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Letter to the Editor

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Glycosaminoglycans and their precursors in osteoarthritis

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Chondroitin (Ch) is a glycosaminoglycan (GAG); and glucosamine (Ga) is an aminosaccharide acting as a substrate for biosynthesis of GAG. Ch undergoes hydrolysis in the intestine; being administered orally, it can also be regarded as a source of precursors for GAG. Hyaluronic acid (HA) is a GAG used for intra-articular injections. These substances are applied for the treatment of osteoarthritis and named chondroprotectants or chondroprotectives. The oral GAG have been discussed within the group of Symptomatic Slow-Acting Drugs in Osteoarthritis (SYSADOA) (Bruyère *et al*., 2016), which is hardly justified: these drugs are supposed to act primarily not upon symptoms but upon the pathogenesis – to compensate for a deficiency of cartilage constituents. The evidence in favor of chondroprotective effectiveness of GAG and their components is conflicting. Despite the popularity of chondroprotectives, there is skepticism in the scientific community (Vista and Lau, 2011). For example, a meta-analysis concluded that "Ch, Ga, and their combination do not have a clinically relevant effect on perceived joint pain or on joint space narrowing" (Wandel *et al*., 2010). Another key remark: "Given that there is an effect, understanding the biochemical basis of this effect might lead to more useful supplements" (Wood, 2010). The point is that the biochemical basis is not readily understandable. GAG and their precursors are not irreplaceable; they are synthesized in the body. It appears doubtful that oral supplementation of precursors can shift an equilibrium between synthesis and degradation in the whole body to such extent that it would be significant for the joint cartilage. Furthermore, source materials such as shellfish chitin and fungi for Ga, or cartilage from mammals, birds or fish for Ch (Black *et al*., 2009), manufacturing methods and contaminants, can influence biological and pharmacological properties of preparations (Volpi, 2009).

With regard to intra-articular injections of HA, a meta-analysis concluded that "currently available evidence suggests that intra-articular GA is not clinically effective" (Arrich *et al*., 2005). The evidence remains inconsistent and controversial (Nguyen *et al*., 2016). Action mechanisms of intra-articular HA are hardly understandable, even the "lubrication at the joint surfaces" i.e. viscosupplementation used both in humans and animals (Lohmander *et al*., 1996; Goodrich and Nixon, 2006). Viscosity changes in consequence of HA injections can be measured e.g. adding HA to cadaverous synovial fluid. Both pre- and post-treatment viscosity values were reported to be within the range of normal values (Brandt *et al*., 2000). Analgesic effects lasting longer than the residence time of the injected HA in joints were reported both in humans and in horses with painful osteoarthritis. Furthermore, it was reported that viscous properties of HA solutions are the determining factors in reducing pains in cat and rat joints as well as promoting the healing of traumatic intra-articular wounds in animal arthritis models (Balazs, 2004). However, the lubrication effect cannot last long: no explanation has been found for the discrepancy between the short intra-articular half-life of injected HA and the reported duration of the clinical carry-over effect in humans. The intra-articular half-life of Hyalgan (sodium hyaluronate) is about 17 h; the low molecular weight component of Synvisc (Hylan G-F 20 constituting about 90% of the preparation) has an intra-articular half-life of 1.5 days; and the component with a higher molecular weight - 8.8 days (Brandt *et al.*, 2000). Nevertheless, the carry-over effect after the treatment lasted from about 3 months with oral chondroprotectives to 6-9 months with intra-articular formulations (Uebelhart, 2008).

HA is a polymer; according to the law of mass action, its local enrichment would displace the chemical equilibrium toward low-molecular precursors, thus contributing to the reduction of viscosity. Therefore, suppositions about "induction of biosynthesis of endogenous HA" (Bruyère *et al.*, 2016) by injections of the same substance are not substantiated. As for molecular mechanisms studied *in vitro* (Brandt *et al.*, 2000), their clinical relevance is questionable because of higher concentrations of tested substances *in vitro* than *in vivo* (Black *et al.*, 2009). Note that Ch, Ga and HA were chosen for supplementation therapy, and a probability of their specific e.g. anti-inflammatory effect (Altman *et al.*, 2018) or "inhibition of chondrodegenerative enzymes" (Xing *et al.*, 2016) would *a priori* be the same as for any substance taken at random.

It should be questioned in conclusion whether a diet rich in natural GAG: joints, tails, chicken legs etc. would be equivalent to a supplementation by drugs and dietary supplements. This idea is not new; it was discussed at conferences. Should randomized controlled trials on Ch and Ga be planned, a cohort of patients on a diet rich in natural GAG can be included for comparison. Effectiveness of a dietary supplementation of natural GAG versus Ch and Ga preparations can be tried for osteoarthritis in animals, particularly dogs, giving them food rich in cartilage. A recent

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review concluded that potential benefits from Gl and Ch in osteoarthritic canines can neither be confirmed nor denied (Bhathal *et al*., 2017). Some animal studies are at risk of funding bias due to a sponsorship. It might be also useful to check osteoarthritis prevalence in vegetarians, receiving no exogenous supply of GAG or their immediate precursors, compared to corresponding age groups in the general population. Considering the abundance of literature, quality of research and possible influence by the industry should be taken into account defining inclusion criteria for studies into meta-analyses and reviews.

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