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More Than Meets the Eye

Using Point-of-Care Imaging Assessments to Improve Joint Health Outcomes in Hemophilia



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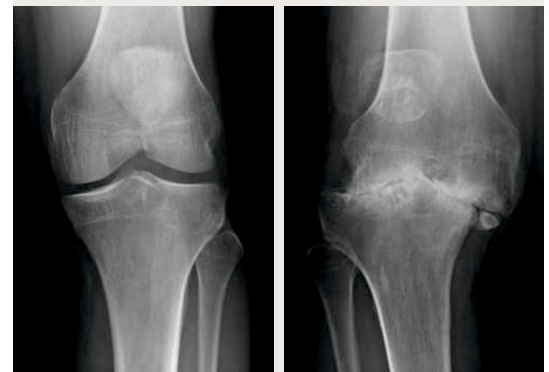
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Preservation of joint health is a key goal of hemophilia management^{1,2}

Approximately 70% to 80% of bleeds in patients with hemophilia occur in the joints.¹ Recurrent hemarthroses lead to chronic inflammation, progressive osteochondral damage, and eventually hemophilic arthropathy. Hemarthrosis is one of the most common complications in patients with hemophilia and is the primary cause of chronic pain, disability, and reduced health-related quality of life.^{1,3-7}

Even a single untreated joint bleed can cause lasting damage and increase the risk of recurrent bleeds, underscoring the importance of prevention, early detection, and treatment of joint bleeding episodes in patients with hemophilia. Importantly, joint bleeds can be asymptomatic or go unrecognized, leading to inaccurately reported bleed rates; it can be difficult for patients to determine whether painful joints are associated with bleeding.^{2,8-12} Furthermore, Manco-Johnson et al have shown that patients with low annualized joint bleed rates (AjBRs) and without clinical evidence of bleeding may still demonstrate joint damage, which suggests that asymptomatic and/or unreported bleeds may play a role in arthropathy.¹² Due to the damaging effects of blood in the joints, the treatment and prevention of all bleeding appears critical.^{3,12,13} While clinical trials have not yet confirmed the impact of undertreated bleeds on joint health, objective imaging assessments of joint status may improve hemostatic management.

Impact of bleeds on joints¹⁴



No history of hemarthrosis

Severe arthropathy from hemarthroses

Adapted from Lobet S et al. *Journal of Blood Medicine*, Dove Medical Press. 2014;5:207-218.

“ Should every bleed be treated? Yes. You have to do something so the bleed goes away, because the blood in the joints causes damage. ”

—Annette von Drygalski
MD, PharmD, RMSK

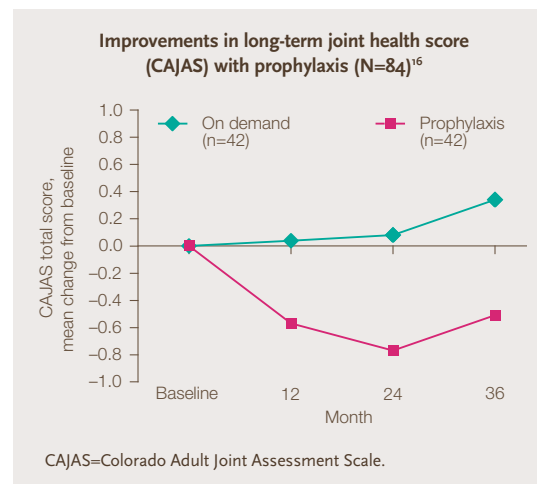
Making joint health the focus of treatment decisions

Early treatment of joint bleeds with factor can preserve joints and improve outcomes¹

To preserve joint health or minimize progressive joint damage, management approaches should aim to prevent and treat all bleeding episodes.¹ Coagulation factors naturally restore hemostasis and have important roles in bleed protection throughout the body.¹⁵ For patients with hemophilia, factor prophylaxis may be required throughout their lives to prevent bleeding and maintain joint health, as well as to treat bleeding in various clinical scenarios (ie, acute bleeds and perioperative management).¹

Prophylaxis with factor replacement therapy has shown benefits for patients' joint outcomes, including bone strength and long-term joint health improvements.^{16,17} Early prophylaxis with factor replacement can help preserve joint structure and function.^{2,16} In addition, clinical trials with extended half-life (EHL) factor products have shown a reduction in bleed rates and joint bleeds, as well as target joint resolution.¹⁸⁻²¹ Recently developed nonfactor therapies have shown reductions in bleeding rates, although their impact on joint health has yet to be determined.^{22,23}

Concomitant administration of therapies that reduce inflammation may be considered with caution to support joint health in patients with hemophilia. Anti-inflammatory agents, such as cyclooxygenase 2 (COX-2) inhibitors, reduce joint inflammation after an acute bleed and in patients with chronic arthritis.¹ Ultrasound-guided intra-articular corticosteroid injections, the standard of care for managing joint pain, have been shown to provide pain relief in patients with hemophilic arthropathy.²⁴ In addition, biological agents, including intravenous immunoglobulin (IVIG), have been investigated for the treatment of inflammatory joint diseases (ie, rheumatoid arthritis) because of the anti-inflammatory properties of IgG Fc.^{25,26}



“ Low bone mineral density and increased risk of fracture are increasingly being identified in patients with hemophilia. As we enter the era of novel therapies, it will be important to understand the impact of all therapies on these observations. ”

—Nihal Bakeer
MD

Ultrasound objectively evaluates joint health and identifies joint bleeds

The World Federation of Hemophilia (WFH) recommends clinical musculoskeletal assessments to evaluate joint health and body function in patients with hemophilia; however, a physical assessment using the Hemophilia Joint Health Score (HJHS) cannot detect asymptomatic bleeds, which, if detected, may provide opportunities for intervention.^{1,9-11} Although magnetic resonance imaging (MRI) is considered the standard for joint imaging, it is not ideal for repeated multijoint monitoring and is not capable of distinguishing simple fluid from blood.²⁷⁻³⁰ However, musculoskeletal ultrasound (MSKUS) is uniquely sensitive and able to detect intra-articular blood in small quantities (3–5 mL), even at low concentrations (up to approximately 10% blood in joint fluid). MSKUS is becoming more established as a diagnostic tool in the point-of-care setting. It can be used fast, routinely and in clinic, and can be performed reliably by trained, non-radiologist health care providers.²⁷⁻³²

MSKUS can also distinguish whether acute joint or musculoskeletal pain is associated with bleeds, eliminating the risk of undiagnosed bleeds. Use of MSKUS has revealed that patients and physicians misdiagnose the cause of musculoskeletal pain approximately 70% of the time. Adjustments made to management based on MSKUS-demonstrated evidence of bleeding have been shown to help improve symptom control in 64% of bleeding events.⁸

Recently developed protocols, such as the Joint Tissue Activity and Damage Examination (JADE), employ scoring algorithms to inform treatment strategy and aid the diagnosis of hemophilic joint abnormalities.^{29,31,33} JADE, for example, uses a quantitative algorithm that is validated based on Outcome Measures for Arthritis Clinical Trials (OMERACT) guidelines. It includes power Doppler imaging of inflammation, vascular changes, and tissue/osteochondral measurements that allow for longitudinal assessment of individual, patient-specific joint findings.^{31,34} Another protocol is the Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) system, a simplified scanning procedure and scoring method that awaits further validation. HEAD-US integrates ultrasound into the routine evaluation of joints for early detection of damage and disease activity.³³

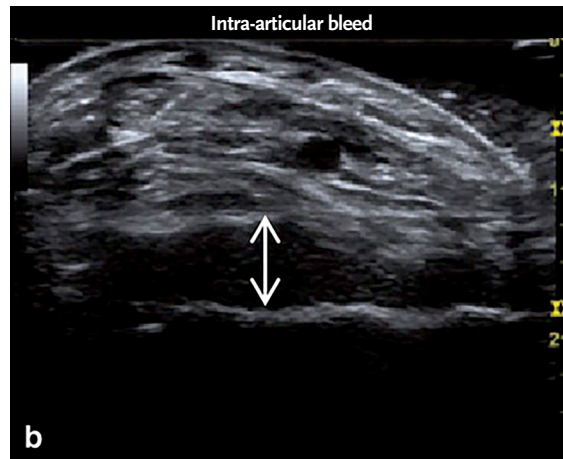
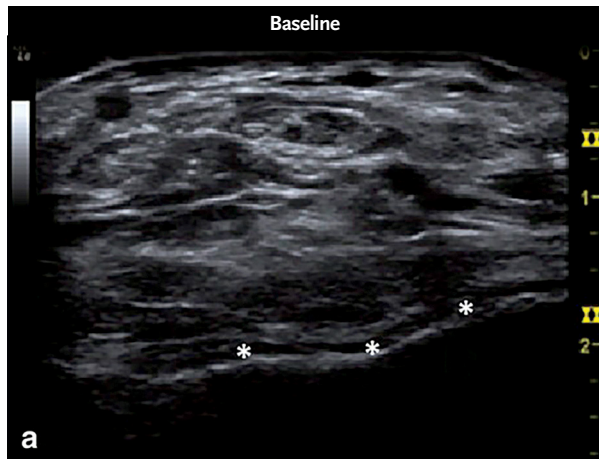
“ We use MSKUS in the comprehensive care setting, as well as during physician or physical therapy visits, if we suspect any bleeds or joint issues. We feel that it modernizes hemophilia care and enhances the physical therapist's assessment and management of patients with hemarthropathies. ”

—Bruno UK Steiner
PT, DPT, RMSK

Objective assessments of joint health can guide clinical practice

Clinical scenario: Accurately identifying acute bleeds to individualize treatment

During patient-reported episodes of pain, ultrasound has been used to detect the presence of intra-articular blood, suggesting acute hemarthrosis. In the point-of-care setting, MSKUS can distinguish between bleed-related pain and other causes so that the appropriate treatment can be identified.⁸

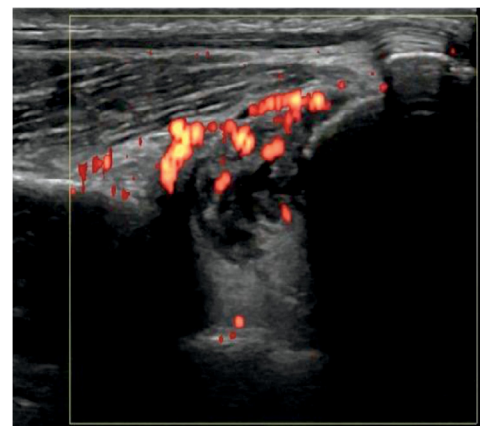


Ultrasound images of the ankle of a 23-year-old with severe hemophilia. Baseline axial view of the ankle showed normal, thin anechoic synovial space in the tibiotalar joint (*). Examination during painful episode showed increase in volume of the tibiotalar synovial space (arrows), which is consistent with complex effusion and bleeding.⁸

Adapted from Ceponis et al. *Haemophilia*. 2013.

Power Doppler exams can also be used to detect the inflammation and vascular remodeling associated with bleeds.³¹

“With MSKUS, it’s very easy to check for bleeding and effusion in the joints. If you identify an acute bleed, then you can treat.” —Dr Annette von Drygalski



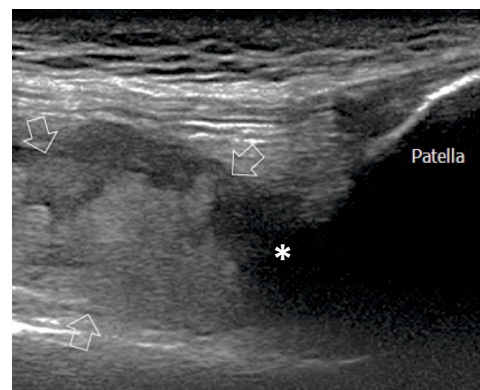
Synovitis, inflammation, and vascular remodeling during a painful episode can be seen in the elbow of an adult patient, shown using power Doppler signalling.

Image courtesy of Annette von Drygalski.

Clinical scenario: Finding evidence of joint damage can reveal undiagnosed bleeds

Joint damage that has gone undetected and undermanaged has been seen with ultrasound. As a supplement to physical examination and patient reporting, ultrasound has helped optimize treatment to address joint damage.^{29,33}

“Early detection of both bleeding episodes and signs of joint disease can lead to early initiation of factor therapy or increased-intensity regimens that may limit progression, rebleeding, and rate of complications.” —Dr Nihal Bakeer



US shows synovial hypertrophy (arrows) and effusion (*) in an asymptomatic knee.²⁹

Adapted from Di Minno MND et al. *J Clin Med*. 2017.

Clinical scenario: Monitoring long-term joint health to ensure treatment success

A patient's joint health status can be monitored by comparing baseline ultrasound scans with images performed in the point-of-care setting. This provides objective clinical evidence for potential improvements in joint health over time.³¹ In practice, this may be useful when switching to a new class of therapy, such as from standard half-life to extended half-life products. Comparing ultrasound images may also provide an opportunity to engage patients with their disease and treatment, allowing them to see any benefits from their new treatment regimen on their joints.

“Having seen objective evidence of joint damage on his first point-of-care joint ultrasound, my patient appreciated the seriousness of repeated joint bleeds and the importance of compliance with replacement therapy; ultimately, he was motivated to find a new position that was lower impact and stress on his joints.” —Dr Nihal Bakeer

“An elderly patient of mine started tertiary prophylaxis 3 years ago and is showing improved joint scores and images in long-term follow-up assessments. It's been remarkable to see the change after starting his factor prophylaxis regimen.” —Dr Annette von Drygalski

Summary

The management of progressive arthropathy is a key unmet need among patients with hemophilia, impacting patient outcomes beyond bleeds.^{1,3-7} To improve patient outcomes, factor replacement remains an important treatment option as it can be used across bleeding scenarios and has the potential to prevent hemarthrosis that may cause joint arthropathy.^{1,2,16,18-21,25,26} The early detection and long-term monitoring of joint damage with MSKUS imaging provides an objective measure of patient outcomes and can facilitate a personalized, outcome-based approach to managing bleeds.^{27,28,31} Positioning joint health as a core and ongoing aspect of clinical practice may have the potential to improve long-term outcomes for patients with hemophilia.^{1,8,27-29,31,33,34}

“MSKUS provides a clear, objective image that can be used in conversations between health care providers and patients about joint health in hemophilia management. Using MSKUS to talk to patients allows them to understand their disease and take ownership of it.”

—Dr Annette von Drygalski



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