Effects of Lyprinol on Expression Profile of Genes Related to Osteoarthritis

Osteoarthritis (OA)

Osteoarthritis (OA) is a degenerative joint disease characterized by joint pain and dysfunction caused by a progressive and irreversible loss of articular cartilage. OA is the most common form of arthritis and the WHO estimates that as much as 40% of people over 70 years of age suffer from OA of the knee. OA is associated with an extremely high economic burden, largely attributable to the effects of disability, comorbid disease, and the expense of treatment.[1]

Current recommendations for the management of OA include a combination of non-pharmacological interventions (e.g. patient education, muscle strengthening exercises and weight reduction) and pharmacologic agents (oral and topical analgesic agents, nonsteroidal anti-inflammatory drugs [NSAIDs] and intra-articular therapies such as corticosteroids and hyaluronan preparations).[2] Surgery may also be an option for patients who do not have satisfactory improvement of pain and function with adequate treatment.

Core outcome measures used to monitor the progression of OA and the effects of therapy include (1) pain, (2) physical function, (3) patient global assessment and (4) joint imaging.[3] Within the symptom severity domains, several validated measurement instruments commonly used are the visual analog scales (VAS), the Western Ontario McMasters Universities Osteoarthritis (WOMAC) Index and the Lequesne Functional Severity Index.[3]

Whilst conventional pharmacologic agents are effective in relieving pain, they are limited by their inability to alter disease progression and are associated with an adverse safety profile. NSAIDs in particular may cause gastrointestinal (GI) bleeding and cardiovascular risks (including hypertension and thrombotic events).[2]

Dietary Supplements for OA

The perception of dietary supplements being “natural” and “safe” may be one of the most compelling reasons why patients use them for treatment of OA. In addition, several supplements have shown to be at least as effective as NSAIDs at relieving the symptoms of OA, and preliminary evidence suggests several of these supplements may have a role in influencing the course of OA.[4]

A number of dietary supplements are marketed for treatment of OA. Glucosamine is one of the most commonly used supplements for OA and most research suggests that glucosamine sulfate can improve symptoms of pain related to OA, as well as slow disease progression in patients with OA of the knee. Chondroitin sulphate (CS) also appears to reduce OA symptoms and there is some evidence that CS may have a role as a structure-modifying agent in the management of patients with knee OA. Several other supplements are promoted for treating OA, such as methylsulfonylmethane, *Perna canaliculus* (green-lipped mussel), *Zingiber officinale* (ginger), *Harpagophytum procumbens* (devil’s claw), *Curcuma longa* (turmeric), and *Boswellia serrata* (frankincense), but more evidence regarding long-term efficacy or safety are required.

Green-Lipped Mussel (GLM)

The mollusc *Perna canaliculus* is endemic to New Zealand, where it is commonly known as green-lipped mussel (GLM). The observation that the coastal Maori population who regularly consumes the mussel suffered less arthritis than their inland counterparts, led to the development of nutritional supplements (e.g. Seatone® and Lyprinol®) containing extracts of the mussel.[5,6]

GLM is made up of a complex mixture of long-chain fatty acids, including polyunsaturated fatty acids (mainly omega-3 fatty acids), such as docosahexaenoic acid, eicosapentaenoic acid, eicosatetraenoic acid and palmitic acid.35 The anti-inflammatory properties of GLM are largely associated with the omega-3 fatty acids, which reduces prostaglandin and leukotriene synthesis via inhibition of the lipoxygenase (LOX) and cyclooxygenase (COX) pathways.[5,7]

A systematic review of GLM in the treatment of OA identified four randomized controlled trials assessing GLM as an adjunctive treatment to conventional medication in mild to moderate OA.[5] Three were placebo-controlled and the remaining one compared the effects of two extracts of GLM (a powder form and lipid extract, Lyprinol®). These trials reported clinical benefits in the GLM treatment group as measured by VAS pain score, morning stiffness, Lequesne functional index, patient and physician global assessment. These studies have reported a low incidence of adverse effects, generally consisting of GI symptoms (e.g. flatulence, epigastric discomfort, nausea).

Although GLM has a plausible biological mechanism for its purported action, more evidence on effectiveness and long-term safety is needed.

Genomic Studies of OA

Several genomic studies on OA have been carried out in recent years. Islama and co-workers used the cDNA microarray and PCR to analyse the expression profile of protein kinase (PTK) genes in primary human OA chondrocytes.[8] A total of 21 PTK genes were identified and several of these have never been shown to be expressed in human OA chondrocytes. For example, mRNA expression of a novel kinase HCK was detected in OA chondrocytes. a novel mutant form of the discoidin domain receptor 2 (DDR2) transcript was also identified.

Meng and co-workers have studied the gene expression levels in temporomandibular joint (TMJ) condylar cartilage during different stages of experimentally induced OA.[9] The gene expression profiles in normal and osteoarthritic cartilage identified a total of 138 genes that were significantly regulated in OA, including matrix-degrading proteases, protease inhibitors and genes involved in cell growth, apoptosis and bone remodeling. Some genes that had never been reported to be related with OA, such as AQP3, SPP2, NOV, DKK3 and EGLN3, were consistently observed to be up-regulated in induced OA, suggesting they may be involved in OA progression.

Aigner and co-workers carried out a large gene expression profiling study based on 78 normal and disease samples,[10] where many differentially expressed genes were identified, including the anabolic and catabolic matrix genes. Important oxidative defense genes, such as the genes for superoxide dismutases 2 and 3 and glutathione peroxidase 3, were prominently down-regulated, indicating that continuous oxidative stress to the cells and the matrix is one major underlying pathogenetic mechanism in OA.

Most recently, the arcOGEN Consortium undertook a large genome-wide association study (GWAS) in thousands of unrelated and retrospectively and prospectively selected patients with severe osteoarthritis.[11] Five genome-wide significant loci were identified for association with osteoarthritis, and about a dozen genes located at or near these loci. For example, an SNP in chromosome 3 encoding a missense polymorphism within the nucleostemin-encoding gene GNL3 was identified. Levels of nucleostemin were raised in chondrocytes from patients with osteoarthritis in functional studies. Other significant genetic markers including ASTN2 on chromosome 9, FILIP1 and SENP6 on chromosome 6, KLHDC5, PTHLH, and CHST11 in chromosome 12, and FTO gene, which is involved in regulation of bodyweight, a strong risk factor for osteoarthritis.

These findings provide the possibility to look into the genetics susceptibility and genomic signatures of OA for prevention and intervention.

Genomic Studies of Effects of GLM (Lyprinol) on OA

There are a number of issues that need to be discussed for the study of the effects of Lyprinol on the expression profile of genes related to osteoarthritis. Some of which are listed below:

1. Study subjects: human or animal or cellular models; scales;
2. Treatment dosages and duration and selection of baseline;
3. Collection and storage of (blood) samples;
4. Selection of genetic and genomic markers;
    a. genetic markers (single nucleotide polymorphysms SNPs) indicating susceptibility of OA – need to initiate GLM treatment
    b. genomic markers (gene expression profiles GEPs) indicating onset and severity of OA – proof of positive effect of GLM treatment
5. Experiments and data analysis;
6. Other outcome measures to monitor the progression of OA.

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