

Low quality of evidence for glucosamine-based nutraceutical compounds in equine joint disease: Review of *in vivo* studies

W. PEARSON and M. LINDINGER†

Department of Plant Agriculture, Equine Sciences Bldg, 50 McGilvray St. University of Guelph, Guelph, Ontario N1G 2W1; and †Department of Human Health and Nutritional Sciences University of Guelph, Guelph, Ontario N1G 2W1, Canada.

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TABLE 3: Overview of *in vivo* studies pertaining to the evaluation of glucosamine-based nutraceutical compounds (GBN) in horses

No. of horses	Age (years)	Description of animals	Study design	Intervention	Control	Duration of intervention	Reported treatment-related effects	Reference	Quality score (%)
<i>Studies of 'Excellent' Quality (QS>80.0)</i>									
No studies identified.									
<i>Studies of 'Good' Quality (70.0<QS≤80.0)</i>									
No studies identified.									
<i>Studies of 'Fair' Quality (60.0<QS≤69.9)</i>									
Experiment 1 4 treatment A 4 treatment B 4 treatment C 4 control	2.5–24	Healthy geldings and mares.	Randomised, controlled trial.	Sasha's EQ ⁱ A: 15 g/day B: 45 g/day C: 75 g/day	No treatment.	84 days	• No treatment effects on blood biochemistry, haematology or urinalysis.	Pearson <i>et al.</i> (2009)	68.7
Experiment 2 5 treatment; 5 control	5–12	Healthy geldings; articular inflammation induced by intra-articular IL-1 injection.	Randomised, controlled trial.	Sasha's EQ ⁱ plus flavouring and molasses 15 g b.i.d.	Flavouring and molasses	28 days	• Inhibition of IL-1-induced PGE ₂ and GAG. • Reduction in synovial fluid PGE ₂ . • Significant increase in synovial fluid GAG. • Reduction in joint circumference.		
8 treatment A 8 treatment B 8 treatment C 8 treatment D	14.4 ± 2.1	Healthy mares	Randomised cross-over.	A: GS ^f 20 mg/kg bwt oral B: GS ^f 20 mg/kg bwt i.v. C: GH ^g 20 mg/kg bwt oral D: GH ^g 20 mg/kg bwt i.v.	none	Single dose	• Significantly higher synovial fluid levels of glucosamine are attained following oral administration of GS compared with GH. • No difference with i.v. dosing.	Meulyzer <i>et al.</i> (2008)	65.8
8 treatment (A–D)	14.4 ± 2.1	Healthy mares; articular inflammation induced by intra-articular LPS injection.	Randomised, cross-over trial.	GH ^g 20 mg/kg bwt in 500 ml sterile saline.	500 ml sterile saline.	Single dose 12 h after induction of lameness by LPS.	• No effect of GH administration on synovial fluid total protein or WBC. • LPS induces significant increase in synovial fluid glucosamine in treatment and control groups.	Meulyzer <i>et al.</i> (2009)	61.0

TABLE 3 (continued): Overview of *In vivo* studies pertaining to the evaluation of glucosamine-based nutraceuticals in horses

No. of horses	Age (years)	Description of animals	Study design	Intervention	Control	Duration of intervention	Reported treatment-related effects	Reference	Quality score (%)
<i>Studies of 'Poor' Quality (QS≤60.0)</i>									
8 treatment A 8 treatment B	6–15	Healthy mares	Randomised 2-way crossover.	A: GH ^a 20 mg/kg bwt i.v. B: GH ^a 20 mg/kg bwt oral.	none	Single dose	<ul style="list-style-type: none"> GH 5.9% bioavailability in horses. Other pharmacokinetic parameters described. 	Laverty <i>et al.</i> (2005)	59.9
8 treatment; 6 control	10.8 ± 0.8	Geldings (n = 9), mares (n = 4) and stallions (n = 1) with lameness due to navicular syndrome.	Double blind, placebo controlled randomised clinical trial.	Cosequin ^a 16.5 g b.i.d.	Identical looking powder containing only excipients.	8 weeks	<ul style="list-style-type: none"> Improvement in median lameness score. Improvement in median algofunctional lameness index. Improvement in overall clinical score. No effect on radiographic signs of navicular syndrome. 	Hanson <i>et al.</i> (2001)	59.1
39 (number of treatments and controls not reported).	N/A	Gender not reported Horses diagnosed with 'naturally occurring osteoarthritis'; lameness score 2–4, (AAEP scale).	Double-blind placebo controlled clinical trial.	Myristol ^k Days 1–14: 113 g/day Days 15–42: 75 g/day.	Undisclosed filler.	42 days	<ul style="list-style-type: none"> Improvement in AAEP lameness score, lameness at walk, lameness after flexion, and pain upon manual joint flexion. 	Keegan <i>et al.</i> (2007)	48.4
4 treatment A; 4 treatment B; 2 control	>2	Healthy nongestating Standardbred mares; articular inflammation induced by osteochondral defect.	Randomised, blinded controlled trial.	A: CS ^h (9600 kDa) 2.5 g B: CS ^h (25000 kDa) 2.5 g	Inactive placebo; composition not provided.	10 weeks	<ul style="list-style-type: none"> Significant decrease in joint circumference. Significant increase in maximum flexion angle. Nonsignificant improvement in stride length. Significant increase in synovial fluid GAG followed by significant decrease after 6 weeks. Significant decrease in synovial fluid PGE₂. Significant reduction in synthesis and/or release of MMP3. 	Verde <i>et al.</i> (2006)	47.4
<i>Experiment 1</i> 10 treatment (A–D)	N/A	Mature horses	Randomised 4-way crossover study.	A: CS ⁿ (8 kDa) 3 g i.v. B: CS ⁿ (8 kDa) 3 g oral C: CS ⁿ (16.9 kDa) 3 g i.v. D: CS ⁿ (16.9 kDa) 3 g oral All treatments administered concurrently with 9g GH ^o .	None	Single dose	<ul style="list-style-type: none"> No measurable GH in peripheral blood. CS (8 kDa) bioavailability 32.2%. CS (16.9 kDa) bioavailability 22%^p. Other pharmacokinetic parameters described. 	Du <i>et al.</i> (2004)	41.5
<i>Experiment 2</i> 2 treatment	N/A	Mature horses; health status not described	2-way crossover	A: GH ⁿ 9 g i.v. B: GH ⁿ 125 mg/kg bwt (~ 60 g) oral.	none	Single dose	<ul style="list-style-type: none"> GH 2.5% bioavailability in horses. Other pharmacokinetic parameters described. 		

TABLE 3 (continued): Overview of *In vivo* studies pertaining to the evaluation of glucosamine-based nutraceuticals in horses

No. of horses	Age (years)	Description of animals	Study design	Intervention	Control	Duration of intervention	Reported treatment-related effects	Reference	Quality score (%)
9 treatment; 7 control	1.3–1.7	Healthy Standardbred horses in early race training.	Randomised, placebo-controlled trial.	GH ^g 4 g b.i.d.	Glucose 4 g twice daily.	48 weeks	<ul style="list-style-type: none"> No effect on serum markers of bone (osteocalcin, pyridinoline crosslinks of type I collagen) or cartilage (keratin sulphate) metabolism. 	Caron <i>et al.</i> (2002)	39.7
10 treatment	N/A	Healthy show jumpers	Open, uncontrolled field study.	Unidentified glucosamine-based product 10 g/day.	None	6 years (+ 2 years pretreatment)	<ul style="list-style-type: none"> Significant reduction in frequency of intra-articular injection of hyaluronan and steroids. Significant increase in mean duration between injections. No further improvement beyond 2 years of supplementation. 	Rodgers (2006)	36.8
25 treatment	6–20	Geldings (n = 17), mares (n = 7) and stallions (n = 1) with lameness due to degenerative joint disease.	Open, uncontrolled clinical trial.	Cosequin ^a 9 ^c or 12 ^d g b.i.d.	None	6 weeks	<ul style="list-style-type: none"> Increase in stride length compared with baseline. Reduction in lameness grade compared with baseline. 	Hanson <i>et al.</i> (1997)	35.8
15 treatment; 5 control	15–35	Mixed breed geldings (n = 11) and mares (n = 9); health status not disclosed.	Double-blind, randomised controlled trial.	Synequin ^e Days 1–35: 20 ^f or 30 ^g g/day Days 35–60: 10 ^f or 15 ^g g/day Days 60–84: 10 g/day.	Filler; composition not provided.	12 weeks	<ul style="list-style-type: none"> Significant improvement in % change in range of motion (weeks 8–12) in treated horses. Significant increase in % change in stride length (weeks 8–12). Significant increase in % change in swing duration. 	Forsyth <i>et al.</i> (2006)	32.8
5 or 6/group (not specified)	1.2–1.7	Quarter horses; health status not provided.	2 x 2 factorial field trial [factors: longeing (+/-); GH treatment (+/-)].	GH ^g Weeks 1–4: 11.0 g/day Weeks 5–6: 7.0 g/day Weeks 7–8: 4.0 g/day.	No treatment	8 weeks	<ul style="list-style-type: none"> No effect of treatment on serum osteocalcin. Increase in serum keratan sulphate in walking horses. 	Fenton <i>et al.</i> (1999)	31.1
6 treatment; 6 control	2–12	Healthy mares (n = 10) and geldings (n = 2); articular inflammation induced by FCA ^b .	Parallel, unblended laboratory study.	Cosequin ^a 9 g b.i.d.	Untreated	36 days	<ul style="list-style-type: none"> No effect on lameness grade, carpal circumference, synovial fluid protein or carpal flexion. 	White <i>et al.</i> (1994)	28.2

TABLE 3 (continued): Overview of *In vivo* studies pertaining to the evaluation of glucosamine-based nutraceuticals in horses

No. of horses	Age (years)	Description of animals	Study design	Intervention	Control	Duration of intervention	Reported treatment-related effects	Reference	Quality score (%)
8 treatment; 8 control	N/A	Riding horses with <i>Grade 1 or 2</i> lameness	Double-blind placebo controlled crossover clinical trial.	Cortaflex [™] ; Days 1–5: 60 ml/day Days 6–14: 30 ml/day.	Aqueous base vehicle containing dextrose, corn syrup, sorbitol, xanthan gum, sodium benzoate and yucca extract.	2 x 2 week treatments in cross-over fashion with 2-week washout between treatments.	• Significant improvement in gait symmetry of the tarsal joints.	Clayton <i>et al.</i> (2002)	25.9

Abbreviations: CS = chondroitin sulphate; GH = glucosamine hydrochloride; PGE₂ = prostaglandin E₂; GAG = glycosaminoglycan; MMP3 = matrix metalloproteinase 3; MMP 9: matrix metalloproteinase 9; WBC: white blood cell count; N/A: not available; SD: standard deviation; LPS = lipopolysaccharide from *E. coli*.

^aNutramax Laboratories, USA; glucosamine hydrochloride (GH; 60%), chondroitin sulphate (CS; 20%), manganese (0.5%), ascorbate (3.5%), undisclosed filler (16%). ^bFreunds Complete Adjuvant [concentrated formulation of mycobacteria (usually *Mycobacterium tuberculosis*) in mineral oil]. ^cfor horses weighing <545 kg. ^dfor horses weighing >545 kg. ^eVetPlus UK; chondroitin sulphate (CS - 19% w/w), GH (50%), N-acetyl-D-glucosamine (5%) and filler (25%). ^ffor horses weighing <500 kg. ^gfor horses weighing >500 kg. ^hSyntex SA, Buenos Aires, Argentina. ⁱInterpath Pty Ltd, Australia; undisclosed percentages of NZGLM, SKC, Biota oil and AB. ^jarithmetic mean; no variability estimates provided. ^kTryan Enterprises, USA; undisclosed filler (74.3%), cetyl myristoleate fatty acid complex (6%), GH (5.9%), methylsulfonylmethane (5.9%), hydrolysed collagen (3.9%), DL methionine (2%), ascorbate (1.3%), manganese (0.3%), zinc (0.3%), copper (0.07%). ^mEquine America, UK; vitamin B6 (1.1%), ascorbic acid (1.06%), glutamine (1.0%), glycine (1.0%), proline (0.31%), glutamic acid (0.30%), manganese (0.11%), glucuronic acid (0.05%), copper (0.04%), sulphur (0.03%), with the remaining 95% comprised of 'animal protein products', individual amino acids and yucca in undisclosed percentages. ⁿTRH122, Nutramax Laboratories, USA. ^oFCHG49, Nutramax Laboratories, USA. ^pnote the very high variability (SD = 22.5%). ^qG1514 Sigma Aldrich. ^rDona, Rotta Pharmaceuticals Inc, New Jersey, USA. ^sTryan Enterprises, Texas, USA.

References

- Caron, J.P., Peters, T.L., Hauptman, J.G., Eberhart, S.W. and Orth, M.W. (2002) Serum concentrations of keratan sulfate, osteocalcin, and pyridinoline crosslinks after oral administration of glucosamine to Standardbred horses during race training. *Am. J. vet. Res.* **63**, 1106-1110.
- Clayton, H.M., Almeida, P.E., Prades, M., Brown, J., Tessier, C., Joel, L. and Lanovaz, J.L. (2002) Double-blind study of the effects of an oral supplement intended to support joint health in horses with tarsal degenerative joint disease. *Proc. Am. Ass. equine Practns.* **48**, 314-317.
- Du, J., White, N. and Eddington, N.D. (2004) The bioavailability and pharmacokinetics of glucosamine hydrochloride and chondroitin sulfate after oral and intravenous single dose administration in the horse. *Biopharm. Drug Dispos.* **25**, 109-116.
- Fenton, J.I., Orth, M.W., Chlebek-Brown, K.A., Nielsen, B.D., Corn, C.D., Waite, K.S. and Caron, J.P. (1999) Effect of longeing and glucosamine supplementation on serum markers of bone and joint metabolism in yearling quarter horses. *Can. J. vet. Res.* **63**, 288-291.
- Forsyth, R.K., Bridgen, C.V. and Northrop, A.J. (2006) Double blind investigation of the effects of oral supplementation of combined glucosamine hydrochloride (GHCL) and chondroitin sulphate (CS) on stride characteristics of veteran horses. *Equine vet. J., Suppl.* **36**, 622-625.
- Hanson, R.R., Smalley, L.R., Huff, G.K., White, S. and Hammad, T.A. (1997) Oral treatment with a glucosamine-chondroitin sulfate compound for degenerative joint disease in horses: 25 Cases. *Equine Pract.* **19**, 16-22.
- Hanson, R.R., Brawner, W.R., Blaik, M.A., Hammad, T.A., Kincaid, S.A. and Pugh, D.G. (2001) Oral treatment with a nutraceutical (Cosequin) for ameliorating signs of navicular syndrome in horses. *Vet. Ther. Res. appl. vet. Med.* **2**, 148-159.
- Keegan, K.G., Hughes, F.E. and Buonomo, F.C. (2007) Effects of an oral nutraceutical on clinical aspects of joints disease in a blinded, controlled, clinical trial. *Proc. Am. Ass. equine Practns.* **53**, 252-255.
- Lavery, S., Sandy, J.D., Celeste, C., Vachon, P., Marier, J.F. and Plaas, A.H. (2005) Synovial fluid levels and serum pharmacokinetics in a large animal model following treatment with oral glucosamine at clinically relevant doses. *Arthritis Rheum.* **52**, 181-191.
- Meulyzer, M., Vachon, P., Beaudry, F., Vinardell, T., Richard, H., Beauchamp, G. and Lavery, S. (2008) Comparison of pharmacokinetics of glucosamine and synovial fluid levels following administration of glucosamine sulphate or glucosamine hydrochloride. *Osteoarthritis Cartilage* **16**, 973-979.
- Meulyzer, M., Vachon, P., Beaudry, F., Vinardell, T., Richard, H., Beauchamp, G. and Lavery, S. (2009) Joint inflammation increases glucosamine levels attained in synovial fluid following oral administration of glucosamine hydrochloride. *Osteoarthritis Cartilage* **17**, 228-234.
- Pearson, W., Orth, M. and Lindinger, M.I. (2009) Response to intra-articular IL-1 by horses receiving an anti-inflammatory dietary nutraceutical and safety of the product over 12-weeks. *Am. J. vet. Res.* In press.
- Rodgers, M.R. (2006) Effects of Oral Glucosamine and chondroitin sulfates supplementation on frequency of intra-articular therapy of the horse tarsus. *Intern. J. appl. Res. vet. Med.* **4**, 155-162.
- Verde, C.R., Simpson, M.I., Villarino, N., Frigoli, A. and Landoni, M.F. (2006) Therapeutic and hematological effects of native and low molecular weight chondroitin sulphate administered orally in horses with experimental arthritis. *Revista Electrónica de Veterinaria REDVET*; 7(1) available at <http://www.veterinaria.org/revistas/redvet/n010106.html>.
- White, G.W., Jones, E.W., Hamm, J. and Sanders, T. (1994) The efficacy of orally administered sulfated glycosaminoglycans in chemically induced equine synovitis and degenerative joint disease. *J. equine vet. Sci.* **14**, 350-353.