Treatment of Haemochromatosis Arthropathy

Advice for patients from the Haemochromatosis Arthropathy Research Initiative (HARI)

Introduction

Genetic Haemochromatosis (GH) is associated with two musculoskeletal manifestations, joint disease (arthropathy) and osteoporosis. This article is concerned with treatment of the arthropathy and does not cover osteoporosis.

Haemochromatosis arthropathy leads to progressive thinning and loss of cartilage within a joint, bone bruising, damage and new bone growth (osteophytes) around the edge of the joint. The processes linking genetic mutations in the HFE and other genes, problems with iron metabolism and arthropathy are not completely understood. It is assumed that ongoing iron overload is the principal cause of joint damage, however this may not be the only explanation. Most patients find that removal of excess iron from the body makes little difference to joint stiffness or pain or long term difference to the progression of joint damage. At the present time there are no scientifically proven treatments available which can prevent healthy joints from becoming affected, or stop the processes that lead to damage in affected joints. This observation means that more research is required to better understand what is causing the arthritis in people with genetic haemochromatosis. Osteoporosis is also associated with haemochromatosis.

Currently 'treatment' of haemochromatosis arthropathy is symptom based, aiming to reduce pain, joint swelling and stiffness and improve function. There is much that can be done to protect joints and reduce symptoms, even though we have no therapies which prevent or slow down the disease process. In the early stages joint pain and stiffness can be effectively reduced with non-pharmacological and pharmacological (medication) interventions and at later stages, when advanced joint damage has occurred, surgery can be a very effective means of controlling pain.

Non pharmacological interventions

1. **Exercises to improve muscle tone and strength**

   Exercises are very important to improve overall cardiovascular fitness and to improve strength and muscle tone throughout the body. Improved muscle strength gives the joint

more stability and as such more protection from injury that might be incurred from everyday use. As arthritis cannot be cured it is important to adopt and continue a regular exercise routine lifelong.

Low impact non-weight bearing exercises are recommended. These are easy to perform and should do no harm. Examples of such exercise are swimming, cycling, movement on a cross trainer, Nordic walking with cushioned shoes and light resistance work on gym equipment. Advice from a personal trainer, physiotherapist or other health care professional with sports and exercise training is recommended to find the best exercises to suit you.

2. Balance and mobility exercises

The disciplines of Pilates and Tai Chi are both excellent ways of maintaining muscle tone, core stability and balance. This will help protect affected joints from unexpected injury incurred through everyday living. A Swiss ball can also be helpful for balance and some toning exercises.

Yoga may not be beneficial as overstretching an affected joint can be harmful. This discipline should be avoided or performed with supervision cautiously.

3. Hand therapy

Pain and stiffness in the knuckles can be helped with specific exercises, ergotherapy, to improve mobility, strengthen grip and reduce strain across the joints with everyday tasks. A range of devices, including splints, may also be of benefit.

4. Gait analysis and shoes

We recommend that if any of the joints in the legs are affected (hips, knees, ankles or feet) careful attention should be given to the way you walk. Misalignment on weight bearing through the legs can overload joints and hasten damage. We recommend that a biomechanical assessment of leg length and gait (walking style) is performed, usually by a podiatrist, and if necessary an orthotic made to fit all shoes. This makes sure that mechanical forces in the ankles and feet are balanced and neutral when standing and walking. This is an important way to protect both the joints in the feet and also the hips and knees.

Shoe choice is also important. We recommend shoes with thick cushioned soles and heels with some ankle support (rather than flat low shoes) as this, in addition to the orthotic

placed in the shoe, will provide protection. Trainers are an example of appropriate cushioned supportive shoes.

Pharmacological interventions

There have been many advances in the treatment of pain in recent years. Medications for pain control come in three categories, all of which have the potential to be helpful, either alone or in combination depending on your symptoms. The choice and order in which medicines from each category are tried should be decided by your doctor.

1. Anti-inflammatory drugs

This group includes non-steroidal anti-inflammatory drugs, steroids and Colchicine.

Non steroidal anti-inflammatory drugs (NSAIDs)

e.g. Celecoxib, Diclofenac, Etoricoxib, Ibuprofen, Meloxicam, Naproxen

These medications can be very effective at reducing stiffness and pain coming from inflammation within a joint. They are given as tablets or as a gel rubbed over the painful joint. Some are short acting (taken 2 – 4 times a day) whilst others are long acting (taken once a day) and a range of doses may be used. The main short term side effects are indigestion or acid symptoms, and potentially ulceration in the stomach or duodenum. This means they may have to be prescribed with an anti-acid medication such as a proton pump inhibitor (e.g. Omeprazole, Lansoprazole) to reduce the chance of this happening. “Acid blockers” have the added advantage for haemochromatosis patients of reducing iron absorption from the intestine. The ‘coxib’ members of this group (e.g. Celecoxib, Etoricoxib, Meloxicam) are less likely to cause acid problems, such as heartburn or indigestion. Longer term side effects of all NSAIDs include high blood pressure and kidney damage and for this reason these drugs are best avoided in patients with raised blood pressure requiring treatment, kidney disease, in the elderly or in anyone for a long time. Ideally they should only be used for short periods of time, for example during a flare of joint pain. If absolutely necessary in the longer-term Naproxen is favoured as the least likely to cause cardiovascular problems.

Topical NSAID therapy (e.g. Diclofenac 2% gel) has several advantages. If symptoms are mainly experienced in a few joints, the treatment can be targeted to those joints. NSAID gel is rubbed sparingly around the joint two or three times a day. Only a small fraction enters the body and so side effects and the potential for harm is much reduced.

Steroids e.g. prednisolone, methyl prednisolone

In haemochromatosis arthorpathy, these may be given by injection directly into a joint or by mouth as tablets. They can be very effective at reducing stiffness and pain coming from inflammation within a joint. The injectable route is preferred, particularly if one or two joints are especially painful. Injections may be performed into small or large joints, with or without ultrasound guidance, to accurately place the steroid in the joint. Any number of joints can be injected but for practical purposes no more than 2 or 3 are likely to be done at any one time. Pain relief can last for several months and repeat injections are felt to be safe if given no more frequently than every 3 – 4 months. This would be our recommended first line treatment if each injection gives good pain relief for this period of time. Side effects from injected steroid are rare but can include a dimple due to fat shrinkage and lightening in colour of the skin at the site of the injection.

In tablet form long term steroid use is not advisable because side effects outweigh the benefits, including weight gain, increased risk of infections, high blood pressure, diabetes and acceleration of osteoporosis. Therefore, if used on a regular basis only low doses are recommended.

Colchicine

This medication is used to treat gout and pseudogout, which cause rapid onset very painful swelling in one or a few joints at a time, and can occur in patients with haemochromatosis. Colchicine is sometimes used in patients with haemochromatosis arthropathy without these attacks. It is given as a tablet up to three times daily. The main side effect is diarrhoea.

2. **Analgesics (painkillers)** e.g. paracetamol and opioids

This group of painkillers includes paracetamol (Acetaminophen), codeine based analgesics (e.g. Co-Codamol, Co-Dydramol) and Tramadol. They can be beneficial for mechanical pain, for example from a damaged joint. If you are in pain every day they are more likely to be effective if taken regularly. They can also be used on a less frequent or as required basis if pain is intermittent. The main side effects are constipation, nausea and drowsiness, especially if used regularly. Paracetamol is most commonly used and has the least side effects. It should be avoided in patients with liver damage and in all cases the maximum dose is 4g daily, lower if there is liver damage.

Buprenorphine, Fentanyl and Morphine are strong opioids and should be used with caution and only for severe pain. Drowsiness, constipation and nausea are common side effects and they also carry a risk of addiciton. Buprenorphine and Fentanyl can be given transdermally as a patch placed anywhere on the body, from which the medication enters through the skin. These are changed every 3 or 7 days depending on the medication used.

3. **Neuropathic painkillers** e.g. Amitriptyline, Pregabalin and Gabapentin

   This group of painkillers works by changing the way the brain responds to sensations coming from the body, including muscles and joints. Chronic pain often leads to a condition called 'sensitisation', in which feelings from the body, such as moving a joint or pressure, are misinterpreted by the brain as being more painful than they really are. Neuropathic painkillers work by changing the way the brain responds to these everyday feelings, re-setting the response closer to normal. All of these agents have been licenced for different indications, such as epilepsy and depression. Whilst pregabalin and gabapentin are also licenced for neuropathic pain, amitriptyline is not, but is effective. There is a dose range and these painkillers are generally taken in low dose initially, and increased if necessary. They are not used as the first choice pain killer in routine practice but can be helpful in patients where there is chronic pain not responding to other painkillers.

   Amitriptylline is given 2 hours before bedtime starting at 10mg, and this often restores a good night's sleep, and reduces burning, tingling and pain from tension in the muscles and joints, including the neck and back. The main side effect is drowsiness and a dry mouth, but if tolerated the dose can be increased to 20mg, 50mg or more.

   Pregabalin is given twice a day, usually starting at 25mg and increasing as necessary to 50mg, 100mg or 150mg twice daily. It can be very helpful for chronic pain, tension and tingling or burning. Side effects also include drowsiness or difficulty concentrating. Gabapentin is similar to Pregabalin, and also has a wide dose range.

We recommend that patients should be permitted a trial of painkillers from each of these three groups (analgesics, anti-inflammatories and neuropathic), either alone or in combination according to licenced indications and usual practice in their country. The choice of medications, and the order in which they are used, should be supervised by a doctor, either a rheumatologist a general

practitioner. Corticosteroid injections will often be the first choice if only a few joints are involved, whereas anti-inflammatories or paracetamol are more likely to be used first when many joints are affected. The aim is to achieve an optimal response by matching the characteristics of the patient and the nature of the pain with the benefits and side effects of the different painkillers available.

Surgical interventions

Operations that are helpful for haemochromatosis arthropathy include joint fusion or joint replacement as appropriate for a particular joint.

Joint fusion is most commonly used for the wrist, ankle and mid foot regions to prevent pain from movement. This is an effective pain relieving operation but because the fused region becomes completely rigid, function is affected with reduced dexterity of the hand and flexibility of the foot, especially when standing and walking on uneven or sloping surfaces.

Joint replacement surgery is commonly performed for hips, knees and shoulders and less commonly for the elbow and ankle. In general, these operations are moderately to highly effective for reducing pain and restoring function, and for the hip and knee good results are often reported for more than 10 years.

There are a variety of operations for the hand including wrist fusion, removal of the bone at the base of the thumb (trapeziectomy) and joint replacements for the MCP joints (knuckles).

Surgery should not be delayed on the basis of young age if joint damage is so severe that pain is significantly interfering with everyday living. Discussion of surgical options with an orthopaedic surgeon to understand the benefits, risks and time spent recovering is strongly recommended if you are struggling with pain, despite trying the non-pharmacological and pharmacological interventions described, and your quality of life is significantly decreased. It usually takes some time to recover from surgery, and maximum benefit requires commitment to exercises and treatment guided by a physiotherapist. For best long-term results exercises to maintain muscle strength and joint movements need to continue, as outlined in the section on non-pharmaceutical interventions.

Conclusion

Haemochromatosis arthropathy has the potential to cause pain and functional difficulties in everyday life. We hope this information will help you manage these difficulties.

The HARI group is committed to improve the care of patients with haemochromatosis arthropathy. We aim to do this via patient and doctor education, research into disease mechanisms, clinical

documentation, and translation of better understanding from all of these endeavours into better care.

Recommended scientific review articles for further reading:

Sahinbegovic E, Dallos T, Aigner E, Axmann R, Manger B, Englbrecht M et al. Musculoskeletal disease burden of hereditary haemochromatosis. Arthritis Rheum 2010; 62: 3792-8.

Guggenbuhl P, Brissot P, Loreal O. Haemochromatosis: the bone and the joint. Best Pract Res Clin Rheumatol 2011; 25: 649-64.

Carroll GJ, Breidahl WH, Bulsara MK, Olynyk JK. Hereditary haemochromatosis is characterised by a clinically definable arthropathy that correlates with iron load. Arthritis Rheum 2011; 63: 286-94.

Husar-Memmer E, Stadlmayr A, Datz C, Zwerina J. HFE-related haemochromatosis: an update for the rheumatologist. Curr Rheumatol Rep 2014; 16:393-9.

Richardson A, Prideaux A, Kiely PDW. Haemochromatosis: unexplained MCP or ankle arthropathy should prompt diagnostic tests; findings from two UK observational cohort studies. Scand J Rheumatol 2016; doi 10.3109/03009742.2016.1155645

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