**PASIG MONTHLY CITATION BLAST: No.31** **June 2008**

Dear PASIG members:

As a follow up to the May Blast, PASIG member Gina Pongetti has provided a new "food for thought" with regards to the upcoming 2008 Beijing Olympics.

> As you watch the Balance Beam and Floor Exercises, notice the flexibility requirements in leaping and jumping for Women's Artistic and Rhythmic competitions. Consider how the spinal flexibility and back leg extension demands (sometimes combined with excessive knee flexion) affect the health of the spine, hip, and knees. What advice would you give a level 8 or 9 athlete with aspirations of Elite competition to prepare her body for such demands?
>
> Gina M. Pongetti, MPT, MA, CSCS, ART-Cert.

Again, a reminder to submit your abstract for CSM! We want to increase the research activities of the PASIG! CSM abstract submission closes on June 18th. Go to http://www.apta.org/csm for more information and to connect to Scholar One Abstract Central for electronic submission. Don't forget, the PASIG sponsors an annual student research scholarship. This award is to recognize students, who have had an abstract accepted to CSM, for their contribution to performing arts medicine and research. For more information on the research award please check our webpage (www.orthopt.org/sig_pa.php). Students with additional questions can contact PASIG President Leigh Roberts (lar@brventures.com).

For the annotated bibliography this month, I've selected the topic *Hylan GF-20*. This month's citations will be added to EndNote libraries available on the PASIG webpage for our members to access and download. (Information about EndNote referencing software can be found at http://www.endnote. com, including a 30-day free trial). If you'd like to suggest a topic or create one, please let me know. As always, your comments and entry contributions to these Citation Blasts are always welcome.

As always, please drop me an e-mail anytime.

Regards,
Shaw

Shaw Bronner PT, PhD, OCS
Chair, PASIG Research Committee
sbronner@liu.edu

**HYLAN G-F 20**

Some of us treat older dancers and other athletes who have developed hip or knee osteoarthritis. New minimally invasive, nonsurgical treatment options in the management of osteoarthritis include intra-articular viscosupplementation. Trials of intra-articular viscosupplementation with hyaluronic acid (hyaluronan and hylan G-F 20) have demonstrated decreases in pain and improved outcomes. The literature reports trials for the sacroiliac joint and shoulder as well as the knee and hip. The mechanism of hyaluronic acid injection involves increasing the viscoelasticity of the synovial fluid, possibly by promoting endogenous hyaluronic acid production. Other research supports two potential mechanisms for viscosupplementation: a biosynthetic-chondroprotective mechanism that may decrease the rate of deterioration of joint structure and an anti-inflammatory mechanism. Analyses of the effects of viscosupplements against 'placebo' controls generally support the efficacy of this class of intervention.

These new treatments appear to have minimal down time and, when combined with proper rehabilitation protocol, can help patients to regain and maintain their mobility gains and overall quality of life. Even more importantly, they may delay the need for total joint replacement.

Shaw Bronner PT, PhD, OCS
PASIG Research Chair

Adams ME, Atkinson MH, et al. (1995). The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: a Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. Osteoarthritis Cartilage **3**(4): 213-25.

To determine the safety and efficacy of viscosupplementation with hylan G-F 20, a cross-linked hyaluronan preparation, used either alone or in combination with continuous non-steroidal anti-inflammatory drug (NSAID) therapy, a randomized, controlled, multicenter clinical trial, assessed by a blinded assessor, was conducted in 102 patients with osteoarthritis (OA) of the knee. All patients were on continuous NSAID therapy for at least 30 days prior to entering the study. Patients were randomized into three parallel groups: (1) NSAID continuation plus three control arthrocenteses at weekly intervals; (2) NSAID discontinuation but with three weekly intra-articular injections of hylan G-F 20; and (3) NSAID continuation plus three injections, one every week, intra-articular injections of hylan G-F 20. Outcome measures of pain and joint function were evaluated by both the patients

and an evaluator at baseline and weeks 1, 2, 3, 7 and 12, with a follow-up telephone evaluation at 26 weeks. At 12 weeks all groups showed statistically significant improvements from baseline, but did not differ from each other. A statistical test for the equivalence, the q-statistic, demonstrated that viscosupplementation with hylan G-F 20 was at least as good or better than continuous NSAID therapy for all outcome measurements except activity restriction. At 26 weeks both groups receiving hylan G-F 20 were significantly better than the group receiving NSAIDs alone. A transient local reaction was observed in three patients after hylan G-F 20 injection; only one patient withdrew from the study as a result and all recovered without any sequela. Hylan G-F 20 is a safe and effective treatment for OA of the knee and can be used either as a replacement for or an adjunct to NSAID therapy.

Adams ME, Lussier AJ, et al. (2000). A risk-benefit assessment of injections of hyaluronan and its derivatives in the treatment of osteoarthritis of the knee. Drug Saf **23**(2): 115-30.

Hyaluronan is critical for the homeostasis of the joint as an organ, in part, because it provides the rheological properties (viscosity and elasticity) of the synovial fluid. These properties depend upon both the concentration and the molecular weight of the hyaluronan in the synovial fluid. In osteoarthritis, the hyaluronan is both smaller in size and lower in concentration. Thus, it is rational and physiologically meaningful to treat osteoarthritis with viscosupplementation, i.e. injection of material designed to increase the rheological properties of the synovial fluid. It is important, though, to assess the risks and benefits of such a physiological treatment. There are various products on the market for viscosupplementation. These include hyaluronan preparations of relatively low molecular weight (Hyalgan and ARTZ), a hyaluronan preparation of intermediate molecular weight, but still lower molecular weight than that of the hyaluronan in normal healthy synovial fluid (Orthovisc), and a cross-linked hyaluronan (a hylan) of high molecular weight (Synvisc). The evidence from in vitro and in vivo models of osteoarthritis and from clinical trials to date suggests that efficacy, as would be expected by mechanistic reasoning, depends strongly upon molecular weight. The available evidence indicates that these products differ little in the incidence and severity of adverse events (about 2 to 4%, almost always local swelling, and with no adverse sequelae). All are very well tolerated in comparison to nonsteroidal anti-inflammatory drug therapy, although direct comparisons are few. The only potentially serious adverse event is joint infection, which is rare and directly dependent upon the number of injections, among other factors. No infection has been related to contamination of any of the products. In summary, treatment with low molecular weight preparations of hyaluronan seems to be effective. However, viscosupplementation with hyaluronan preparations may have slightly higher risk and less benefit than viscosupplementation with hylans, because the relatively lower molecular weight hyaluronan preparations require more injections which may incur higher costs and theoretically an increased chance of infection. Viscosupplementation with hylans is clearly effective, and the available evidence suggests that the benefits almost certainly outweigh the risks.

Bagga H, Burkhardt D, et al. (2006). Longterm effects of intraarticular hyaluronan on synovial fluid in osteoarthritis of the knee. J Rheumatol **33**(5): 946-50.

OBJECTIVE: Intraarticular (IA) hylan injections constitute second-line therapy for osteoarthritis (OA) of the knee, but human studies suggesting a possible mechanism of action are lacking. We examined the effect of IA Hylan GF-20 injections on synovial fluid (SF) hyaluronan (HA) concentration, viscosity, and elasticity over a 6-month period in patients with mild to moderate OA of the knees. METHODS: Patients with symptomatic knee OA (Osteoarthritis Research Society International grade 1-2) had SF aspirated from the study knee pre- and 3 and 6 months post-Hylan injection. Primary endpoints included

SF HA concentration, viscosity, and elasticity. SF HA concentration was determined using uronic acid assay, and rheology measured using a micro-Fourier rheometer. RESULTS: Sequential SF samples were available from 32 of 60 subjects injected at baseline (15 men, 17 women; mean age 65 yrs) at 3 months post-injection. The mean HA concentration had increased by 13% ($p<0.0008$), and the complex shear modulus had increased by 16% ($p<0.03$). Sufficient SF was also available from 19 of these subjects at 6 months post-injection when mean HA concentration was 2.24+/-0.62 mg/ml compared to their baseline mean of 2.02+/-0.52 mg/ml, an increase of 10% ($p<0.053$). CONCLUSION: This open-label study showed a statistically significant change from baseline in both SF HA concentration and complex shear modulus at 3 months following IA Hylan GF-20 injection among subjects with mild to moderate knee OA. These results suggest that one possible mechanism of action of viscosupplementation is to promote endogenous HA production. Longer-term studies are required to identify whether these changes in SF measures are important for modification of disease progression in knee OA.

Bellamy N, Campbell J, et al. (2005). Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev(2): CD005321.

BACKGROUND: Osteoarthritis (OA) is the most prevalent chronic joint disorder worldwide and is associated with significant pain and disability. OBJECTIVES: To assess the effects of viscosupplementation in the treatment of OA of the knee. The products were hyaluronan and hylan derivatives (Adant, Arthrum H, Artz (Artzal, Supartz), BioHy (Arthrease), Durolane, Fermathron, Go-On, Hyalgan, Hylan G-F 20 (Synvisc Hylan G-F 20), NRD-101, Orthovisc, Ostenil, Replasyn, SLM-10, Suplasyn, Synject and Zeel compositum). SEARCH STRATEGY: MEDLINE, EMBASE, PREMEDLINE, Current Contents up to July 2003, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched. Specialised journals and reference lists of identified randomised controlled trials (RCTs) and pertinent review articles up to April 2004 were handsearched. SELECTION CRITERIA: RCTs of viscosupplementation for the treatment of people with a diagnosis of OA of the knee were eligible. Single and double-blinded studies, placebo-based and comparative studies were eligible. At least one of the four OMERACT III core set outcome measures had to be reported (Bellamy 1997). DATA COLLECTION AND ANALYSIS: Each trial was assessed independently by two reviewers (NB, JC) for its methodological quality using a validated tool. All data were extracted by one reviewer (JC) and verified by a second reviewer (VR). Continuous outcome measures were analysed as weighted mean differences (WMD) with 95% confidence intervals (CI). Dichotomous outcomes were analyzed by relative risk (RR). MAIN RESULTS: Sixty-three trials with a median quality score of 3 (range 1 to 5) were identified. Follow-up periods varied between day of last injection and one year. Thirty-seven trials included comparisons of hyaluronan/hylan and placebo, nine trials included comparisons of intra-articular (IA) corticosteroids, and five trials included comparisons of nonsteroidal anti-inflammatory drugs (NSAIDs). The pooled analyses of the effects of viscosupplements against 'placebo' controls generally supported the efficacy of this class of intervention. In these same analyses, differential efficacy effects were observed for different products on different variables and at different timepoints. Of note is the 5 to 13 week post injection period which showed a percent improvement from baseline of 11 to 54% for pain and 9 to 15% for function. In general, comparable efficacy was noted against NSAIDs and longer-term benefits were noted in comparisons against IA corticosteroids. In general, few adverse events were reported in the hyaluronan/hylan trials included in these analyses. AUTHORS' CONCLUSIONS: Based on the aforementioned analyses, viscosupplementation is an effective treatment for OA of the knee with beneficial effects: on pain, function and patient global assessment; and at different post injection periods but especially at the 5 to 13 week post injection period. It is of note that based on non-randomised groups, the

magnitude of the clinical effect, as expressed by the WMD and standardised mean difference (SMD) from the RevMan 4.1 output, is different for different products, comparisons, timepoints, variables and trial designs. However, there are few randomised head-to-head comparisons of different viscosupplements and readers should be cautious, therefore, in drawing conclusions regarding the relative value of different products. The clinical effect for some products, against placebo, on some variables at some timepoints is in the moderate to large effect-size range. Readers should refer to relevant tables to review specific detail given the heterogeneity in effects across the product class and some discrepancies observed between the RevMan 4.1 analyses and the original publications. Overall, the analyses performed are positive for the HA class and particularly positive for some products with respect to certain variables and timepoints, such as pain on weight bearing at 5 to 13 weeks postinjection.In general, sample-size restrictions preclude any definitive comment on the safety of the HA class of products; however, within the constraints of the trial designs employed no major safety issues were detected. In some analyses viscosupplements were comparable in efficacy to systemic forms of active intervention, with more local reactions but fewer systemic adverse events.In other analyses HA products had more prolonged effects than IA corticosteroids. Overall, the aforementioned analyses support the use of the HA class of products in the treatment of knee OA.

Conrozier T, Bertin P, et al. (2006). Clinical response to intra-articular injections of hylan G-F 20 in symptomatic hip osteoarthritis: the OMERACT-OARSI criteria applied to the results of a pilot study. Joint Bone Spine **73**(6): 705-9.

OBJECTIVE: To assess, using the OMERACT-OARSI criteria, the clinical response of patients presenting with symptomatic hip osteoarthritis (OA) to one intra-articular injection of hylan G-F 20. METHODS: Open-label, multi-centre, prospective, pilot study. Fifty-six patients presenting with primary hip OA, Kellgren-Lawrence grade II-III, age > or =40, with walking pain measuring 50-90 mm on a 100 mm visual analogue scale (VAS). Intra-articular injection of a single 2 ml dose of hylan G-F 20 into the hip joint under fluoroscopic guidance. A second injection could be administered at day (D) 30, 60 or 90 if pain was unchanged or returned to baseline levels. EFFICACY CRITERIA: The outcome of the first injection in the intent-to-treat (ITT) population was analysed 90 days after the injection in those patients that received a single injection, and on the day of the second injection in those patients that required two injections, using OMERACT-OARSI responder criteria (obtained from WOMAC A and C indices and the patient's global evaluation) and variation in walking pain on VAS. RESULTS: The percentage of responders according to the OMERACT-OARSI response criteria was 53.6%. An inverse correlation was observed between reduction in pain and joint space narrowing score (P=0.03). CONCLUSION: In the absence of a control group, the efficacy of the treatment cannot be determined conclusively. Nevertheless these data suggest that hylan G-F 20 is a symptomatic treatment of hip OA, particularly in less severe radiological cases. A double-blind, controlled study is required to confirm these data.

Greenberg DD, Stoker A, et al. (2006). Biochemical effects of two different hyaluronic acid products in a co-culture model of osteoarthritis. Osteoarthritis Cartilage **14**(8): 814-22.

OBJECTIVES: To compare the effects of two hyaluronic acid (HA) formulations on mediators of matrix turnover and inflammation in an IL-1-treated cartilage-synovium co-culture model with the aim of elucidating mechanisms by which viscosupplementation exerts beneficial effects in osteoarthritic joints. DESIGN: A co-culture model (100 ng/ml interleukin-1beta (IL-1beta) added to canine synovial and cartilage explants) was used to investigate the effects of HA on cartilage-synovium interactions. Three concentrations (1x, 0.5x, and 0.1x) of two commercial sources of HA (A: Synvisc [hylan G-F 20]; B: Hyalgan [sodium hyaluronate]) were used. Co-cultures without IL-1beta (negative) or with IL-1beta (positive)

but neither HA product served as controls. The liquid media were collected every 3 days and explants of cartilage and synovium were collected on days 3, 6, and 20. Media and explants were analyzed histologically, biochemically, and immunohistochemically. RESULTS: Glycosaminoglycan (GAG) content was measured in cartilage explants. GAG content in explants was higher in both HA groups at the beginning and the conclusion of the study compared to the IL-1beta-treated group. GAG content of the media was significantly ($P<0.05$) lower in the Synvisc group than all other groups early. The Hyalgan group demonstrated progressively less GAG release later in the study. The addition of Synvisc did not decrease the matrix metalloproteinase (MMP)-3 concentrations at any point. MMP-3 concentrations were significantly ($P<0.05$) lower among the 1x and 0.5x Hyalgan groups on day 20 compared to the IL-1beta-treated group. On day 3, prostaglandin E(2) concentrations were significantly ($P<0.05$) higher in the IL-1beta-treated group compared to other groups. Both HA groups had less nitric oxide production than the control groups throughout the study. CONCLUSIONS: This study supports two potential mechanisms for viscosupplementation: a biosynthetic-chondroprotective mechanism, with a possible delay in onset depending on the form of HA; and an anti-inflammatory mechanism.

Pagnano M, Westrich G (2005). Successful nonoperative management of chronic osteoarthritis pain of the knee: safety and efficacy of retreatment with intra-articular hyaluronans. Osteoarthritis Cartilage **13**(9): 751-61.

CONTEXT: Although there are many nonsurgical therapies available for the treatment of pain associated with osteoarthritis (OA), their long-term use and safety have not been systematically followed. Intra-articular hyaluronan therapy has been used in the treatment of symptoms associated with OA of the knee with a very favorable safety profile. Five intra-articular hyaluronan products are approved in the US. No systematic review of the safety and efficacy of their chronic use has been reported. OBJECTIVE: To evaluate the literature on the efficacy and safety of repeat courses of hyaluronan therapy in patients with OA of the knee. DATA SOURCES: MEDLINE, EMBASE, searched through October 2004. STUDY SELECTION: Databases were searched using the terms hyaluronan, sodium hyaluronate, hyaluronic acid, hylan, hylan G-F 20, osteoarthritis, adverse events, repeat treatment, and multiple courses. DATA SYNTHESIS: There are some data that support the benefit and safety of repeat treatment for all products. Data also indicate that one formulation of sodium hyaluronate (molecular weight [MW] 500-730 kDa) is well tolerated and as effective after multiple courses of treatment as it is after a single course. There is also clinical evidence that prolonged use of sodium hyaluronate (MW 500-730 kDa) may significantly decrease the rate of deterioration of joint structure. Localized severe acute inflammatory reactions reported with repeated treatment in some patients are not a class effect but may be linked to physicochemical characteristics of hylan-based treatment. CONCLUSIONS: Repeat courses of the hyaluronans are safe and effective in the treatment of pain associated with OA of the knee.

Silverstein E, Leger R, et al. (2007). The use of intra-articular hylan G-F 20 in the treatment of symptomatic osteoarthritis of the shoulder: A preliminary study. Am J Sports Med.

BACKGROUND: While hylan G-F 20 is an approved therapy for the treatment of knee osteoarthritis, there are few reports of its use in shoulder osteoarthritis. HYPOTHESIS: Hylan G-F 20 can reduce pain and improve function in patients with glenohumeral osteoarthritis. STUDY DESIGN: Case series; Level of evidence, 4. METHODS: Thirty consecutive patients with idiopathic glenohumeral osteoarthritis who failed to respond to standard conservative measures were enrolled. Patients received 3 weekly intra-articular hylan G-F 20 injections in their affected shoulder and completed a visual analog scale for pain, the UCLA score, and the Simple Shoulder Test at baseline and at 1, 3, and 6 months

after the third injection. RESULTS: Of the 30 patients, 3 withdrew during the washout period before treatment; the remaining patients (17 men and 10 women) had an average age of 62 years. The mean baseline visual analog scale score was 54, UCLA score was 15.7, and Simple Shoulder Test score was 5.7 (of 12 possible "yes" responses). At the 6-month follow-up, hylan G-F 20 significantly improved visual analog scale (mean 30, P < .001), UCLA (mean 24, P < .001), and Simple Shoulder Test (7.6 "yes" responses, P < .001) scores. More patients slept comfortably after treatment (56%) versus before treatment (15%). Nine patients had a visual analog scale improvement >40 points after 6 months. No device-related adverse events were observed. CONCLUSION: Hylan G-F 20 may have a beneficial therapeutic effect on some symptomatic patients with glenohumeral osteoarthritis.

Srejic U, Calvillo O, et al. (1999). Viscosupplementation: a new concept in the treatment of sacroiliac joint syndrome: a preliminary report of four cases. Reg Anesth Pain Med **24**(1): 84-8.
BACKGROUND AND OBJECTIVES: We describe a new therapeutic modality for sacroiliac joint syndrome that represents an alternative to other treatment modalities. We report on four cases of sacroiliac joint syndrome with severe pain. METHODS: Three patients had undergone operative treatment of the lumbar spine and one patient suffered from severe osteoarthritis of the spine. All patients were diagnosed with sacroiliac joint syndrome by means of patient history, physical examination, and intra-articular local anesthetic injection preceded by sacroiliac arthrogram. All patients received three injections of Hylan GF 20 in the sacroiliac joints 2 weeks apart. RESULTS: Twelve to 16 weeks after the injections, the pain was reported to be 40-67% better when measured on the visual analog scale. The duration of the beneficial effect of Hylan on arthralgia and joint function was undetermined. CONCLUSIONS: Viscosupplementation of the sacroiliac joint induced a significant degree of analgesia in all four patients. This treatment modality could represent an option in the management of sacroiliac joint pain and dysfunction.

Vad VB, Sakalkale D, et al. (2003). Role of hylan G-F 20 in treatment of osteoarthritis of the hip joint. Arch Phys Med Rehabil **84**(8): 1224-6.
OBJECTIVE: To study the efficacy of hylan G-F 20 in the treatment of osteoarthritis (OA) of the hip joint. DESIGN: Prospective within-group study. SETTING: Musculoskeletal rehabilitation clinic. PARTICIPANTS: Twenty-two patients (25 hips) with hip joint OA who had failed to find pain relief from conservative methods such as physical therapy, exercises, and steroid injections. Demographics included 14 men and 11 women (mean age, 56.4y), 21 of whom had mild to moderate OA and 4 of whom had severe OA of the hips. INTERVENTION: Each hip joint was injected with 2mL of hylan G-F 20 at 2, 3, and 4 weeks and fluoroscopic lavage with 100mL of normal saline at week 1. All patients had standard hip exercise regimen after the injection. MAIN OUTCOME MEASURES: American Academy of Orthopaedic Surgeons (AAOS) Lower Limb Core Scale score and visual numeric pain score. RESULTS: At 1-year follow-up, the AAOS Lower Limb Core Scale score improved from a preinjection mean of 44.2 to a follow-up mean of 86.1 (P<.05). The mean visual numeric pain score improved from a preinjection mean of 8.7 (range, 6.4-10) to a follow-up mean of 2.3 (range, 0-7.2). The overall success rate was 84%. In patients with mild to moderate OA, the mean pain score decreased from a preinjection value of 7.8 to a follow-up value of 1.7. The success rate was 90.5% in that subgroup. In patients with severe OA, the mean pain score decreased from a preinjection value of 9.1 to a follow-up value of 3.8. The success rate was 50% in that subgroup. There were no complications related to the injection. CONCLUSION: Use of hylan G-F 20 injection is a viable option for treatment of mild to moderate OA of the hip joint.

Wen DY (2000). Intra-articular hyaluronic acid injections for knee osteoarthritis. Am Fam Physician **62**(3): 565-70, 572.

Knee osteoarthritis is a common but often difficult problem to manage in primary care. Traditional nonsurgical management, consisting of lifestyle modification, physical therapy and pharmacologic therapy (e.g., analgesics, anti-inflammatory medications), is often ineffective or leaves residual symptoms. Viscosupplementation is a newly available option for patients with symptomatic knee osteoarthritis that involves a series of intra-articular injections of hyaluronic acid. The exact mechanism of action is unclear, although increasing the viscoelasticity of the synovial fluid appears to play a role. Clinical experience and studies of the two hyaluronic acid products available, hyaluronan and hylan G-F 20, are inconclusive but seem to indicate beneficial effects with minimal adverse reactions in a significant number of patients. The exact indications for viscosupplementation are still evolving, but it currently can be considered for use in patients who have significant residual symptoms despite traditional nonpharmacologic and pharmacologic treatments. In addition, patients who are intolerant of traditional treatments (e.g., gastrointestinal problems related to anti-inflammatory medications) can be considered for these injections. Family physicians with the ability to perform intra-articular knee injections should consider them an option in patients with symptomatic knee osteoarthritis.