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Glucosamine and Probiotics:

for Osteoarthritis Joint Pain Relief.

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Introduction

Osteoarthritis (OA) is the most prevalent form of arthritis (mostly affecting the cartilage of a joint) and commonly targets the joints of the knee and less frequently joints of the hip, shoulder, spine (most commonly zygapophyseal, apophyseal, or facet joints of the spine, especially in the mid and lower cervical spine, and in the lower lumbar spine (L3 to L5), hands and toes. Musculoskeletal disease is a major cause of disability and handicap, and arthritis is the most prevalent form.[1]

Healthy cartilage allows bones to glide over each other and assists in absorbing the shock of joint movement. In OA, the top layer of cartilage breaks down and wears away. This then leads the bones below the cartilage to brush together, causing pain, swelling, and loss of joint motion; factors that maintain the joint in a local pro–inflammatory state. With no known cure or proven disease-modifying therapy, the first-choice recommended pharmacological treatment for mild to moderate pain of the knee or hip is paracetamol, with a maximum dose of 4g/day.[2] In the absence of a beneficial response, or presence of pain and inflammatory sequelae, alternate therapy with a non-steroidal anti-inflammatory drug (NSAID) is indicated. Gastrointestinal tract (GIT) safety, however, may be compromised with an increased risk of GIT dysbiosis with long-term intake of these medications as they are associated with gastric or peptic ulcers,[3,4] irritable bowel syndrome[5] including dyspepsia (indigestion as discomfort experienced in the upper abdomen),[6] chronic constipation,[7] diarrhoea[8] and morphological changes such as intestinal ulceration and increased GI inflammation and permeability.[4,9]

Musculoskeletal diseases are associated with increased symptoms of GIT dysbiosis.[10,11] The extensive use of medications used for the treatment of these rheumatic disorders, such as NSAIDs, steroids and disease-modifying drugs, has been associated with significant GI adverse events.[12,13] In addition, chronic disorders have been shown to be associated with significant impairment to quality of life and predisposition to depressive disorders. NSAIDs are well-known for causing GIT adverse events. Mortality likelihood aside, patients with rheumatic disorders usually experience more non-life threatening GIT symptoms that can severely impair their quality of life.[14]

Given that rheumatic diseases include more than 150 different conditions and syndromes with the common denominators being local pain and inflammation[15,16,17] a number of supplements have been reported in the treatment of OA [Table 1].

The GIT microbiome prompts the normal development of a number of protective, immune and metabolic functions, which altogether have an immense impact on the nutritional and health status of the host. The indigenous gut microbiota and transient bacteria (food-associated and probiotics) are known to influence the development and regulation of the host's defences, both immune and non-immune in nature, via interaction with the epithelium and the gut-associated lymphoid tissue.[18]

The rationale for the co–administration of glucosamine with a multistrain probiotic.

The most widely studied supplement for the treatment of OA has been glusosamine. The published clinical data though has been contentious [Table 2 and 3] with no feasible scientific explanation for this confusion. We have postulated that the GIT may play a significant role in the efficacy of supplements such as glucosamine.[19] The GIT microbiota that colonises the human GIT exhibits a high phylogenetic diversity reflecting their immense metabolic potential. How bacteria colonise the GIT provides initial clues as to the cues the GIT needs to develop a regulated immuno–metabolic–competent profile. It is hence possible that GIT function and integrity may influence the therapeutic efficacy of glucosamine.[11]

Thus, GIT dysbiosis due to the overuse of analgesic medications may be an important contributing factor to the lack of efficacy experienced with glucosamine. Gut microbial metabolism of nutraceuticals such as glucosamine may be critically important for efficacy outcomes. Hence, a glucosamine plus multistrain probiotic supplement provides a biologically plausible mechanism by which OA treatment efficacy may be augmented. Mechanistically, such a combination may rescue the dysbiotic gut and its local pro–inflammatory state that is then translated systemically, thereby attenuating joint pain mobility and flexibility. An additional benefit of the administration of a glucosamine plus multistrain probiotic combination would be the reduction in analgesic medications used.

Research evidence in support from a laboratory animal study.

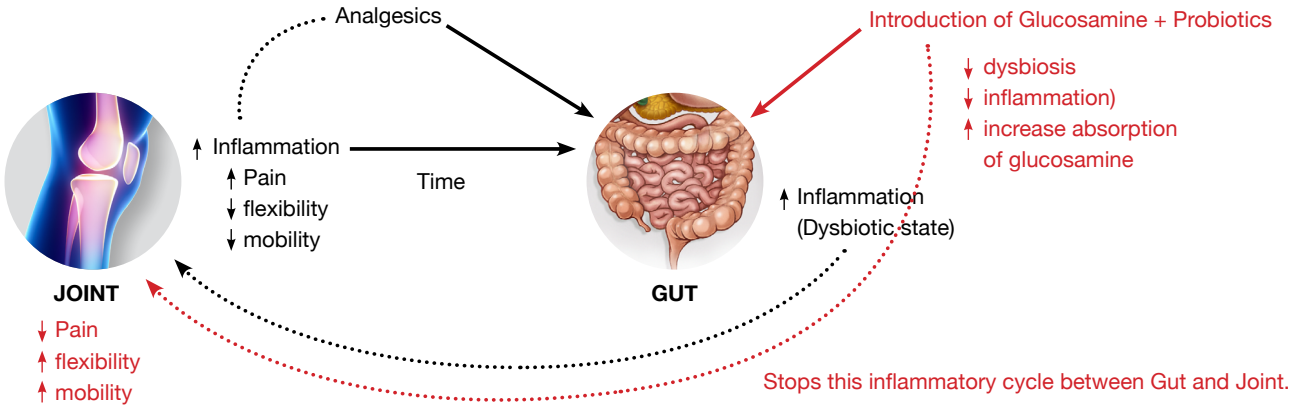
In an animal model of OA, where experimental OA was induced by intra-articular injection of monosodium iodoacetate in Wistar rats, the study demonstrated that oral administration of *L. casei* together with collagen and glucosamine more effectively reduced pain, cartilage destruction, and lymphocyte infiltration than the treatment of glucosamine or *L. casei* alone. [20] This co-administration also decreased expression of various pro-inflammatory cytokines that included interleukin-1β (IL-1β), IL-2, IL-6, IL-12, IL-17, tumur necrosis factor-α (TNF-α), interferon-γ (IFN-γ) and matrix metalloproteinases (MMP1, MMP3, MMP13), while up-regulating anti-inflammatory cytokines (IL-4 and IL-10).

The addition of collagen may not further alleviate joint pain. These results are attendant with reduced translocation of NF-κB into the nucleus and increased expression of the tissue inhibitor of MMP1 (TIMP1) and collagen in chondrocytes possibly explaining the intracellular mechanisms involved. Furthermore, this study provides evidence that a probiotic strain such as *L. casei* could act as a potent nutraceutical modulator for OA treatment by reducing pain, inflammatory responses, and articular cartilage degradation and damage progression.

Other probiotic strains such as *L. acidophilus* and *B. bifidum* have also been demonstrated to have anti–inflammatory activity.[21]

The inflammatory pathway in the GIT (Figure 1) is subject to multiple signals. Probiotic bacteria can modulate signaling pathways by interacting with several mediators within the GIT, namely dendritic cells, the gut epithelium luminal receptors (toll–like receptors) and tight junction proteins to rescue and maintain a regulated inflammatory state within the GIT. This regulated inflammatory state can then be translated systemically and to the joints.

Figure 1: Introduction of Glucosamine and Probiotics to Inflammatory Pathways in the GIT.



*This is Biologically Plausible

Over time, local inflammation at the joint causes inflammation and dysbiosis in the GIT.
Analgesic medications cause dysbiosis inflammation in the gut.
Pro-inflammatory and dysbiotic gut has a cyclical effect on inflammation at the joint. (This is biologically plausible.)
Glucosamine and probiotics may reduce translation of inflammation from GIT to joint.

Table 1: Supplements with Reported / Demonstrated Therapeutic Anti–inflammatory and Analgesic Activity.[28]

Supplement	Purpose	Indications	Dosages	Contraindications and Cautions
Glucosamine sulfate Glucosamine hydrochloride	Anti–inflammatory Chondroprotective	OA	1500mg/day usually in divided doses Most research has been conducted on glucosamine sulfate	Occasional mild digestive problems, headache, drowsiness and skin reactions. Avoid in patients with shellfish allergy. Avoid or caution with warfarin treatment.
Chondroitin	Chondroprotective	OA	1200mg/day usually in divided doses	
Collagen hydrolysate	Chondroprotective	OA	10g/day	
Lipids (avocado / soybean unsaponifiables)	Chondroprotective	OA	300–600mg/day	
Methylsulfonylmethane	Chondroprotective	OA	500mg TID alone or in combination with glucosamine	
NZ green-lipped mussel	Anti–inflammatory	OA Results still remain inconclusive	1050–1150mg/day of freeze-dried powder	GI discomfort, gout, skin rashes and one case of granulomatous hepatitis have been reported in trials. Contraindicated in people with shellfish allergies. Theoretical caution with hypertension due to sodium content.
SAMe	Anti–inflammatory	OA	A lower dose of 400mg/day may be used as a maintenance dose once a response occurs	Tricyclic and SSRI antidepressants as serotonin syndrome theoretically possible. Thyroxine – monitor. Betaine – monitor. Extreme caution in bipolar disorder, schizophrenia, schizoaffective disorder and Parkinson's disease.
Fish oils	Anti–inflammatory	OA	1–3g/day	

Table 2: Rotta Preparations of Glucosamine for Osteoarthritis

Glucosamine Form/Dose per day	Comparator	Duration	Use of Rescue Medication	Reported Adverse Events	References	Pooled Clinical Results Cochrane Database Syst Rev 2005 Apr 18;(2):CD002946
GS 400mg IV/IA 1500mg Oral	Piperazine/ chlorbutanol or placebo	7 days 14 days	Not Specified*#	None reported	Curr Med Res Opin 1980;2:104-9.	WOMAC: Pain: Statistically significant Function: Statistically significant Stiffness: Not statistically significant TOTAL: Glucosamine was statistically significantly superior to placebo. Lequesne Index Scores: Significant improvement: Glucosamine compared to placebo; No statistical difference between glucosamine and NSAIDs.
GS 400mg IV/IA 1500mg Oral	Piperazine/ chlorbutanol or placebo	7 days 14 days	Not Specified*#	None reported	Pharmatherapeutica 1981;2(8):504-8.	
GS 1500mg	Placebo	30 days	Not specified*	Constipation (2T 3P) Nausea (1T 2P) Heart burn (1T) Halitosis (1P) Diarrhoea (1P)	Clinical Therapeutics 1980;3(4):260-72.	
GS 1500mg	Ibuprofen 1200mg	8 weeks	Not specified*	Heartburn (1T 2C) Nausea (1T) Abdominal pain (1C) Headache (1C)	Curr Med Res Opin 1982;8:145-9.	
GS 1500mg	Placebo	6-8 weeks	None allowed	Dizziness (1P)	Curr Med Res Opin,1980;7(2):110-4.	
GS 1500mg	Placebo	4 weeks	None allowed	Gastrointestinal (11P, 8T)	Osteoarthr Cartilage 1994;2:51-9.	
GS 1500mg	Placebo	3 year	Acetaminophen	Gastrointestinal (28P, 25T)	Arch Intern Med 2002;162:2113-23.	
GS 1500mg	Ibuprofen	4 weeks	None allowed	Gastrointestinal (33C, 6T)	Osteoarthr Cartilage 1994;2:61-9.	
GS 1500mg	Placebo	3 years	Acetaminophen or NSAIDs	Abdominal pain (18P, 13T) Dyspepsia (8P, 4T) Diarrhoea (11P, 10)	Lancet 2001;357:251-6.	
GS 1500mg	Acetaminophen 3g/day or placebo	6 months	Ibuprofen	Dyspepsia (4P, 2C, 5T) Abdominal pain (4P, 4C, 3T) Diarrhoea (4P, 4C, 3T)	Arthritis Rheum 2007;56(2):555-67.	

* Use of other medications not specified; # No other medications were given that could interfere with evaluation of results. Patients allowed to continue other medications for other illnesses; (T) Treatment, (P) Placebo, (C) Comparator.

Table 3: Non-Rotta Preparations of Glucosamine for Osteoarthritis.

Glucosamine Form/Dose per day	Comparator	Duration	Use of Rescue Medication	Reported Adverse Events	References	Pooled Clinical Results Cochrane Database Syst Rev 2005 Apr 18;(2):CD002946
GS 1500mg	Placebo	6 months	NSAIDS and/or acetaminophen	Minimal, not specified.	Arthritis Rheum 2004;51(5):738-45.	WOMAC: Pain: No statistical significance Function: No statistical significance Stiffness: No statistical significance TOTAL: No statistical significance between glucosamine and placebo.
GS 1500mg	Chondroitin sulfate 1200mg GH 1500mg + Chondroitin 1200mg Celecoxib 200mg	24 weeks	Acetaminophen: max 4g/day	77 serious adverse events were reported in 61 patients including headache, nausea, vomiting, increased blood pressure, musculoskeletal.	NEJM 2006;354(8):795-808.	
GS 1500mg (+ vitamin C 900mg + calcium carbonate 900mg + manganese 15mg)	Placebo	6 months	NSAIDs and Paracetamol	Constipation (3P, 2T) Diarrhoea (1P, 2T) Gastrointestinal (3P, 0T)	Rheumatology 2002;41:279-84.	
GS 1500mg (n=162 Rotta) GH 1500mg (n=43 Non-Rotta)	Placebo	12 weeks	Acetaminophen	Gastrointestinal (6P, 4T) Constipation (1P, 0T)	Amer J Med 2004;117:643-9.	
GS 1500mg	Placebo	2 years	Pain medication allowed but not specified	Abdominal pain (10P, 14T) Stomach symptoms (19P, 25T) Intestinal symptoms (17P, 19T)	Amer Coll Phys 2008;148:268-77.	
GS 1500mg	Placebo	8 week randomised 8 week open	Acetaminophen: max 4g/day	About 12% of both placebo and glucosamine had mild GI symptoms (gas, bloating, and/or cramps).	J Rheumatol 1999;26:2423-30.	
G (*) 1500mg	Placebo	8 weeks	Pain medication allowed but not specified	Adverse events in both groups included loose stools, nausea, heartburn, diarrhoea, constipation.	West J Med 2000;172:91-4.	

(T) Treatment, (P) Placebo, (C) Comparator; * Not specified.

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