THR) resection or percutaneous treatment of pseudotumours, fasciotomy for compartment syndrome, and neurolysis of the ulnar nerve.

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