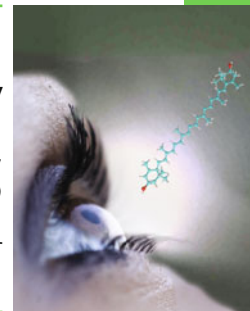


Joint health: What degree of evidence is necessary to support health claims for food supplements, taking glucosamine as an example?

Jürgen Bernhardt, Christof Jaenicke, Peter Prock, Ulrich Schneider



Correspondence to:
Jürgen Bernhardt
j.bernhardt@biotesys.de

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Abstract

Arthropathies present a major challenge for the public health system, both in terms of epidemiology and health economics, particularly against the background of demographic changes in the Western world. Much attention must be paid to prevention, because of the limited options and high technical and financial expenditure with respect to treatment. Among other factors, nutrition plays an important role. However, many and various unsolved questions must be answered before health claims for food constituents in the field of joint

health can be established for use as consumer information, as will be described taking glucosamine as an example. These questions will be discussed and possible alternatives to conventional practice considered.

Introduction

The World Health Organisation (WHO) has characterised two conditions as “high burden diseases with no curative treatments”: osteoarthritis and Alzheimer’s disease [1]. Currently, 540,000 knee replacements and 760,000 hip replacements are performed in Europe per year. Hence, interventions that support joint health and mobility and help to delay the progression of joint cartilage degradation are increasingly important, especially against the background of a continuously growing elderly population [2, 3]. Nutritional management plays an important role in the maintenance of tissues and organs in a healthy state and can support better health in old age, avoiding the unnecessary use of medication and surgery or loss of viability and quality of life. Nutritional management means the adequate supply of essential vitamins and minerals, as well as other valuable nutrients and food components through a varied and balanced diet, which may be complemented in a targeted way by concentrated sources of these substances (for example,

Jürgen Bernhardt (✉)
BioTeSys GmbH
Schelztorstr. 54–56
73728 Esslingen, Germany
j.bernhardt@biotesys.de
tel +49 711 31057150
fax +49 711 31057151

Christof Jaenicke
analyze&realize GmbH
Berlin, Germany

Peter Prock
European Nutraceutical Association
Basel, Switzerland

Ulrich Schneider
Osteoarthritis Research Center
Tegernsee, Germany

in the form of dietary supplements). The fact that certain food constituents can have positive health effects is already well accepted. One example for cardiovascular health is the maintenance of health-related biomarkers and risk factors such as low-density lipoprotein (LDL) cholesterol levels, blood pressure and blood glucose levels. In other health areas, current scientific knowledge supporting a relationship between a food ingredient and a beneficial health effect may be promising, but convincing, fully conclusive evidence is very often lacking. Although the reasons for this are manifold, one fundamental problem is the paucity of generally accepted singular biomarkers as indicators of the risk to health presented by chronic diseases [4]. Elevated LDL cholesterol, which is usually referenced in connection with the topic of biomarkers, is actually one of the very few good examples. However, for most diseases there are no clear links between biomarkers and the disease risk or maintenance of health, which is why much effort is being made to establish such biomarkers; they are essential for preventive nutrient research.

A clear causal relationship is always desirable in research, and a high degree of evidence must be sought. At the same time, however, it is important to consider in a reasoned manner the fundamental limitations of such a compulsive requirement.

Often in nutrient research it is not possible to draw clear conclusions on (patho-)physiological processes from individual factors or biomarkers. Instead, an overall view of the findings at various levels is needed to describe the physiological network and to demonstrate a causal relationship between a food constituent and the influence on human health. This is particularly true of the early and subclinical changes with which health promotion is primarily concerned. It is important to consider the polyvalent nature, small effect size and often homeostatic control of nutrients. When judging the level of evidence, these striking differences between drugs and nutrients should be taken into account [5]. The situation is no different in research into joint health.

The pathobiology of the onset and early progression of joint disease, including osteoarthritis, is still poorly defined. There is no sharp threshold between health and disease, and the onset of a disease can be described as a multidimensional ongoing process, with different organ systems in the same individual exhibiting varying sensitivities. This is also true for joint disease [5].

We aim to illustrate these problems with the example of research into glucosamine, an amino sugar and building block in the formation of glycosaminoglycans (GAGs), a major constituent of joint cartilage. We will discuss whether it is reasonable to demand “convincing, fully conclusive evidence” for an association between intervention with glucosamine and a preventive effect to support maintenance of joint health, or whether we should accept “evidence with high probability” in order to allow for correctly worded health-oriented consumer information to be given, especially in light of the aforementioned critical situation in health care. Due to the current legal situation with the requirement for “convincing evidence”, the European Food Safety Authority (EFSA) has rejected all applications to obtain health claims for substances in the field of joint health, with the exception of vitamin C for the normal function of cartilage.

The role of glucosamine in joint physiology

Glucosamine is a well-characterised amino sugar and building block in the formation of glycosaminoglycans (GAGs), a major constituent of joint cartilage. Glucosamine is synthesised by the body and in addition can be taken up as food including supplements.

Various studies (animal and human) have provided significant scientific evidence for the bioavailability and the uptake of glucosamine into joints. It has been shown that supplemental glucosamine reaches the site of action, i.e., the joints and the synovial fluid [6–11]. Supplemental glucosamine can therefore be utilised by the cells to maintain the balance between the breakdown and synthesis

of the extracellular cartilage matrix (homeostasis). Persistent or permanent metabolic imbalances favouring the breakdown of cartilage material will culminate in the process of cartilage degeneration, which is one important factor resulting in permanently impaired joint function and potentially in osteoarthritis.

In vitro research has shown that glucosamine promotes anabolic actions while inhibiting catabolic processes in the cartilage. The benefit of glucosamine has not only been demonstrated in inflamed chondrocytes and osteoarthritic chondrocytes with early disease-related signs, but also in normal chondrocytes [12].

Furthermore, mechanistic animal models, which allow the investigation of a defined stress on a particular healthy tissue, have demonstrated supporting effects of glucosamine on metabolic imbalances in the joints [13–15].

Thus, *in vitro* and animal models provide clear supportive evidence for the mode of action and beneficial role of glucosamine on the maintenance of joints in a healthy state.

Most of the human clinical trials examining the efficacy of glucosamine have been carried out in patients suffering from knee osteoarthritis. Structural changes of joint space width or changes of joint functionality (like morning stiffness and pain) can be measured in this diseased population.

However, in the “healthy”, pre-arthritis population, changes in cartilage mass or symptomatic disturbances of joint functionality are not measurable or experienced. Up to now, no methods have been available for the detection of minimal structural changes in cartilage. This is true for imaging techniques, even those as accurate as magnetic resonance imaging (MRI), and this accordingly hampers endpoint measurements in healthy people. This current gap could be closed by identifying biomarkers of joint metabolism, which change in diseased as well as healthy states, and which may be affected by supplemental glucosamine.

During the synthesis and degradation of cartilage,

different cartilage matrix compounds reach the synovial fluid and enter the systemic circulation. Biomarkers of cartilage homeostasis have been identified that may reflect early changes in the development of osteoarthritis *in vivo*.

Fragments of C-terminal cross-linked telopeptides of type II collagen (CTX-II) have been shown to be one of the most reliable biomarkers for cartilage degradation [16]. Components of type II collagen are recognised as valuable biomarkers for joint disorders [17]. Moreover, the ratio of type II collagen breakdown to synthesis markers can be used for predicting the progression of joint damage [18, 19]. A study by Christgau et al. (2004) documented a reduction in the elevated CTX-II levels seen in osteoarthritic patients showing high cartilage turnover, upon supplementation with 1500 mg of glucosamine sulphate daily [20]. The reduction in CTX-II translates into a reduction in cartilage catabolism. In addition, Yoshimura et al. (2009) showed that in soccer players, who represent a non-diseased population group with a high work load and a high risk of developing osteoarthritis, the urinary CTX-II level was elevated after intense training. Glucosamine supplementation significantly reduced initially elevated levels of CTX-II in the soccer players [21]. This work is supported by recent findings of Momomura et al. (2013), who demonstrated that glucosamine could dose-dependently prevent type II collagen degradation while maintaining synthesis in comparison to placebo in a group of bicycle racers. The authors concluded that glucosamine may exert a chondroprotective action in athletes of various sports [22]. In conclusion, recent literature provides evidence that CTX-II urinary levels can be positively affected by glucosamine supplementation in the healthy and diseased states [20–22]. In the latter case, a correlation between reduction in CTX-II and degenerative structural changes of cartilage (inhibition of joint space loss) by glucosamine has already been proven.

Besides the influence on cartilage markers, glucosamine may also exert anti-inflammatory activ-

ity, which is also of interest in the area of joint health. A recent study by Navarro et al. (2015) verified that supplementation with glucosamine and chondroitin significantly reduced C-reactive protein (CRP) levels in healthy overweight individuals. Proteomic profiles indicated that cytokine activity and other inflammation-related pathways were significantly decreased [23]. The strength of this study is that effects of supplementation were shown in a healthy but at-risk population in terms of joint health due to their overweight. These results are again supported by *in vitro* and animal studies demonstrating the anti-inflammatory properties of glucosamine [24, 25] as well as human observational data, which show an association between glucosamine users and lower concentrations of CRP levels and prostaglandin-metabolites (PGE-M) [26]. In a study by Damlar et al. (2015), the effect of a glucosamine/chondroitin supplement was evaluated in young women (average 29 years) with internal temporomandibular joint derangements in early and intermediate stages. Joint overload plays an essential role in the aetiology. Inflammatory markers were measured in the synovial fluid. Supplementation with glucosamine and chondroitin significantly reduced inflammatory markers compared to a control group using a narcotic analgesic, confirming the anti-inflammatory properties at the site of action [27].

Taken as a whole, therefore, this shows that there are many factors that are strongly indicative of a causal relationship between the beneficial role of glucosamine and the maintenance of joint health, in terms of bioavailability, uptake, physiological function and effects, based on chemical, mechanistic and human data. This is a scientific approach with a high, but not conclusive, degree of evidence, summarising the existing data on glucosamine in osteoarthritic patients (in whom joint space narrowing/changes in joint structure and biomarkers of joint degeneration can be measured) and extrapolating these data to non-diseased populations. Although joint space narrowing/changes in joint

structure cannot be measured in healthy people, due to the very slow progression of changes in joint structure, beneficial effects on biomarkers can already be demonstrated, one of several possible endpoints mentioned by the EFSA (see below).

Discussion

In 2012, the EFSA refused a health claim application for glucosamine containing the aforementioned scientific relationships documented in the literature up to 2010 [28]. The main reason for the refusal was the argument that there are no convincing intervention studies on healthy subjects. Furthermore, findings from studies with a diseased population – people with osteoarthritis – were not acknowledged. In May 2012, the EFSA published a guidance paper on the scientific requirements for health claims related to bone, joints, skin and oral health [29], suggesting possible endpoints for suitable studies. However, the interesting fact here is that, with the exception of the mention of biomarkers, these are endpoints that do not permit a measurable positive change after intervention in healthy subjects (functional changes, pain, stiffness, width of the joint space). Starting from this point of view, it must be stressed that the “convincing evidence” from the general healthy population in the classical sense required is simply not possible with the research means available today. In contrast, a large number of high-quality research results show that there are many factors that are strongly indicative of a causal relationship between glucosamine and benefits for joint function and joint health (bioavailability, uptake, physiological function and effects, based on chemical, mechanistic, and human data), as stated above. Overall, looking at the results of all the scientific work carried out up to 2010, it can be stated that the question of a benefit of glucosamine for the general healthy population can be answered positively with high probability; convincing evidence already exists for the diseased state [30]. More research supporting the beneficial role of glucosamine in terms of joint health has been pub-

lished since the EFSA assessment. The Hohenheimer consensus conference provided recommendations for further research to better understand the polyvalent nature of glucosamine in a healthy population [31]. As outlined above, the anti-inflammatory properties of glucosamine in the general population [23] were confirmed and another study suggesting chondroprotective activity of glucosamine in athletes (bicycle racers) was published [22]. Furthermore, the research is now (2015) very much to the fore with the first randomised controlled trial in the prevention of osteoarthritis. In the glucosamine arm of Runhaar et al.'s study (2015), the first preventive effects of glucosamine against the incidence of knee osteoarthritis after 2.5 years were shown (OR 0.60; 95% CI: 0.31–1.12) in a high-risk group of middle-aged women with a body mass index (BMI) ≥ 27 kg/m² and without clinical signs of knee osteoarthritis at baseline [32]. Taken together, the recent scientific research strengthens the level of high probability for the benefit of glucosamine in joint health.

In light of the epidemiological and health economic problems in the field of joint health, the question must be asked whether it is always reasonable to demand “convincing, fully conclusive evidence” or whether we should accept “evidence with high probability” in order to allow for correctly worded health-oriented consumer information. In practice, this affects consumers who would use such a food constituent because of diverse risk factors such as obesity, excessive joint loading, advanced age and possibly mild pain, but without any diagnosable osteoarthritis.

Grading of evidence is standard practice in other areas of preventive medicine. For instance, in their pioneering report on the risk of cancer in connection with nutrition and physical activity, the World Cancer Research Fund (WCRF) together with the American Institute of Cancer Research (AICR) [33] most certainly does distinguish between different degrees of evidence.

Furthermore, food constituents have to be by defi-

nition safe substances with an outstanding risk-benefit ratio. In contrast, the situation for pharmaceutical products is completely different, which is why convincing evidence must be presented here to show a risk-benefit ratio that justifies their use. However, it is a fundamentally flawed approach to apply all the principles of research into disease treatment as such to research into health maintenance and prevention, which is usually the rationale for carrying out research in nutritional science [34].

In view of these considerations, grading of evidence should be taken into account and classified accordingly in the global assessment of health claims. Recent findings may further be confirmed in the future by new data obtained, for instance, as a result of newly developed, more sensitive technical methods. Such new findings, for example, might give deeper insight into the mechanisms of the pathobiology of the onset (and progression) of osteoarthritis, which will possibly move the evidence level from “high probability” to “convincing”, even for the prevention of osteoarthritis in the healthy population. In any event, in the meantime, the consumer should be able to receive information on promising emerging science, e.g., using qualified language for a health claim.

Currently, no applications for joint health claims have been successful in the EU, with the exception of vitamin C for the normal function of cartilage. As things stand, this means that for the time being consumers will not be informed about the potential beneficial effects that food constituents such as glucosamine, a structural component of cartilage, may have on their joints. They will not be able to experience potential benefits in the early stages of emerging science and make informed choices. Ultimately, they may miss out on valuable health benefits.

Therefore, when assessing applications for possible health claims for food constituents, we advocate the integration of additional elements, namely grading of evidence, consideration of the risk-benefit ratio and last, but not least, epidemiological and health economic factors.

Conflict of interest

Jürgen Bernhardt and Christof Jaenicke declare that they have been sponsored by the Glucosamine Alliance for drafting the article. Peter Prock and Ulrich Schneider declare that they have no conflict of interest.

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References

- Kaplan W, Laing R (2004) Priority medicines for Europe and the world. World Health Organization Department of Essential Drugs and Medicines Policy, Geneva
- OECD (2010) Health at a glance: Europe 2010. OECD Publishing. http://dx.doi.org/10.1787/health_glance-2010-en
- Arthritis Foundation (2010) A national public health agenda for osteoarthritis 2010. http://www.arthritis.org/media/Ad-Council101/OA_AGENDA_2011REV.PDF (Accessed December 2012)
- de Vries J, Antoine JM, Burzykowski T, Chiodini A, Gibney M, Kuhnle G, Meheust A, Pijls L, Rowland I (2013) Markers for nutrition studies: review of criteria for the evaluation of markers. *Eur J Nutr* 52:1685–1699
- Blumberg J, Heaney RP, Huncharek M, Scholl T, Stampfer M, Vieth R, Weaver CM, Zeisel SH (2010) Evidence-based criteria in the nutritional context. *Nutr Rev* 68:478–484
- Setnikar I, Giachetti C, Zanol G (1984) Absorption, distribution and excretion of radioactivity after a single intravenous or oral administration of [¹⁴C] glucosamine to the rat. *Pharmatherapeutica* 3:538–550
- Setnikar I, Palumbo R, Canali S, Zanol G (1993) Pharmacokinetics of glucosamine in man. *Arzneimittelforschung* 43:1109–1113
- Setnikar I, Rovati LC (2001) Absorption, distribution, metabolism and excretion of glucosamine sulfate. A review. *Arzneimittelforschung* 51:699–725
- Block JA, Oegema TR, Sandy JD, Plaas A (2010) The effects of oral glucosamine on joint health: is a change in research approach needed? *Osteoarthritis Cartilage* 18:5–11
- Meulyzer M, Vachon P, Beaudry F, Vinardell T, Richard H, Beauchamp G, Laverty S (2009) Joint inflammation increases glucosamine levels attained in synovial fluid following oral administration of glucosamine hydrochloride. *Osteoarthritis Cartilage* 17:228–234
- Persiani S, Rotini R, Trisolino G, Rovati LC, Locatelli M, Paganini D, Antonioli D, Roda A (2007) Synovial and plasma glucosamine concentrations in osteoarthritic patients following oral crystalline glucosamine sulphate at therapeutic dose. *Osteoarthritis Cartilage* 15:764–772
- Derfoul A, Miyoshi AD, Freeman DE, Tuan RS (2007) Glucosamine promotes chondrogenic phenotype in both chondrocytes and mesenchymal stem cells and inhibits MMP-13 expression and matrix degradation. *Osteoarthritis Cartilage* 15:646–655
- Naito K, Watari T, Furuhashi A, Yomogida S, Sakamoto K, Kurosawa H, Kaneko K, Nagaoka I (2010) Evaluation of the effect of glucosamine on an experimental rat osteoarthritis model. *Life Sci* 86:538–543
- Chen D, Zhang Z, Cao J, Zhang D, Jia B (2010) [Effect of glucosamine hydrochloride capsules on articular cartilage of rabbit knee joint in osteoarthritis]. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi* 24:287–291
- Oegema TR Jr, Deloria LB, Sandy JD, Hart DA (2002) Effect of oral glucosamine on cartilage and meniscus in normal and chymopapain-injected knees of young rabbits. *Arthritis Rheum* 46:2495–2503
- Scarpellini M, Lurati A, Vignati G, Marrazza MG, Telese F, Re K, Bellistri A (2008) Biomarkers, type II collagen, glucosamine and chondroitin sulfate in osteoarthritis follow-up: the “Magenta osteoarthritis study”. *J Orthop Traumatol* 9:81–87
- Garnero P, Piperno M, Gineyts E, Christgau S, Delmas PD, Vignon E (2001) Cross sectional evaluation of biochemical markers of bone, cartilage, and synovial tissue metabolism in patients with knee osteoarthritis: relations with disease activity and joint damage. *Ann Rheum Dis* 60:619–626
- Cahue S, Sharma L, Dunlop D, Ionescu M, Song J, Lobanok T, King L, Poole AR (2007) The ratio of type II collagen breakdown to synthesis and its relationship with the progression of knee osteoarthritis. *Osteoarthr Cartil* 15:819–823
- Sharif M, Kirwan J, Charni N, Sandell LJ, Whittles C, Garnero P (2007) A 5-yr longitudinal study of type IIA collagen synthesis and total type II collagen degradation in patients with knee osteoarthritis: association with disease progression. *Rheumatology (Oxford)* 46:938–943
- Christgau S, Henrotin Y, Tanko LB, Rovati LC, Collette J, Bruyere O, Deroisy R, Reginster JY (2004) Osteoarthritic patients with high cartilage turnover show increased responsiveness to the cartilage protecting effects of glucosamine sulphate. *Clin Exp Rheumatol* 22:36–42
- Yoshimura M, Sakamoto K, Tsuruta A, Yamamoto T, Ishida K, Yamaguchi H, Nagaoka I (2009) Evaluation of the effect of glucosamine administration on biomarkers for cartilage and bone metabolism in soccer players. *Int J Mol Med* 24:487–494
- Momomura R, Naito K, Igarashi M, Watari T, Terakado A, Oike S, Sakamoto K, Nagaoka I, Kaneko K (2013) Evaluation of the effect of glucosamine administration on biomarkers

- of cartilage and bone metabolism in bicycle racers. *Mol Med Rep* 7:742–746
23. Navarro SL, White E, Kantor ED, Zhang Y, Rho J, Song X, Milne GL, Lampe PD, Lampe JW (2015) Randomized trial of glucosamine and chondroitin supplementation on inflammation and oxidative stress biomarkers and plasma proteomics profiles in healthy humans. *PLoS ONE* 10:e0117534
 24. Largo R, Martinez-Calatrava MJ, Sanchez-Pernaute O, Marcos ME, Moreno-Rubio J, Aparicio C, Egido J, Herrero-Beaumont G (2009) Effect of a high dose of glucosamine on systemic and tissue inflammation in an experimental model of atherosclerosis aggravated by chronic arthritis. *Am J Physiol Heart Circ Physiol* 297:H268–H276
 25. Azuma K, Osaki T, Wakuda T, Tsuka T, Imagawa T, Okamoto Y, Minami S (2012) Suppressive effects of N-acetyl-D-glucosamine on rheumatoid arthritis mouse models. *Inflammation* 35:1462–1465
 26. Kantor ED, Lampe JW, Navarro SL, Song X, Milne GL, White E (2014) Associations between glucosamine and chondroitin supplement use and biomarkers of systemic inflammation. *J Altern Complement Med* 20:479–485
 27. Damlar I, Esen E, Tatli U (2015) Effects of glucosamine-chondroitin combination on synovial fluid IL-1beta, IL-6, TNF-alpha and PGE2 levels in internal derangements of temporomandibular joint. *Med Oral Patol Oral Cir Bucal* 20(3):e278-83
 28. EFSA Panel on Dietetic Products N.a.A.N. (2012) Scientific opinion on the substantiation of a health claim related to glucosamine and maintenance of normal joint cartilage pursuant to Article 13(5) f Regulation (EC) No 1924/2006. *EFSA J* 10(5):2691
 29. EFSA Panel on Dietetic Products, N.a.A.N. (2012) Guidance on the scientific requirements for health claims related to bone, joints, skin and oral health. *EFSA J* 10(5):2702
 30. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacomelli G, Rovati LC (2002) Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Arch Intern Med* 162:2113–2123
 31. Henrotin Y, Chevalier X, Herrero-Beaumont G, McAlindon T, Mobasheri A, Pavelka K, Schön C, Weinans H, Biesalski H (2013) Physiological effects of oral glucosamine on joint health: current status and consensus on future research priorities. *BMC Res Notes* 6:115–116. doi: 10.1186/1756-0500-6-115
 32. Runhaar J, van Middelkoop M, Reijman M, Willemssen S, Oei EH, Vroegindewij D, van Osch G, Koes B, Bierma-Zeinstra SM (2015) Prevention of knee osteoarthritis in overweight females; the first preventive randomized controlled trial in osteoarthritis. *Am J Med* 10 pii: S0002-9343(15)00244-2. doi: 10.1016/j.amjmed.2015.03.006
 33. World Cancer Research Fund/American Institute for Cancer Research. 2007. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. AICR, Washington, DC
 34. Somogyi A, Hathcock J, Biesalski HK, Blumberg JB, Antoine JM, Edwards G, Prock P (2011) Scientific issues related to Codex Alimentarius goals: a review of principles, with examples. *Regul Toxicol Pharmacol* 60:161–164