Joint Damage in Hemophilia

by Dr. David Clark

Damage caused by bleeding into the joints is the most common symptom of hemophilia. Called hemophilic arthropathy, joint damage can lead to chronic pain and loss of joint function resulting in a decrease in quality of life for the hemophilia patient. The good news is that prophylactic treatment with clotting factor can minimize or eliminate joint damage. However, once damage has occurred, prophylaxis may halt further damage, but in most cases, the damage cannot be reversed.

Many hemophilia patients, especially those not on prophylaxis and those with inhibitors, develop target joints. Target joints are often defined as joints with four or more bleeds within six months. A joint bleed is called a hemarthrosis. Bleeding may be spontaneous or in response to injury. The most common target joints are the ankle, knee and elbow, although other joints like the hip, wrist and shoulder may also become targets. About 25% of all severe hemophilia patients have at least one target joint.

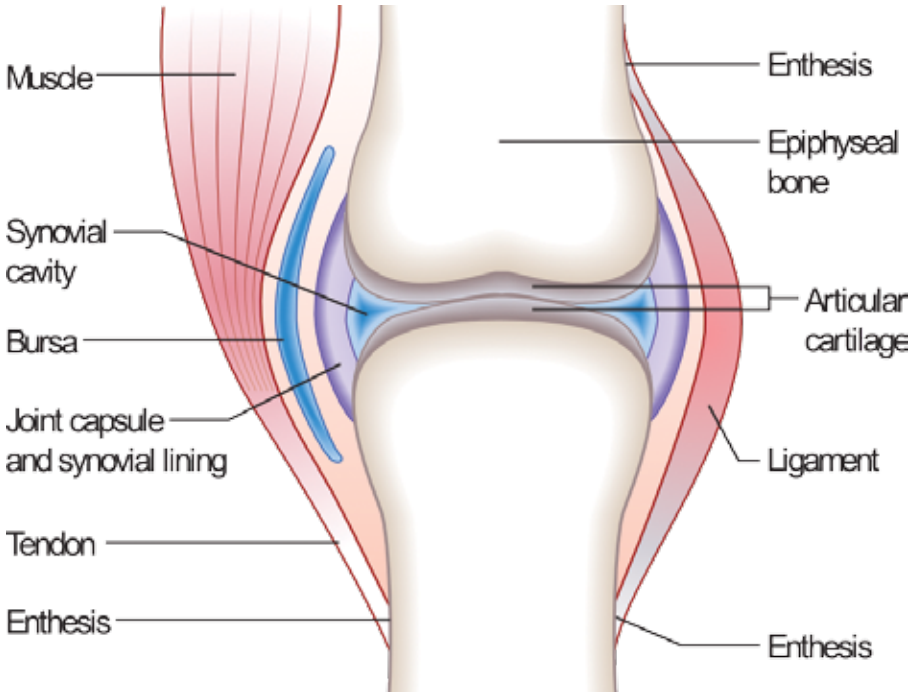
Mechanisms of Joint Damage

In spite of the fact that bleeding into the joints has been recognized as a symptom of hemophilia since 1868, the reason it happens and the mechanisms that lead to joint damage are still not well understood. There is evidence that the tissues around the joints provide an environment that does not promote clotting. Joints contain relatively low amounts of tissue factor, a protein that initiates clotting by the extrinsic clotting pathway, one of the two pathways that lead to formation of a clot. The other, intrinsic pathway involves factor VIII and factor IX, so with both pathways blocked hemophilia patients are especially vulnerable to bleeding in the joints. The joint tissues also produce several anticoagulant proteins that inhibit clotting.

The diagram below shows the structure of a typical synovial joint, like a knee or elbow joint. The ends of the two bones that meet in the joint are covered with cartilage. The cartilage provides a smooth, slippery surface that allows the bones to move while providing a cushion for the loads supported by the joint. The joint is surrounded by a flexible covering called the joint capsule, which is lined inside with the synovial membrane or synovium and contains synovial fluid. Synovial fluid is produced by the synovium and helps to lubricate the joint as well as to provide oxygen and nutrients to the cartilage cells, which are not connected to the bloodstream. The synovium has an underlying layer that is rich in blood vessels, which is where joint bleeding occurs.

Joint damage usually begins in infancy with periodic joint bleeds, which the patient often senses first as a tingling or aura in the joint. The joint may become stiff and warm with tenderness or pain. Untreated, recurrent bleeds eventually lead to destruction of the cartilage in the joint.

Bleeding into a joint causes a complex series of reactions that begin with synovitis, inflammation and swelling of the synovium that appears to be triggered by iron in the blood. The swollen synovium invades the space inside the joint cavity where it starts to affect the cartilage. The inflammation reactions and exposure of the cartilage to blood causes loss of proteoglycans, which are proteins that hold the cartilage together. New blood vessels are also formed in the swollen synovium. These new vessels tend to be fragile and bleed easily, leading to a vicious cycle of continuing cartilage damage. Since the cells that produce the cartilage repair themselves very slowly, the damage



becomes permanent after repeated bleeds.

The extent of the damage to the joints varies from person to person suggesting that there is also a genetic component to the process. Two severe hemophilia patients with similar ages, treatment patterns, activity levels and other characteristics can exhibit very different degrees of joint damage. Up to 10% of severe hemophilia patients experience no joint bleeds.

Treatment

The best results are obtained by preventing joints bleeds in the first place. Primary prophylactic therapy has been shown to significantly decrease the number of joint bleeds and the amount of joint damage. It is more effective than either secondary prophylaxis or on-demand treatment, especially when started at an early age before any significant damage occurs. It is unknown whether adult joints are as susceptible to damage as growing joints in children and whether discontinuing prophylaxis after reaching adulthood can lead to new joint damage. Unfortunately, prophylaxis is not available to everyone.

Patients with inhibitors, even those treated with bypassing agents (NovoSeven or FEIBA), have more frequent joint bleeds and more severe arthropathy than do patients without inhibitors. Target joint bleeds in inhibitor patients are often less responsive to therapy. Immediate treatment (within 1 - 2 hours) and higher initial doses of the bypassing agents appear to be important for relieving pain and minimizing joint damage.

A number of methods have been developed to determine the degree and type of joint damage. They start with a history of the problems, an assessment of the joint's range of motion and associated pain, and an evaluation of its effect on the ability to perform normal activities of daily life. All of these employ scoring systems to quantify the extent of damage.

The most frequently used test is radiography (X-rays or CT scans). MRI (magnetic resonance imaging) and ultrasound are also used, since they can detect some of the early changes occurring in a joint better than radiography can, especially in the soft (non-bony) tissues. MRI appears to be more useful for the ankle and elbow, and ultrasound is usually more useful with the knee. Other more specialized tests are also being developed to detect still earlier changes including damage to the cartilage.

RICE therapy (Rest, Ice, Compression, Elevation) is often recommended in response to joint bleeds. Physical therapy and anti-inflammatory drugs may also be used. However, the most important response is immediate factor infusion, continuing until the symptoms cease, and possibly longer. Some physicians believe that it is important to continue therapy even after the bleeding stops to give the synovium time to repair itself. Aspiration of joints to remove blood after a bleed is also recommended by some physicians.

Physical therapy can be very helpful both in recovery from joint bleeds and also in helping to prevent further damage. Splints and orthotics may be used to help stabilize a joint, to prevent excessive or un-natural stresses and to relieve pain. Studies have shown that physical activity and some sports can help by strengthening the muscles around a joint, giving it better support.

Uncontrolled joint bleeds and synovitis in children can lead to uneven growth of the bones and skeletal deformities. Treatment may include physical therapy, traction, orthopedic braces and other treatments. More advanced cases may require surgery.

When synovitis becomes established, synovectomy, removal of part of the synovium, is often recommended. It may be undertaken surgically or using radiation. Synovectomy tends to reduce joint pain and the number of bleeding episodes but does not stop deterioration of the joint.

Advanced joint disease in which much of the cartilage in the joint has been destroyed requires more extensive orthopedic procedures. The bones in some joints, like the ankle, can be fused together while still allowing relatively normal use. However, especially in older patients total joint replacement often becomes necessary.

In younger patients, it may be possible to delay joint replacement by repairing or regenerating the damaged cartilage. Procedures such as debridement and arthroplasty remove damaged tissue that interferes with motion of the joint. In the process, the bone is abraded, which tends to stimulate it to grow new cartilage.

Some newer therapies such as transplantation of cartilage tissue and transplantation of bone marrow stem cells to grow new cartilage have not yet been used in hemophilia patients. They have shown some success in non-hemophilia patients who tend to have less extensive amounts of cartilage damage, but are still somewhat experimental. It is also not clear whether these therapies would work in an environment of continued joint bleeding.

With the increasing use of prophylaxis, joint damage will hopefully become less common. However, there is still a large number of patients for whom prophylaxis is not possible or who grew up before it was widely practiced. Knowledge and treatment options for hemophilic joint problems are slowly expanding. Because of the complex nature of the problems and therapies, the wide range of resources available in many hemophilia treatment centers offer one of the best sources for evaluation and treatment.