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Associations Between Glucosamine and Chondroitin Supplement Use and Biomarkers of Systemic Inflammation

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Abstract

Objectives: Glucosamine and chondroitin supplements have been shown to have anti-inflammatory properties in both *in vitro* studies and animal models; however, little is known about these relationships in humans. The VITamins and Lifestyle (VITAL) biomarker study evaluated the associations between use of these supplements and a panel of circulating inflammatory biomarkers.

Design: Study participants included 217 men and women age 50–75 years living in the Seattle metropolitan area. Use of glucosamine and chondroitin supplements was ascertained by home interview/supplement inventory. Inflammation was assessed by using blood and urine collected at the time of home interview. Measures of systemic inflammation included plasma high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor (TNF)-α, soluble TNF receptors I and II, and urinary prostaglandin E_2-metabolite (PGE-M). Multivariate-adjusted linear regression was used to evaluate the associations between supplement use and biomarkers of inflammation.

Results: High users (14 or more pills/week) of chondroitin had 36% lower hsCRP (ratio, 0.64; 95% confidence interval [CI], 0.39–1.04; p for trend = .03) and 27% lower PGE-M (ratio, 0.73; 95% CI, 0.5–0.98; p for trend = .07) than nonusers. Compared with nonusers, high users of glucosamine had 28% lower hsCRP (ratio, 0.72; 95% CI, 0.47–1.08; p for trend = .09) and 24% lower PGE-M (ratio, 0.76; 95% CI, 0.59–0.97; p for trend = 0.10). Use of glucosamine and chondroitin supplements was not associated with the other markers of inflammation.

Conclusions: These results support prior research suggesting that use of glucosamine and chondroitin is associated with reduced hsCRP and PGE_2, but further work is needed to more definitively evaluate the anti-inflammatory potential of these supplements.

Introduction

Glucosamine and chondroitin are among the most popular nonvitamin, nonmineral ''specialty'' supplements in the United States. They are often taken together as a single daily supplement for osteoarthritis. It has been estimated that 7.4% of older Americans use glucosamine-chondroitin, a prevalence of use similar to that for acetaminophen.[1] While the biologic effects of these supplements remain poorly understood, *in vitro* and animal studies of glucosamine and chondroitin suggest that these popular supplements may have anti-inflammatory properties.[2–18] Limited evidence from a small human trial suggests that glucosamine-chondroitin may reduce prostaglandin E_2 (PGE_2) concentrations.[19] In a recent study of nearly 10,000 adults included in the National Health and Nutrition Examination Survey (NHANES), use of glucosamine and chondroitin supplements was associated with reduced concentrations of high-sensitivity C-reactive protein (hsCRP).[20] However, no human studies have evaluated the association between use of these supplements and other biomarkers of inflammation.

Understanding the patterns of association between use of these supplements and biomarkers of inflammation may shed light on the involved biologic mechanisms. It is important to understand the potential anti-inflammatory action of these supplements because reducing inflammation may offer a feasible prevention strategy for diseases with a

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possible inflammatory cause, such as cancer and cardiovascular disease.[21–27] To this end, glucosamine and chondroitin supplements were recently found to be associated with reduced risk of colorectal cancer,[20,28] lung cancer,[28,29] and total mortality.[30,31]

The current study has therefore been conducted to examine the association between use of glucosamine and chondroitin supplements and a panel of inflammatory biomarkers: plasma hsCRP, interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor (TNF)-α, soluble TNF I (sTNFRI), soluble TNF II (sTNFRII), and urinary PGE metabolite (PGE-M).

Materials and Methods

Study population

This study was conducted within the VITamins and Lifestyle (VITAL) biomarker study, which includes 220 persons drawn from the overall VITAL cohort. The VITAL cohort is a prospective study of 77,719 western Washington residents aged 50–76 that targeted supplement users at recruitment and was designed to assess the relationship between supplement use and cancer risk.[32] Cohort participants who completed their baseline questionnaire between October 2000 and February 2001 were randomly selected for participation in the VITAL biomarker study. Sampling was stratified by sex so as to obtain equal numbers of men and women, with oversampling of high users of the following supplements: vitamin C, vitamin E, and calcium. Persons with type 1 diabetes or any conditions preventing the collection of fasting blood were excluded from the biomarker study. In addition, persons with Alzheimer disease were excluded, as were persons living outside the Seattle metropolitan area.

Two hundred and twenty (76%) of the 290 eligible participants contacted agreed to participate and completed the study protocol. Persons included in the VITAL biomarker study completed a second self-administered mailed questionnaire and participated in an in-home visit, during which an interview was conducted and blood and urine were collected. All study participants provided written informed consent; the Fred Hutchinson Cancer Research Center (FHCRC) Institutional Review Board approved the study procedures.

Exposures

Use of glucosamine and chondroitin supplements was ascertained by supplement interview/inventory conducted at the time of home visit. Participants were asked to report on frequency (days/week) of use of currently used supplements, the number of pills taken per occasion of use, and the date of last use. Persons reporting use of a given supplement within the 2 weeks prior were classified as current users, and those reporting no use or last use more than 2 weeks prior were classified as nonusers. Glucosamine or chondroitin users reported using a range of brands and formulations (i.e., glucosamine alone, glucosamine plus chondroitin, glucosamine plus methylsulfonylmethane, glucosamine plus chondroitin plus methylsulfonylmethane).

Glucosamine and chondroitin were classified in terms of the average number of pills/week of use (nonuse, low use [<14 pills/week], or high use [≥ 14 pills/week]). Persons missing information on the number of pills/occasion of use ($n=7$ for glucosamine, $n=5$ for chondroitin) were assumed to use 1 pill/occasion to allow for calculation of pills/week. This value was selected because most study participants with use of glucosamine and chondroitin reported 1 pill/occasion of use.

Outcomes

Concentrations of hsCRP, IL-1β, IL-6, IL-8, TNF-α, sTNFRI, and sTNFRII were measured in plasma and PGE-M was assessed in spot urine. These biomarkers were largely selected on the basis of association with glucosamine or chondroitin in prior human,[19,20] animal,[6–9,12] or *in vitro* studies.[2,5,13–18] The blood and urine samples were collected at the home visit and were processed (ie, the blood was centrifuged, biologic specimens were divided into aliquots) for storage at the FHCRC Specimen Processing Laboratory within approximately 2 hours of collection. The aliquots were frozen at -80°C until the time of assay in 2010–2011. Values for hsCRP were assessed at the FHCRC Public Health Sciences Biomarkers Laboratory using the CRP Ultra Wide Range Reagent (Sekisui Diagnostics, LLC, Lexington, MA). IL-1β, IL-6, IL-8, and TNF-α were assayed at the Biomarkers Laboratory using the MILLIPLEX High Sensitivity Human Cytokine kit (Millipore, St. Charles, MO). The lowest standard of this 4-plex assay was 0.182 pg/mL, and values returned as <0.182 were replaced with half of this value (0.091) (IL-1β, $n=50$; IL-6, $n=13$; and TNF-α, $n=1$). The two soluble TNF receptors (sTNFRI and sTNFRII) were also assayed at the Biomarkers Laboratory using the Millipore Human Soluble Cytokine Receptor Panel kit. Urinary PGE-M was assayed at the Vanderbilt Eicosanoid Core Laboratory using unacidified urine. The liquid chromatography–mass spectrometry tandem method was used to assess urinary PGE-M, the stable metabolite of PGE_2.[33] PGE-M analyses were corrected for urinary creatinine, and values of PGE-M are expressed as ng/mg creatinine.

Seven persons lacking available urine samples were excluded from PGE-M analyses, leaving a total sample of 213 for analyses of PGE-M. To exclude persons with acute illness from the analyses, persons were further excluded from all analyses if their CRP level was in the top 2% for their age/body–mass index (BMI)/sex group ($n=3$), with cutoffs for each group based on a large, nationally representative sample from NHANES.[20] After the above-listed exclusions were made, 210 persons remained for analyses of PGE-M and 217 remained for all other biomarkers.

Confounders

A priori, the following variables were selected as adjustment factors for all analyses: age (continuous), sex, and BMI (kg/m^2; continuous). Additional covariates were selected for inclusion by evaluating their association with each outcome in this minimally adjusted model. The broad set of potential confounding variables evaluated included various demographic factors (age, sex, race, and education), lifestyle factors (smoking, alcohol consumption, and physical activity), medical history (cancer, cardiovascular disease, and diabetes), current medication use (regular aspirin, baby aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, hormone replacement therapy, and cholesterol-lowering drugs),

dietary factors (energy intake, fiber intake, saturated fat intake, α-tocopherol intake, γ-tocopherol intake, vitamin C, β-carotene, and long-chain ω-3 polyunsaturated fatty acids), supplement use (fiber, vitamin E, vitamin C, β-carotene, fish oil, and multivitamins), as well as dietary plus supplemental intake (total fiber, total α-tocopherol, total vitamin C, and total β-carotene).

Variables associated with a given outcome at the $\alpha = 0.10$ level in the minimally adjusted model were included as covariates in analyses of the association between glucosamine or chondroitin supplement use and that outcome. Analyses also adjusted for the indication for use of glucosamine and chondroitin; specifically, all analyses of glucosamine and chondroitin were adjusted for arthritis or chronic joint pain. Covariates included in the final models are listed in the footnotes of Table 1.

Statistical analysis

All biomarker outcomes were log-transformed by using the natural logarithm to normalize their distributions; consequently, geometric means, rather than arithmetic means, have been presented for each biomarker outcome (Table 2). Linear regression was used to evaluate the associations between age, sex, and BMI and each log-transformed outcome. As outcomes were log-transformed, the β-coefficients have been exponentiated so as to present results in terms of ratios; for example, presented are the ratio of hsCRP per 10-year increase in age, the ratio of hsCRP comparing men to women, and the ratio of hsCRP per 5-unit increase in BMI (Table 2).

Glucosamine and chondroitin are presented by using indicator variables (indicating no use, low use, or high use). A *p*-value trend was derived from a model in which glucosamine or chondroitin use was modeled as a single linear variable with exposure levels corresponding to 1, 2, or 3; the *p*-value from the Wald test for this grouped linear variable corresponds to the *p*-value for trend. The models presented in Table 1 (between glucosamine and chondroitin use and markers of inflammation) were multivariate-adjusted, as described above. All analyses were conducted by using Stata software (version 12; Stata Corp., College Station, TX).

Results

The study participants ranged from 50 to 75 years of age, and 49% were female (Table 3). Participants were predominantly (94.5%) white; 38% of the study population had a normal BMI, 45% were overweight, and 17% were obese. Increasing age was associated with increased concentrations of hsCRP, IL-6, IL-8, TNF-α, sTNFRI, sTNFRII, and PGE-M (Table 2). Although male sex was associated with lower concentrations of hsCRP and IL-6, it was conversely associated with higher concentrations of sTNFRI and PGE-M. Increased BMI was associated with increased concentrations of hsCRP, sTNFRI, and sTNFRII.

In multivariate models, high users (>14 pills/week) of glucosamine had 28% lower hsCRP than nonusers (ratio: 0.72; 95% CI, 0.47–1.08; *p* for trend = 0.09) and high users of chondroitin had 36% lower hsCRP than nonusers (ratio, 0.64; 95% CI, 0.39–1.04; *p* for trend = .03). Compared with nonusers, high users of glucosamine had 24% lower PGE-M (ratio, 0.76; 95% CI, 0.59–0.97; *p* for- trend = .10), while high users of chondroitin had 27% lower PGE-M (ratio, 0.73; 95% CI, 0.55–0.98; *p* for trend = .07). It appeared that low use (<14 pills/week) of glucosamine and chondroitin led to a partial benefit in terms of CRP reduction, but reduction in PGE-M was limited to those who took at least 2 pills per day. Neither of these supplements was not statistically significantly associated with the other biomarkers of systemic inflammation, including IL-1β, IL-6, IL-8, TNF-α, sTNFRI, and sTNFRII (all *p* for trend 0.20).

Discussion

This study suggests that use of glucosamine and chondroitin supplements is associated with reduced hsCRP and PGE-M concentrations. High users of chondroitin had 36% lower hsCRP than nonusers (ratio, 0.64; 95% CI, 0.39–1.04; *p* for trend = .03). Results were similar, though not statistically significant, for glucosamine (ratio for high use vs no use, 0.72; 95% CI, 0.47–1.08; *p* for trend = .09). The finding of an inverse association between glucosamine/chondroitin and hsCRP supports the authors' prior study of nearly 10,000 adults conducted within NHANES, in which current regular use of glucosamine was associated with a 17% reduction in hsCRP (ratio, 0.83; 95% CI, 0.71–0.98) and current regular use of chondroitin was associated with a 22% reduction in hsCRP (ratio, 0.78; 95% CI, 0.67–0.92).[20]

Only one other human study examined the association between use of glucosamine or chondroitin and CRP concentrations. Nakamura and colleagues randomly assigned 51 persons with rheumatoid arthritis to receive 1500 mg of glucosamine per day or placebo for 12 weeks.[34] Those authors reported that glucosamine supplementation did not affect CRP concentrations. However, participants in the experimental group were given glucosamine only, as opposed to glucosamine plus chondroitin. Furthermore, results from that trial may not be generalizable, given that it was conducted among persons with rheumatoid arthritis, a population with high systemic levels of inflammation. Importantly, study participants were allowed to continue their normal medication regimen for their rheumatoid arthritis, which may also diminish the differences between groups, obscuring any potential anti-inflammatory effect of the glucosamine.

In the current study, PGE-M concentrations were 24% lower among the high users of glucosamine (ratio, 0.76; 95% CI, 0.59–0.97) and 27% lower among the high users of chondroitin (ratio, 0.73; 95% CI, 0.55.98), although the *p* values for trends did not reach statistical significance (*p* values trend = .10 and .07, respectively). Only one other human study has examined the association between glucosamine/chondroitin use and PGE concentration: In a trial of patients with osteoarthritis, 36 persons were given 1500 mg glucosamine plus 675 mg chondroitin daily for 12 weeks.[19] Study authors reported that glucosamine plus chondroitin treatment reduced PGE concentrations ($p < 0.01$), with the end-of-study PGE concentrations among the glucosamine plus chondroitin group similar to those of 25 age-matched healthy controls. The results of this small trial align with the current observation that high use of glucosamine and chondroitin supplements is associated with reduced PGE-M concentrations.

Glucosamine and chondroitin supplements are often taken together in a single daily supplement, and it is therefore possible that these results are driven by either of these supplements. To address this issue, sensitivity analyses

Table 1. Associations Between Glucosamine and Chondroitin Use and Biomarkers of Inflammation

Supplement	Patients, n (%)	CRP[a]		IL-1β[b]		IL-6[c]		IL-8[d]		TNF-α[e]		sTNFRI[f]		sTNFRII[g]		PGE-M[h]	
		Ratio	*(95% CI)*	*Ratio*	*(95% CI)*	*Ratio*	*(95% CI)*	*Ratio*	*(95% CI)*	*Ratio*	*(95% CI)*	*Ratio*	*(95% CI)*	*Ratio*	*(95% CI)*	*Ratio*	*(95% CI)*
Glucosamine[i]																	
No	165 (76.1)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Low (< 14 pills/wk)	20 (9.22)	0.82	(0.50–1.34)	1.41	(0.67–2.96)	0.96	(0.46–2.02)	1.09	(0.79–1.52)	1.07	(0.7–1.63)	1.05	(0.89–1.22)	1.06	(0.93–1.21)	1.25	(0.92–1.69)
High (≥ 14 pills/wk)	32 (14.8)	0.72	(0.47–1.08)	0.80	(0.43–1.46)	0.84	(0.46–1.54)	0.90	(0.69–1.19)	0.77	(0.54–1.09)	1.02	(0.89–1.16)	1.01	(0.91–1.13)	0.76	(0.59–0.97)
p for trend		*0.09*		0.67		0.57		0.60		0.21		*0.70*		*0.62*		*0.10*	
Chondroitin[i]																	
No	183 (84.3)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Low (< 14 pills/wk)	15 (6.91)	0.65	(0.37–1.14)	0.93	(0.41–2.13)	0.58	(0.26–1.32)	0.99	(0.68–1.43)	0.86	(0.53–1.37)	0.91	(0.76–1.08)	0.99	(0.85–1.15)	1.05	(0.74–1.48)
High (≥ 14 pills/wk)	19 (8.76)	0.64	(0.39–1.04)	1.01	(0.49–2.11)	0.95	(0.46–1.98)	0.99	(0.71–1.38)	0.93	(0.61–1.43)	1.10	(0.94–1.29)	1.04	(0.91–1.18)	0.73	(0.55–0.98)
p for trend		*0.03*		*0.98*		*0.56*		*0.93*		*0.60*		*0.46*		*0.64*		*0.07*	

[a]Analyses of CRP adjusted for age (continuous), sex, current body mass index (BMI) (continuous), pack-years smoked (ordered categorical), current hormone replacement therapy use (no/yes), history of cardiovascular disease (no/yes), any moderate of vigorous physical activity (no/yes), dietary fiber (continuous), dietary saturated fat (continuous), dietary α-tocopherol (continuous), dietary γ-tocopherol (continuous), dietary vitamin C (continuous), dietary β-carotene (continuous), dietary eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) intake (continuous), energy (continuous).

[b]Analyses of IL-1β adjusted for age (continuous), sex, BMI (continuous), baby aspirin use in prior month (ordered categorical: none, low, high), dietary fiber (continuous), dietary saturated fat (continuous), energy (continuous).

[c]Analyses of IL-6 adjusted for age (continuous), sex, BMI (continuous), dietary saturated fat (continuous), and energy (continuous).

[d]Analyses of IL-8 adjusted for age (continuous), sex, BMI (continuous), diabetes (no/yes), history of cardiovascular disease (no/yes).

[e]Analyses of TNF-α adjusted for age (continuous), sex, BMI (continuous), dietary fiber (continuous), dietary saturated fat (continuous), dietary EPA plus DHA (continuous), and energy (continuous).

[f]Analyses of sTNF-RI adjusted for age (continuous), sex, BMI (continuous), history of cancer (no/yes), current multivitamin use (no/yes), energy (continuous).

[g]Analyses of sTNF-RII adjusted for age (continuous), sex, BMI (continuous), current hormone replacement therapy use (no/yes), history of cancer (no/yes), any moderate or vigorous physical activity (no/yes), alcohol consumption (categorical tertiles), energy (continuous), dietary saturated fat (continuous), dietary vitamin C (continuous), dietary EPA plus DHA (continuous), supplemental vitamin E (ordered categorical: none, low, high), supplemental β-carotene (ordered categorical: none, low, high).

[h]Analyses of PGE-M adjusted for age (continuous), sex, BMI (continuous), pack-years smoked (ordered categorical), baby aspirin use in prior month (ordered categorical: none, low, high), and history of cancer (no/yes).

[i]Analyses of glucosamine, chondroitin, and methylsulfonylmethane further adjusted for indication of arthritis or chronic pain.

CRP, C-reactive protein; IL, interleukin; TNF, tumor necrosis factor; sTNFRI, soluble TNF receptor I; sTNFRII, soluble TNF receptor II; PGE-M, prostaglandin E_2 metabolite; CI, confidence interval.

Table 2. Distribution of Inflammatory Biomarkers and Association Between Each Biomarker and Age, Sex, and Body–Mass Index

Variable	*Geometric mean (geometric 25th, 75th percentile)*	*Ratio[a] per 10-y increase in age (95% CI)*	*Ratio[b] for sex: male vs. female (95% CI)*	*Ratio[c] per 5-unit increase in BMI (95% CI)*
CRP (mg/L)	1.75 (0.72, 4.03)	1.25 (1.04–1.50)	0.45 (0.34–0.59)	1.67 (1.42–1.95)
IL-1β (pg/mL)	0.77 (0.11, 2.58)	1.11 (0.85–1.46)	0.80 (0.53–1.21)	0.96 (0.76–1.22)
IL-6 (pg/mL)	3.62 (1.50, 12.0)	1.39 (1.06–1.83)	0.63 (0.42–0.95)	1.19 (0.94–1.50)
IL-8 (pg/mL)	2.24 (1.44, 3.47)	1.17 (1.04–1.33)	0.91 (0.75–1.10)	0.97 (0.87–1.08)
TNF-α (pg/mL)	5.77 (3.38, 11.6)	1.22 (1.05–1.43)	0.91 (0.72–1.15)	1.03 (0.90–1.18)
sTNFRI (pg/mL)	1430 (1186, 1732)	1.12 (1.06–1.19)	1.09 (1.00–1.20)	1.05 (1.00–1.11)
sTNFRII (pg/mL)	5677 (4768, 6683)	1.17 (1.11–1.23)	1.04 (0.97–1.12)	1.06 (1.02–1.11)
PGE-M (ng/mg creatinine)	5.43 (3.38, 8.55)	1.16 (1.04–1.30)	1.20 (1.01–1.42)	1.04 (0.94–1.16)

[a]Adjusted for sex and BMI (continuous).
[b]Adjusted for age (continuous) and BMI (continuous).
[c]Adjusted for age (continuous) and sex.
BMI, body mass index; PGE-M, prostaglandin E_2 metabolite.

examined the association between glucosamine alone and either hsCRP or PGE-M; no association was observed between use of glucosamine alone and either of these biomarkers. However, this study could not examine the associations between chondroitin alone and these biomarkers because all chondroitin users also reported use of glucosamine. It is therefore possible that the results for glucosamine and chondroitin are driven by either chondroitin or the combination of glucosamine plus chondroitin.

This work is supported by a body of *in vitro* and animal studies suggesting that glucosamine and chondroitin have anti-inflammatory properties. Both glucosamine[2] and chondroitin[3] reduce inflammation *in vitro* via inhibition of nuclear factor κ B (NFκB), a transcription factor that lies upstream of various inflammatory processes. NFκB resides in an inactive state in the cytoplasm, bound by the inhibitory subunit, IκB. When IκB is degraded by inflammatory stimuli, NFκB can freely translocate to the nucleus and potentiate the inflammatory cascade, eventually resulting in the production of both CRP (via IL-6 production) and PGE_2 (via the cyclooxygenase enzyme).[35,36] Largo and colleagues have shown that glucosamine inhibits NFκB activation by preventing the degradation of IκB in a dose-dependent manner.[2] Supporting *in vitro* studies have further shown that glucosamine and chondroitin reduce the production of inflammatory biomarkers downstream of NFκB, including IL-6, IL-8, TNF-α, and PGE_2.[2,4,5,11,13–16] Animal studies have corroborated this growing body of *in vitro* evidence, with several studies showing that administration of glucosamine and/or chondroitin reduces circulating concentrations of CRP, IL-1β, IL-6, and TNF-α.[6–9,12]

Table 3. Characteristics of VITamins and Lifestyle Biomarker Study Participants

Characteristic	*Participants,* n *(%)*
Age	
50–<55 y	53 (24.4)
55–<60 y	53 (24.4)
60–<65 y	37 (17.1)
65–<70 y	30 (13.8)
≥70 y	44 (20.3)
Sex	
Female	106 (48.9)
Male	111 (51.2)
Race	
White	205 (94.5)
Nonwhite	12 (5.53)
Body mass index	
<25 kg/m^2	83 (38.3)
25–<30 kg/m^2	97 (44.7)
≥30 kg/m^2	37 (17.1)

Beyond the observed associations between glucosamine and chondroitin use and hsCRP and PGE-M, weak, non–statistically significant inverse associations were seen between use of these supplements and IL-1β, IL-6, IL-8, and TNF-α. However, these estimates were imprecise and a larger study is needed to evaluate these associations with more statistical power. Because the mechanism by which glucosamine/chondroitin is thought to affect CRP likely involves IL-6 as an intermediate,[36] it is not clear why the association was stronger for CRP than IL-6. It also remains unclear why no association was observed with the soluble TNF receptors. Although this may be due to chance, this pattern of association might reflect the complex biologic mechanisms underlying the potential anti-inflammatory action of these supplements. Given the complex nature of these inflammatory pathways, further work is needed to elucidate the role of these supplements in the inflammatory process.

Limitations of this study include the small sample size and the fact that study participants were instructed not to use any supplements on the day of home visit. However, most study participants reporting use of these supplements reported use within the previous day. Another limitation of this study is that assays were run in blood and urine stored at −80°C for several years, which may result in some degradation in the inflammatory biomarkers of interest.[37] Furthermore, the study oversampled supplement users, which may affect the generalizability of these results.

However, it is notable that the oversampling of supplement users is also one of the greatest strengths of this study: with a population enriched in supplement users, most nonusers of glucosamine and chondroitin are using other supplements. This likely increases the comparability of the exposed and unexposed

groups in terms of measured and unmeasured health behaviors, reducing concern about residual confounding. Another strength of this study is the effort to identify and control for potential confounding factors. The study was also able to evaluate the associations between use of these supplements and multiple systemic biomarkers of inflammation. Finally, supplement use was ascertained by interview and an in-home supplement inventory, likely increasing the accuracy of exposure assessment.

In conclusion, this study suggests that use of glucosamine and chondroitin supplements is associated with lower concentrations of hsCRP and PGE-M. Little research has been conducted on the association between glucosamine/chondroitin use and inflammation in humans, and thus this study offers an important piece of evidence to suggest that these supplements might have anti-inflammatory potential. It is important to expand on these associations in larger, more well-powered observational studies and in randomized controlled trials. Such trials will likely be necessary to evaluate the effect of each supplement individually because glucosamine and chondroitin are often taken together in a single daily supplement and therefore the individual effects of each of these supplements cannot be evaluated observationally. Further work is warranted, as identifying ways of reducing inflammation may lead to future potential preventive measures for diseases with which inflammation has been implicated, such as cardiovascular disease and cancer.

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Disclosure Statement

No competing financial interests exist.

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