

**Viscosupplementation in the treatment of knee joint  
osteoarthritis – a snapshot summary report (June 2009)**

• **Key messages**

- The evidence for viscosupplementation is limited compared to other interventions in the management of osteoarthritis of the knee joint.
- The available evidence, when reviewed systematically, suggests that when administered with hyaluronan or hylan products, viscosupplementation reduces pain and improves function for up to 26 weeks.

**Definition**

Viscosupplementation refers to the intra-articular injection of hyaluronic acid (HA) in the form of a hyaluronate which is produced from rooster combs.

**Background**

Hyaluronic acid (HA) is the major constituent of a 1-2µm layer on the surface of articular cartilage; it is also a major constituent of synovial fluid. HA has many properties including exerting an anti-inflammatory effect; it acts as a lubricant when movements in the joint are slow, and as a shock absorber when movements are fast. The molecular weight of HA is reduced in arthritis; HA is diluted by the exudative properties occurring in inflammation. Arthritis therefore reduces the viscosity and elasticity of synovial fluid producing a fall in its lubrication and shock absorbing properties and making articular cartilage more vulnerable<sup>1</sup>. Four preparations are available, namely Orthovisc, Supatz, Hyalgan, and Synvisc<sup>2</sup>.

About 25% of people over the age of 55 years complain of chronic knee pain; this is usually diagnosed as osteoarthritis (OA)<sup>3</sup>; for 10% of that group, the pain is disabling<sup>4</sup>. The changes within a joint can produce a range of symptoms in patients, many of these symptoms are seen in osteopathic practice. Knee joint replacement is now regarded as a more successful treatment intervention, but the age at which this procedure is first offered to patients remains from 60-80<sup>5</sup>, except in unusual circumstances. Many patients are left to manage their pain with a variety of other approaches. Information from the GOSc snapshot survey of 2001 showed that 6% of all osteopathic consultations related to knee pain<sup>6</sup>, and physical treatments without pharmacological interventions are regarded as the recommended first line of treatment for osteoarthritis<sup>7</sup>. Osteopathic literature addressing the management of knee pain has been largely based in America and, therefore, includes pharmacological and surgical interventions<sup>8,9</sup>. Supporting advice and the role of weight and exercise in the management of OA knee joints has also been investigated by American osteopaths<sup>10</sup>.

The actual changes to the joint surfaces can be seen in the image below:

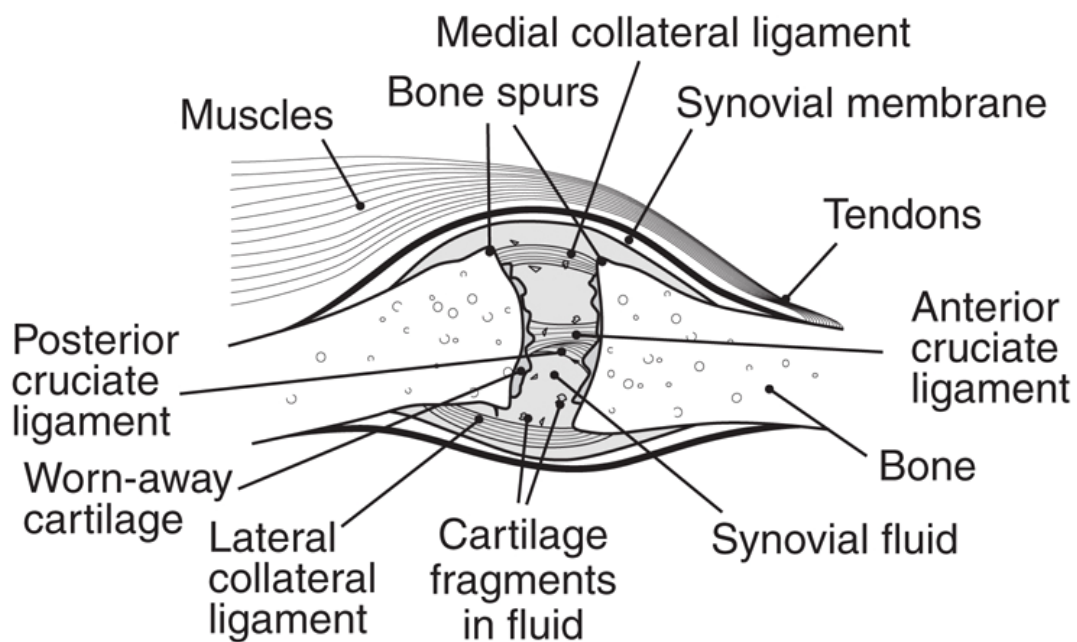


Image provided by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. <http://images.niams.nih.gov>.

As pain and disability increases, additional alternative options are offered to patients in secondary care; one such option is viscosupplementation. This intervention is being

offered more commonly to patients; this consideration of the evidence is intended to be helpful to patients and osteopaths alike when discussing this treatment option.

## **Osteoarthritis (OA) and the knee**

Clinically, osteoarthritis of the knee is characterised by focal areas of damage to the cartilaginous surfaces. Clinical features including pain, bony tenderness and crepitus are frequently accompanied by swelling and instability of the joint. The combined features commonly result in disability<sup>11</sup>. Radiographic changes are not commonly associated with levels of disability<sup>12</sup>, or the clinical progression of symptoms<sup>13</sup>.

Osteoarthritis of the knee is commonly defined radiographically as the presence of joint space narrowing with osteophyte or cyst formation, sclerosis, or attrition. A variety of sub-classifications of radiographic changes of the knee have been proposed, mainly according to radiographic patterns of compartmental disease<sup>14</sup>.

## **Mechanism for intra-articular viscosupplementation**

Viscosupplementation as a procedure has been proposed to try and reverse the changes described, re-establish the normal properties of synovial fluid and produce an anti-inflammatory reaction<sup>15,16</sup>. Intra-articular injections are known to produce a large placebo effect which will also contribute to any therapeutic benefit.

A number of different types of intra-articular therapies exist in addition to viscosupplementation, the commonest of which is glucocorticoids. A large number of case series exist concerning the use of glucocorticoids but relatively few randomised studies have been published on which to base judgements for efficacy. A working group report concluded that any benefit from intra-articular injections of glucocorticoids for OA is transient and merely underpins the successful actions of other therapies<sup>17</sup>.

Many compounds have been used historically for intra-articular injections to give symptomatic relief to patients with OA. Corticosteroids, for example, represent a very potent anti-inflammatory agent but their injection is thought to suppress cartilage proteoglycan synthesis, worsen cartilage lesion, or even cause degenerative lesions in normal cartilage<sup>18</sup>.

## **Biochemical changes**

A number of studies have been conducted to try and identify biochemical changes as a result of OA changes and to discriminate between early and end-stage disease to act as parameters to measure disease severity. Honsawek *et al*<sup>19</sup> identified that plasma levels

of bone morphogenic protein-7 significantly correlated with disease severity. In further studies they found that osteopontin in both plasma and synovial fluid is related to progressive OA joint damage<sup>20</sup>. Scanzello *et al*<sup>21</sup> found that Interlekin-15 (IL-15) is elevated in early OA of the knee suggesting the activation of an innate immune response in the synovial membrane.

## Evidence for effectiveness

A small number of placebo controlled trials have taken place and a summary of their findings is given in the table below.

Authors	Sample size	Comparator	Blinding	Outcome measure	Outcome	Time when benefit
Grecomoro et al., 1987 <sup>22</sup>	40 knees	Placebo	Yes	Pain score	HA better from 3 weeks	3-8 weeks
Dixon et al., 1988 <sup>23</sup>	63 subjects	Weaker form of HA	Yes	Change in pain score	Stronger form of HA better than placebo	5-23 weeks
Puhl et al., 1993 <sup>24</sup>	209	Weaker form of HA	Yes	Change in pain	Stronger form of HA better than placebo	9-13 weeks
Henderson et al., 1994 <sup>25</sup>	91	Saline	Yes	Not disclosed	No difference, return to baseline scores at 5 months	5 weeks to 5 months
Menkes, 1994 <sup>26</sup>		Methylprednisolone		Pain	HA better	5 and 8 weeks
Jones <i>et al.</i> , 1995 <sup>27</sup>	63	Triamcinolone hexacetonamide		Pain and joint effusion	HA better than triamcinolone hexacetonamide	6 months
Leardini <i>et al.</i> , 1987 <sup>28</sup>		Methylprednisolone		Pain	No difference	45 days

The Cochrane Collaboration undertook a systematic review of the evidence for viscosupplementation in 2005<sup>29</sup>. A total of 63 randomised controlled trials (RCTs) were examined and the authors concluded that for patients with osteoarthritis of the knee, viscosupplementation with either hyaluronan or hylan products, reduces pain and improves function for up to 26 weeks.

## **Factors affecting clinical effectiveness**

A number of preparations of HA exist which have different concentrations and molecular weights. One particular form of HA, Synvisc, differs in that it contains cross-linked hyaluronans which are intended to enhance the lubrication and shock-absorbing powers; this should also promote a longer retention time in the synovial space. The need for a series of weekly injections is one of the disadvantages of HA. Most treatment protocols recommend a series of five or more injections. This can affect tolerability for patients. Synvisc, by comparison, uses only three injections which will benefit tolerability<sup>15</sup>.

The dilution of the viscosupplementation has also been investigated to promote outcome. Waddell and Marino<sup>30</sup> found that interpatient variation was not affected by the difference in hyaluronan product injected. They stressed that the presence of joint effusion produced dilution of the injected product and pre-injection aspiration could improve functional outcome. Conrozier *et al*<sup>31</sup> examined multiple factors affecting outcome: they concluded that moderate effusion, injection lateral to the patella, joint space loss in a single compartment, and radiological meniscal calcinosis were all associated with good outcome.

## **Cost effectiveness**

Study data to allow pharmaco-economic evaluation aren't currently available. The presence of a large placebo effect is an important factor in attempting to produce cost-effectiveness data. Only one study currently exists that compares the effect of intra-articular therapy with placebo, viscosupplementation and glucocorticoids. This tentatively concluded that HA may have a slightly longer period of benefit than glucocorticoids; the study has the disadvantage of a high dropout rate in its long term follow up<sup>27</sup>.

## **Adverse reactions and contraindications**

Contraindications for injection of intra-articular HA are the same as those for any joint injection and others particular to HA including:

- infection in the overlying skin
- allergies to avian products

Adams *et al*<sup>32</sup> found that the commonest adverse reaction was joint infection, which was rare and directly dependent on the number of injections. One case of a systemic reaction

has been reported by Rees and Wojtulewski<sup>16</sup>. Bellamy *et al*<sup>29</sup> found that the studies they examined detected no safety issues, but the sample sizes for the study precluded any definitive comments on safety. This suggestion has been supported by Espallargues and Pons<sup>33</sup>, and Wobig<sup>34</sup>.

## Conclusion

Although the evidence for viscosupplementation is limited compared to other interventions in the management of osteoarthritis of the knee joint, available evidence, when reviewed systematically, suggests that when administered with hyaluronan or hylan products reduces pain and improves function for up to 26 weeks<sup>29</sup>.

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