



CONSUMER'S PERCEPTION OF THE EFFICACY AND TOLERANCE OF GLUCOSAMINE IN JOINT DISEASES

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ABSTRACT

Introduction: In Australia, 18% of the population, experience or are diagnosed with some form of joints diseases (IJD) such as arthritis. The average cost of arthritis treatment per person per year is reported as Au\$6200; 61% of arthritis costs are covered by the individuals themselves. Glucosamine is a complementary or alternative medicine used in the treatment of Inflammatory Joint Disease (IJD).

Aim: The aim of this study was to explore consumers' perception of the efficacy and tolerance of glucosamine preparations in IJD.

Method: A 20-question survey was administered to members of the public to capture their experience of the efficacy, the side-effects of glucosamine and to investigate if it was prescribed or self-selected. Also, which glucosamine salt was used, for how long it was used and at what dose?

Results: From 87 participants, 91.9% stated that glucosamine reduced their pain and 91.7% stated that it improved their joint movement. In 46.5% participants pain reduced by 3-4 points and in 51.7% joints movement improved by 1-2 points. Glucosamine was used by 60% for 6 months or more where improvement in pain and joint function by at least 1-point was reported. Six participants reported glucosamine was not effective. There were no reports of glucosamine intolerance. Five participants diagnosed with rheumatoid arthritis; reported improvement in pain and joint movement by up to 2-points after taking daily 1500mg of Glucosamine Sulphate for over 6 months.

Discussion: This study provided insight on the possible benefits of glucosamine in relieving pain and joints function associated with arthritis. Most studies reviewed that reported effectiveness of glucosamine used glucosamine sulphate whilst those deemed glucosamine ineffective had used the hydrochloride formulation. No research has been conducted on the antioxidant activity of glucosamine in all IJD.

Conclusion: Five out of 87 participants had rheumatoid arthritis reported they found it was effective. It is therefore recommended that further research be conducted to measure the efficacy of glucosamine in treatment of different types of IJD and examining its antioxidant property.

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INTRODUCTION

In Australia, it is reported that 18% of the population experience joint diseases (JD); approximately 3.85 million people [1]. A public opinion poll (2008) [2] showed that Australians were more worried about developing arthritis than any other disease. The average cost of arthritis treatment per person is Au\$6200 a year, and 61% of arthritis costs are borne by the individual patients themselves.

Glucosamine is not a prescription medicine in Australia, but a complementary medicine, self-selected for the treatment of osteoarthritis (OA) [3]. There is supporting evidence for its effectiveness in treating OA of the knees but its effectiveness in inflammatory joint diseases (IJD) such as Rheumatoid Arthritis (RA) is lacking [4]. Recent *in vitro* research has shown strong antioxidant activity of glucosamine [5, 6, 7, 8]. This paper presents arthritis and IJD patient experience of the efficacy and tolerability of glucosamine in both OA and RA.

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Background

Rheumatoid Arthritis

RA is a systemic auto-immune inflammatory process manifesting with joint swelling and tenderness [9]. The inflammation is responsible for stimulating destructive mechanisms in the joint, leading to functional decline and disability [10]. The rheumatoid joint contains numerous cell types that are involved [9, 10, 11].

IL-1 and tumour necrosis factor alpha (TNF- α) share many pro-inflammatory actions in RA; and the rheumatoid joint also contains other pro-inflammatory cytokines. Under normal physiological conditions, the actions of pro-inflammatory cytokines are balanced by anti-inflammatory cytokines. In the rheumatoid joint, the balance swings in favour of the pro-inflammatory cytokines [12].

Nitric oxide (NO) is produced through constitutive and inducible pathways responsible for its pathogenic roles. NO combines with reactive oxygen species (ROS) to produce peroxynitrite (ONOO⁻), which promotes chondrocyte apoptosis [13, 14, 15].

Osteoarthritis

OA is the most prevalent of IJDs. It differs from RA in its aetiology; OA aetiology varies among individuals, with possible roles for systemic factors, such as genetics and obesity, as well as for local biomechanical factors, such as muscle weakness, joint laxity, traumatic injury and stress. OA is particularly frequent in the large, weight-bearing joints of the lower limbs [16, 17].

As in RA, the inflammation of OA involves cytokines such as IL-1, TNF- α , IL-6, IL-8, and NO, acting on chondrocytes to cause a catabolic cascade where proteases break down proteins in cartilage leading to inflammation. This creates a positive amplification loop leading to further protease production and further cartilage degradation [18, 19, 20]. PGE 2 and NO play important roles in cartilage catabolism in OA.

The role of Reactive Oxygen Species and Oxidative Stress in Pathogenesis of Inflammatory Joint Disease

ROS are normal by-products of cellular metabolism, but in disease states, overproduction occurs [21]. Amongst ROS, O₂⁻ plays a pivotal role in inflammation, particularly in patients with IJD [22]. The enzyme superoxide dismutase (SOD) neutralises O₂⁻ by transforming it into H₂O₂, thereby preventing the formation of highly aggressive compounds such as ONOO⁻ and HO⁻ [23].

In IJD, pro-inflammatory cytokines and prostaglandins are released, together with ROS [24] and NO [25]. These are associated with low SOD concentrations in joint fluid [23]. Studies of nitrotyrosine residues in synovial tissues from patients with RA [26] or exposure of chondrocytes to synthetic ONOO⁻ in vitro [27] established that the combination of O₂⁻ and NO causes cartilage damage. Further evidence comes from a study where intra-articular injections of native SOD (bovine orgotein) produced greater improvements than intra-articular aspirin in RA [28].

Oxidative Stress in Rheumatoid Arthritis

Although the causes of RA are unknown, involvement of ROS is clear. In vitro, ONOO⁻ formation is associated with

decreased production of type 2 collagen and aggrecan, and with a diminished chondrocyte response to the growth factor IGF-1. In addition, ONOO⁻ increases the expression of MMP-3 and MMP-13 and decreases the production and activity of the tissue inhibitors of MMPs [24, 29]. Together, these changes increase matrix breakdown.

TNF- α overproduction is thought the main contributor to increased ROS release in RA. TNF- α cause cell damage and inhibits SOD, decreasing enzyme activity neutralising O₂⁻ [30, 31].

Oxidative Stress in Osteoarthritis

IL-1-Beta (IL-1 β) is one of the most active factors involved in OA [32]. It diminishes expression of type-2 collagen and aggrecan, and increases expression of MMPs-1 and 3. IL-1 β stimulates NO production, leading to the formation of ONOO⁻, which targets guanine repeats in DNA telomeres, explaining the link between oxidative stress and telomere erosion [33]. Aging of cartilage and chondrocytes may be central to the pathogenesis and progression of OA. Nitrotyrosine, formed when tyrosine is oxidised in the presence of NO, can serve as a measure of oxidative damage in vivo. Its presence in cartilage was associated with older age and with OA, suggesting a role of oxidative stress in cartilage aging and degeneration [34].

Pharmacological Treatment of Rheumatoid Arthritis

A combination of therapies is recommended in the treatment of RA [4, 35, 36]:

- Rapidly acting anti-inflammatory medications, including non-steroidal anti-inflammatory Drugs (NSAIDs) and systemic and IA glucocorticoids.
- Disease Modifying Antirheumatic Drugs (DMARDs), including nonbiologic (traditional small molecule or synthetic) and biologic DMARDs, and an orally administered small molecule kinase inhibitor, which all have the potential to reduce or prevent joint damage.

The non-biologic DMARDs most frequently used include hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide [35, 36]. Biologic DMARDs, generally target cytokines or their receptors, or are directed against other cell surface molecules. These include anticytokine therapies, such as the TNF- α inhibitors, etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol; the IL-1 receptor antagonist, anakinra; and the IL-6 receptor antagonist, tocilizumab. They also include other biologic response modifiers such as the T-cell co-stimulation blocker, abatacept, which affects the Cytotoxic T Lymphocyte Antigen 4 (CTLA4-Ig), and the anti-Cluster of Differentiation 20 B (CD20)-cell depleting monoclonal antibody drug, rituximab [35, 36, 37, 38].

Several kinase inhibitors are in development for use in RA. Tofacitinib is in use in the USA and is under review for approval in Europe. Tofacitinib is an orally administered small molecule DMARD that inhibits cytokine and growth factor signalling through interference with Janus kinases [35, 36].

Pharmacological Treatment of Osteoarthritis

According to the Osteoarthritis Research Society International (OARSI) Treatment Guidelines Committee, there is no cure for OA; treatment should manage symptoms, reducing pain

[39, 40, 41]. Standard therapy is based on a combination of pharmacological (e.g. paracetamol, NSAIDs, glucosamine) and non-pharmacological methods (e.g. self-management and education about exercise, diet, appropriate footwear) [4].

OARSI pharmacological intervention recommendations also include three additional pharmacological interventions [4]:

- Topical use of NSAIDs and capsaicin as adjuncts or alternatives to oral analgesic/anti-inflammatory agents in knee OA.
- Treatment with glucosamine and/or chondroitin sulphate in knee or hip OA.
- The use of weak opioids and narcotic analgesics for refractory pain in patients with hip or knee OA, when other pharmacological agents have been ineffective or are contraindicated.

Paracetamol (acetaminophen) is an aniline analgesic, generally the first-line treatment recommendation [42]. Guidelines suggest that NSAIDs should be used with or without concurrent paracetamol if symptom relief is not sufficient with paracetamol alone [4, 43]. NSAIDs doses should be the minimum for effective results, and long-term use avoided [4]. They may be only slightly better than placebo in providing short-term pain relief [4], and are associated with important side effects: Gastrointestinal bleeding, the most significant side effect, causes approximately 16,500 and 2200 deaths, and 107,000 and 12,000 hospital admissions in the USA and United Kingdom respectively, and is of particular concern in older patients [44, 45].

Intra-articular (IA) corticosteroid injections can provide rapid relief for up to four weeks [46]. IA hyaluronic acid injections administered weekly for 3-5 weeks [47] have provided slower onset but more prolonged (up to 12 weeks) relief than corticosteroids [48, 49].

Glucosamine

Glucosamine was first used in the 1960's as a topical medication for OA pain in Germany [50, 51]. Subsequently, it was developed as an oral preparation available on prescription (Rx) in Europe [52, 53]. It is available in many countries without prescription and is marketed to alleviate arthritic pain of the knee, and as a prophylactic agent against joint damage due to age or overuse [54]. Typically, glucosamine is formulated as the N-acetyl, sulphate, or hydrochloride (HCL) salt. In Australia glucosamine is usually formulated as a sulphate or HCL salt and alone or combined with chondroitin sulphate in capsules of 500 mg of glucosamine salt and 400 mg chondroitin sulphate, with a recommended daily dose of three capsules per day [55].

Pharmacological Mechanism of Action of Glucosamine

Glucosamine as a Stimulant for the Synthesis of Glycosaminoglycan

Glucosamine is preferentially incorporated by chondrocytes into the components of glycosaminoglycan chains in cartilage [56], stimulating synthesis of physiological proteoglycans [57, 58, 59] and decreasing the activity of catabolic enzymes in the cartilage, including matrix metalloproteinases (MMPs) [60]. In vivo, it is effective in animal models of OA [61, 62]. Initially, the mechanism of action was considered simply as above. However, this seems an oversimplification. While metabolic effects exerted at the level of articular cartilage

might support a long-term joint structure-modifying activity, they hardly explain the relatively short-term symptomatic benefit outlined in clinical trials [63].

Recent studies demonstrate high glucosamine concentrations stimulate glycosaminoglycan synthesis in vitro [64], and may exceed the concentrations achieved in biological fluids after oral administration to humans [65]. Nevertheless, in vitro models also show it was effective in increasing proteoglycan levels by up-regulating the expression of corresponding genes at concentrations 100-fold lower and compatible with those found in biological fluids during human treatment [57]. An alternative hypothesis suggests the existence of glucosamine metabolic activities in tissues where extracellular glucosamine concentrations might be higher, including the intestine, liver and kidney, such that it might modulate the compound's anti-arthritis effects [66]. Yet another alternative hypothesis suggests that the increase in the production of cartilage extracellular matrix is mediated by glucosamine-induced up-regulation of Transforming Growth Factor-[beta](TGF β), which has been observed at clinically relevant concentrations in the low micromolar range [67].

Glucosamine as an Inhibitor of the Cytokine Pro-Inflammatory Process

A unifying hypothesis for glucosamine sulphate's mechanism of action in OA was recently proposed. This refers to glucosamine-induced reversal of the pro-inflammatory and joint-degenerating effects of IL-1 β [68, 69] through the blockade of the cytokine intracellular signalling cascade, by inhibiting the activation of the NF κ -B pathway [70]. It inhibits the IL-1 β -induced activation and nuclear translocation of NF κ -B in human osteoarthritic chondrocytes [71]. Further, it inhibits both gene expression and protein synthesis of COX 2 selectively over COX 1, via the inhibition of NF κ -B activation, preventing the release of PGE 2 into the culture medium [70]. Several new lines of evidence are emerging to further substantiate this mechanism. NF κ B activity has been found to be inhibited by glucosamine sulphate in both human chondrocytes and synoviocytes, with subsequent decrease in COX 2 protein synthesis, PGE 2 and NO release, showing a pattern that differs from that of other potential antiosteoarthritic agents and NSAIDs [72]. Moreover, glucosamine sulphate consistently decreased IL-1 β -induced MMP synthesis in both types of cell [71].

An in vitro study confirmed the suppressive effect of glucosamine on both anabolic and catabolic gene expression in the osteoarthritic cartilage [73]. The authors speculate that the effect of glucosamine sulphate as a potential disease-modifying agent might be due to anti-catabolic activities, rather than anabolic activities. Interestingly, glucosamine sulphate has been found to be a stronger inhibitor than the hydrochloride [70]. This and other recent human pharmacokinetic findings help to explain the different findings of recent clinical trials between these two glucosamine salts.

Glucosamine as an Antioxidant

Glucosamine also has strong antioxidant and immunostimulating properties [5, 6, 7, 8]. The general reduction reaction equation for glucosamine, using N-Acetyl-D-glucosamine as an example is as follows [73]:

N-Acetyl-D-glucosamine + O₂ → N-Acetyl-D-glucosaminatate + H₂O₂

Recent research by Xing, Liu, Guo et al. (2006) [6] investigating the antioxidant activity of glucosamine HCL in vitro showed strong scavenging activity for superoxide/HO⁻ and pronounced reducing power. This was shown to increase with increasing concentration, was quite linear and similar to that of ascorbic acid (vitamin C). The reducing properties of glucosamine HCL are associated with the presence of reductones that have been shown to exert antioxidant action by breaking the free-radical chain through donating a hydrogen atom [6].

Studies of the antioxidant activity of glucosamine sulphate produced similar results. The scavenging ability of glucosamine sulphate was pronounced; increasing with increasing concentration and its reducing power was also strong. In addition glucosamine sulphate was shown to inhibit radical mediated expression and activation of NFκ-B proteins, and enhance reduced GSH level in oxidatively stressed human chondrocytes, thus improving cellular redox balance [5, 7].

Another study demonstrated that glucosamine exhibited strong antioxidant ability in terms of its chelating effect on ions such as the ferrous ion (Fe²⁺). This ability, removed ions from substances such as deoxyribose, lipid and protein such that they were protected from oxidative damage. In terms of immuno-stimulating ability, D-glucosamine exerted a strong effect on the phagocytosis of macrophages, indicating that pre-treatment could augment the humeral and cellular immune response [8]. This study presented the first evidence of sulphated glucosamine being efficacious in attenuating oxidation-related damage to cells via mechanisms involving radical scavenging, and suggests a superior treatment efficacy compared to non-sulphated glucosamine. Particularly, this effect was observed in cells involved in OA, such as chondrocytes and macrophages. From the results of this study, both glucosamine and sulphated glucosamine act to prevent oxidation of membrane lipids.

The ROS-mediated protein damage has been reported to be higher in OA patients, thus the role of sulphated glucosamine in protecting DNA from damage mediated through OH produced from the concerted action of H₂O₂ and Fe²⁺ is highly significant [8]. In addition, consistent with a role for oxidative stress in pathogenesis of OA, clinical and preclinical studies have correlated increases in markers of oxidative stress and lower levels of the body's natural antioxidants, such as GSH, with disease severity [8]. GSH is up-regulated in the presence of sulphated glucosamine, and this ability promotes its potency against intracellular oxidative stress.

Aim

The aim of this study was, to explore consumer's perception of the efficacy and tolerance of glucosamine preparations in inflammatory joint diseases.

METHOD

The first component was a qualitative observational survey. A 20-question survey was administered to members of the community who self-selected to use glucosamine, recruited through a poster campaign in local community pharmacies, to capture their personal experience of the efficacy and toxicity. Survey questions were based on validated clinical methods for

assessing pain and joint functional movement, using a visual pain scale and visual joint-function scale [74, 75, 76, 77, 78, 79, 80, 81, 82, 83].

The survey data was found to be not normally distributed. Non-parametric tests were used to test the statistical significance of the results. The tests used were:

- The Shapiro Wilk test [84]
- The Wilcoxon signed-rank sum test [85]
- The Kruskal-Wallis test [86]
- The Bonferoni adjustment method [87]

RESULTS

Out of 87 participants (aged 40-84 years), 91.9% and 91.7% stated that glucosamine reduced their pain and improved their movement (Table 1).

Table 1 Reduction in joint pain versus time since started glucosamine

	Total	Less than 6 months	6 months to a year	1-2 years	More than 2 years
Total answering	86	13	24	16	10
	100%	100%	100%	100%	100%
Yes	79	7	24	16	10
	91.9%	53.8%	100%	100%	100%
No	7	6	-	-	-
	8.1%	46.2%			

Pain was significantly reduced by 3-4 points (out of possible 5) in 46.5% of participants. Joint movement reported significant improvement of 1-2 points out of a possible 5, in 51.7% of the participants (Table 2).

Statistical analysis was performed to ascertain whether the difference between pain scores and joint movement scores before and after taking glucosamine was significant. Due to the data being not normally distributed, the Wilcoxon signed-rank sum test was used. For both joint pain and joint movement/function, the score difference before compared to after taking glucosamine was found to be statistically significant with Prob>z = 0.00001. This suggests that after taking glucosamine participants experienced a significant reduction in pain and improvement in joint movement.

All of the participants who indicated that they had used glucosamine for more than six months, reported pain reduction and joint-movement improvement after using glucosamine ranging from 1-2 points through to 5 or more points on the rating scales. Six participants indicated that glucosamine was not effective in reducing their pain and four participants indicated that it did not improve their joints function. The participants reporting negative results took glucosamine for less than 6 months (Table 3).

Insert Table 3 here

Statistical testing was conducted to ascertain whether the difference between pain scores and joint-movement scores in participants taking glucosamine for more than six months compared to those taking glucosamine for less than six months was significant.

For joint pain, the score difference between taking glucosamine for more than six months and taking glucosamine for less than six months was significant, with Prob>z = 0.0018 (Wilcoxon signed-rank sum test).

Table 2 Comparison between Pain Improvements

	Total	Gender (male)	Gender (female)	Age 40-53	Age 54-61	Age 62-67	Age 68-84	<1 year of glucosamine	1-3 years of glucosamine	3+ years of glucosamine
Total answering	86	44	42	22	23	20	21	33	36	17
	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
No pain improve-ment	8	4	4	3	3	2	-	6	-	2
	9.3%	9.1%	9.5%	13.6%	13.0%	10.0%	-	18.2%	-	11.8%
Pain improve-ment (1-2 points)	28	16	12	10	7	4	7	14	12	2
	32.6%	36.4%	28.6%	45.5%	30.4%	20.0%	33.3%	42.4%	33.3%	11.8%
Pain improve-ment (3-4 points)	40	19	21	8	10	11	11	10	20	10
	46.5%	43.2%	50.0%	36.4%	43.5%	55.0%	52.4%	30.3%	55.6%	58.8%
Pain improve-ment (5+ points)	10	5	5	1	3	3	3	3	4	3
	11.6%	11.4%	11.9%	4.5%	13.0%	15.0%	14.3%	9.1%	11.1%	17.6%

Table 3 Reduction in joint pain versus time since started glucosamine

	Total	Less than 6 months	6 months to a year	1-2 years	More than 2 years
Total answering	86	13	24	16	10
	100%	100%	100%	100%	100%
Yes	79	7	24	16	10
	91.9%	53.8%	100%	100%	100%
No	7	6	-	-	-
	8.1%	46.2%	-	-	-

This suggests that taking glucosamine for longer than six months results in significant reduction in overall pain.

For joint-movement improvement, the score difference between taking glucosamine for more than six months and taking glucosamine for less than six months was significant, with $Prob > z = 0.0343$. Taking glucosamine for a period longer than six months had a statistically significant improvement in overall joint movement.

Most participants indicated that their arthritic pain was associated with the knees, and most had been diagnosed with OA. However, five of the participants had been diagnosed with RA, and all of the RA participants reported significant decreases in pain and improvement in joint movement ranging from 1-2 points through to 5 points on the visual scale after taking daily 1500mg of Sulphate for over 6 months.

There were no reports of glucosamine intolerance across the sample (44 males and 43 females). Most participants started taking glucosamine on the advice of their pharmacist (50%) or their doctor (50%) to improve joints pain and function even if they did not receive a medical diagnosis of arthritis.

DISCUSSION

Efficacy of Glucosamine

Studies relating to the efficacy of glucosamine have been primarily concerned with glucosamine as a supplementary/complementary treatment for OA rather than RA, and have yielded mixed results. A number of meta-analyses have been conducted on glucosamine, and have shown that glucosamine may provide better pain relief and improve function compared to placebo, while others have not reported benefit [88, 89, 90, 91, 92, 93, 94, 95]. A possible explanation for the mixed findings is a study reporting that glucosamine sulphate consistently produced better symptomatic benefits compared to glucosamine HCL [94].

This suggests that the form of glucosamine being used might possibly influence results. Two studies involving either paracetamol (acetaminophen) or NSAIDs as the comparator have shown that glucosamine sulphate was at least equal to, and in some studies superior to, NSAIDs in providing symptomatic pain relief [96].

The critical analysis of a selected neutral/negative result study reveals the following:

A study conducted in 1999 [97] concluded that there was no significant difference between glucosamine and placebo in terms of pain-score results. An analysis of the study reveals that 118 patients with moderate pain for at least six months due to primary knee OA and with radiological changes. The patients were given 1500 mg daily of glucosamine HCL versus placebo for eight weeks. Patients who had previously taken glucosamine or those who had received an IA injection of corticosteroids within the previous six months were excluded. The negative results may be largely due to the experimental design/methodology of the study. The current best-practice guidelines based on meta-analyses conducted in 2006, 2008 and 2010 [88, 89, 95] recommend a dose of 1500 mg for a period of six months for full benefits to be achieved. Furthermore, these guidelines recommend the use of glucosamine sulphate rather than the HCL version for better results.

Critical analysis of a positive-result study [96] found that the study concluded that administration of glucosamine to OA patients resulted in significant improvement in terms of the Lequesne index pain scores versus placebo. The study consisted of 318 patients with moderate pain for at least three months who were given 1500 mg daily of glucosamine sulphate versus placebo for six months. Patients already taking glucosamine were excluded from the study. These positive results may be largely due to the experimental design aligning with current best-practice recommendations pertaining to the use of glucosamine in the treatment of OA [88, 89, 95].

Safety and Toxicity of Glucosamine

A 2008 review of 20 clinical trials reported no significant side effects from the use of glucosamine [91]. This is consistent with other evidence indicating that the long-term use of glucosamine is associated with only minor and infrequent adverse effects – primarily mild and temporary gastrointestinal symptoms. It is believed that glucosamine does not carry risks such as gastric bleeding or ulcers, and does not raise the risk of

heart attack, stroke, or kidney disease, as do some first-line pharmacological treatments [88].

However, one potential safety concern involves blood sugar regulation. An initial study in a diabetic animal model raised concerns that glucosamine supplementation might increase insulin resistance [98, 99]. Subsequent studies conducted in 2006 and 2007 in patients with diabetes and OA found that glucosamine did not directly affect blood-glucose levels or cause worsening of insulin sensitivity. In addition, it had no effect on levels of either high-density lipoprotein (HDL) or apolipoprotein A1, a constituent of HDL [100, 101]. A recent meta-analysis of clinical studies indicates that glucosamine may decrease insulin sensitivity and increase fasting glucose. The proposed mechanism is as follows: Glucosamine is thought to be a competitive inhibitor of beta cell glucokinase. Glucokinase in beta cells has a role in sensing glucose and stimulating insulin secretion. Thus, glucosamine may raise the glucose threshold for glucose stimulated insulin secretion and lead to higher plasma fasting glucose levels as a result [102]. Until definitive information is available, blood sugar levels should be closely monitored if glucosamine preparations are given to diabetic and glucose-intolerant patients.

A further safety consideration is that, since most glucosamine is prepared from shellfish, it should not be recommended to patients with significant seafood allergy, although case reports show that patients do not typically react to glucosamine [103]. A study conducted by Knudsen and Sokol (2008) [104] discussed the possibility that glucosamine may result in a potential interaction between warfarin (an anti-coagulant medication) and glucosamine that is associated with an increase in the International Normalised Ratio (INR). The USA Food and Drug Administration (FDA) MedWatch database identified 20 reports of glucosamine or glucosamine-chondroitin sulphate use with warfarin associated with altered coagulation (manifested by increased INR, or increased bleeding or bruising). The study further states that the World Health Organisation (WHO) adverse drug reactions database documented 21 spontaneous reports of increased INR associated with glucosamine use, 17 of which resolved when glucosamine was stopped. The study concludes, however, that the mechanism is not understood, and that more research is required to identify the mechanism.

Despite the above it is assessed that it is unlikely that glucosamine will have adverse interactions with other drugs since glucosamine is mainly absorbed via glucose transporters and does not compete for general absorption mechanisms. In addition, it is mainly metabolised independently of the cytochrome P450 enzyme system [105].

Significance of Results

The results of the study indicate that glucosamine is effective in the treatment of OA. A majority (91.9%) of respondents equally distributed between male and female, stated glucosamine had helped reduce pain in their joints. Only 8.1% stated glucosamine had been ineffective. Further, 91.7% of respondents stated that taking glucosamine had improved the movement in their joints. Likewise, 93.2% of respondents indicated that taking glucosamine has helped to improve the function of their joints due to the pain reduction.

It is clear from the study that those patients who used glucosamine for more than six months perceived a significant

reduction in pain and an improvement in joint movement. The results show that all respondents (100%) reported that glucosamine was beneficial in reducing their joint pain and improving their joint-movement after using glucosamine ranging from 1–2 points through to 5 or more points on the rating scales.

However, amongst those respondents who took glucosamine for less than six months, nearly half reported no benefit from taking glucosamine. This leads to the conclusion that for glucosamine to be effective in reducing joint pain, it must be taken for a period exceeding six months. This is supported by the existing literature. The current best-practice guidelines recommend a glucosamine dose of 1500 mg daily for a period of six months for full benefits to be achieved. The guidelines further recommend the use of glucosamine sulphate rather than the HCL formulation [88, 90, 95, 106]. A recent meta-analysis conducted in 2013 agrees with this assessment, concluding that whilst glucosamine HCL was ineffective for pain reduction in patients with knee OA, glucosamine sulphate was effective when administered for more than six months [107]. A small number of the total number of participants in the study indicated that glucosamine had not been effective. All of these participants took glucosamine for less than six months, corroborating the supporting literature.

The literature review in this study provided insight on the possible benefits of glucosamine in relieving oxidative stress associated with arthritis. A small group of participants reported that they were diagnosed with RA (five out of 87 participants), and 100% of those participants reported a highly significant decrease in pain ranging from 1–2 points through to 5 points or more on the visual scale. They also reported a significant improvement in joint function/movement ranging from 1–2 points through to 5 or more points. All of the participants with a self-reported RA diagnosis indicated they had been taking glucosamine for longer than six months at the recommended dose of 1500mg per day. Given the role of ROS and the resultant oxidative stress found in both the pathogenesis and disease progression of RA, and the reported antioxidant activity of glucosamine, inferences can be made regarding the findings of this study which may be rationalised as follows: That is, the antioxidant properties of glucosamine may be directly responsible for the positive effects of glucosamine reported by RA sufferers who took part in this study.

A critical literature review revealed that few studies have investigated the effectiveness of glucosamine in other types of arthritis and to date; no research has been conducted regarding the antioxidant/pro-oxidant activity of glucosamine in human patients suffering from IJDs. Particularly, there has also been very little research conducted on the efficacy of glucosamine in the treatment of RA patients. Nakamura et al. (2007) [108] found that glucosamine treatment produced noticeable improvements in symptoms of RA patients. However, antioxidant status was not measured in this study.

Limitations

This study is based solely upon patient perceptions not any formal investigations. Nevertheless the reported benefits appear strong and it is unlikely that the results were purely placebo.

CONCLUSION

The results of this study indicated that health professionals have a degree of confidence in the benefits of glucosamine as a complementary treatment of Osteoarthritis. However further study is required regarding efficacy.

In further examining the antioxidant effect of glucosamine, a further research question arises regarding what possible role glucosamine may have in the treatment of other diseases associated with oxidative stress. The existing literature reports antioxidant properties of glucosamine. Further research examining the possible role of glucosamine in the treatment of other diseases associated with oxidative stress is surely warranted.

Declarations

Ethics: ethical clearance was approved by the Research in Human Ethics committee of Charles Darwin University, Darwin, Australia. All survey procedures and content were performed in strict accordance with the Charles Darwin University ethics approvals. All participants consented to participate and voluntarily enrolled.

Consent for publication: all authors have consented for submission and publication.

Availability of data and material: all data and material are available on request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: The First author conducted the research, the second and third authors contributed equally towards the development of the research concept and the drafting of the paper.

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