Utilità degli integratori «utili» nella patologia muscolo-scheletrica

Arrigo F.G. Cicero

Dip. di Scienze Mediche e Chirurgiche

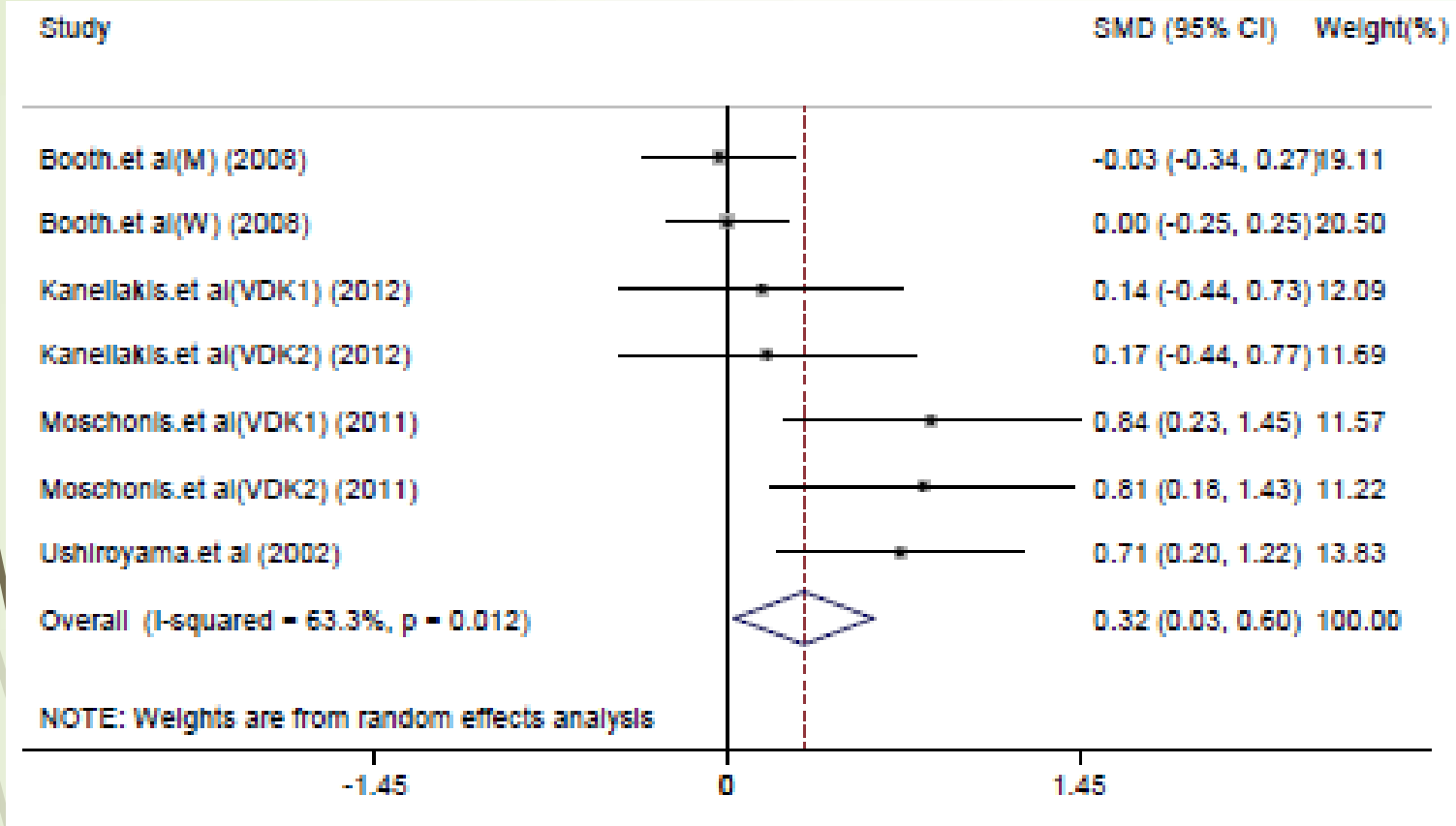
Alma Mater Studiorum Università di Bologna

Premessa

- Le patologie muscolo-scheletriche sono entità estremamente diverse e l'approccio nutraceutico dovrebbe essere sartoriale
- Nella maggioranza dei casi l'integrazione ha un razionale se adeguatamente dosata, cronica, continuativa
- Farmacocinetica e farmacodinamica sono principi fondamentali della nutraceutica

Osteopenia:
Un approccio multistep con alcune «lacune» …

- Approccio dietetico-comportamentale +
- Calcio
- Vitamina D
- Vitamina K2
- Acido ortosilicico



The combination effect of vitamin K and vitamin D on human bone quality: a meta-analysis of randomized controlled trials

Food Funct. 2020 Apr 30;11(4):3280-3297.

Contents lists available at ScienceDirect

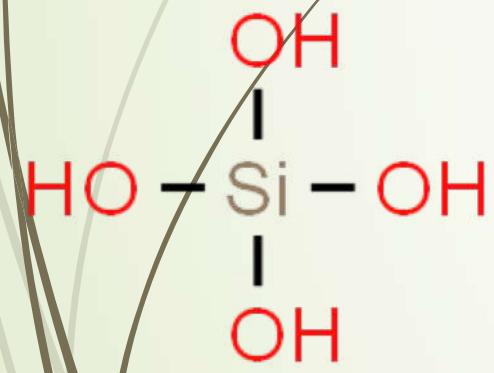
Journal of Arthroscopy and Joint Surgery

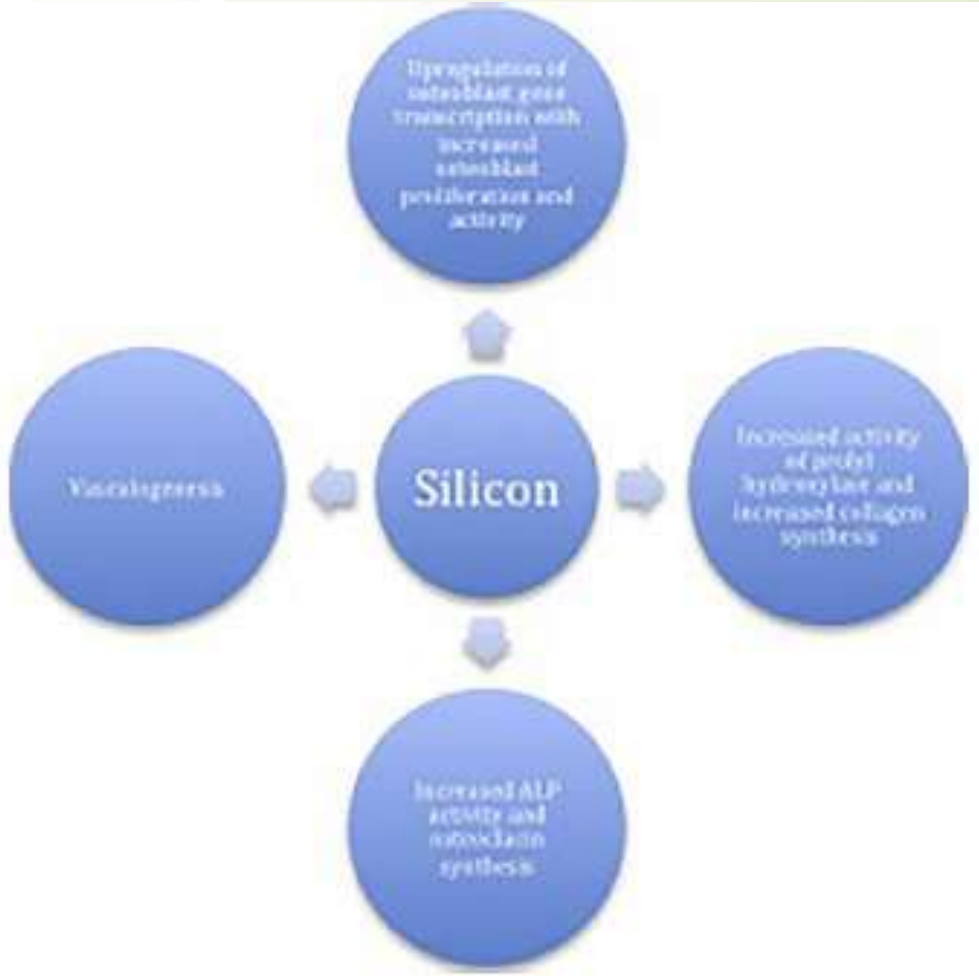
journal homepage: www.elsevier.com/locate/jajs

Review article

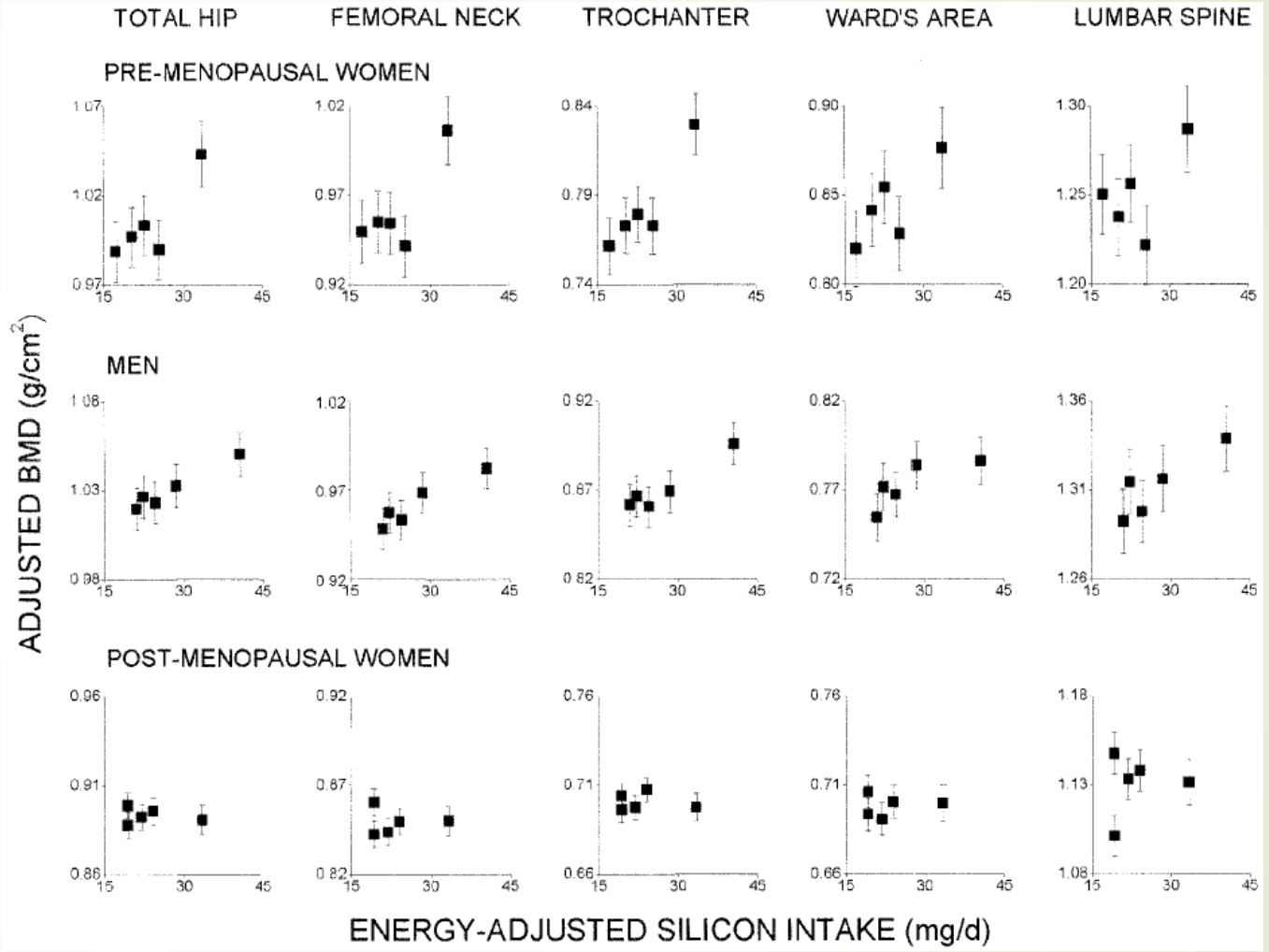
The Promise of Silicon: bone regeneration and increased bone density

M. Arora[a,*], E. Arora[b]





The Framingham Offspring cohort data



J Bone Miner Res. 2004;19(2): 297-307.

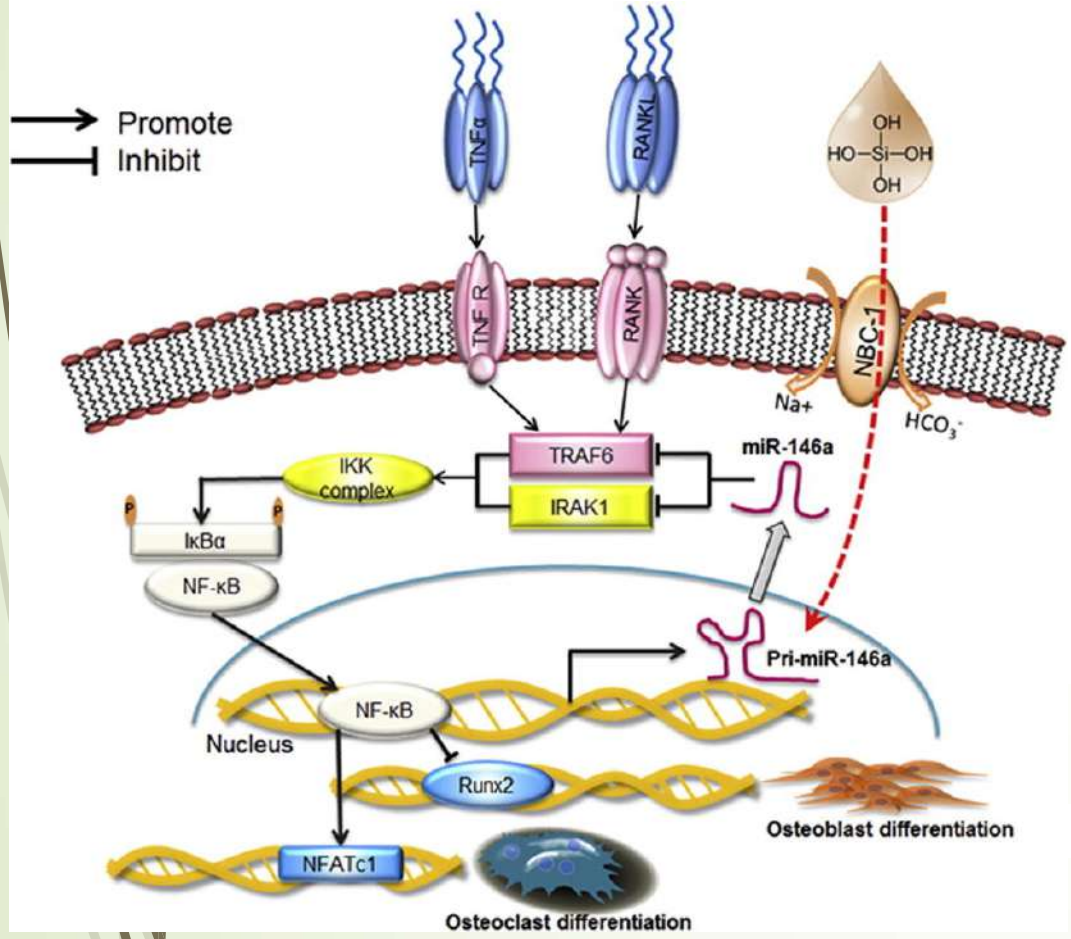
Silicon: A neglected micronutrient essential for bone health

Mariangela Rondanelli[1,2], Milena A Faliva[3], Gabriella Peroni[3], Clara Gasparri[3], Simone Perna[4], Antonella Riva[5], Giovanna Petrangolini[5] and Alice Tartara[3]

[1]IRCCS Mondino Foundation, Pavia 27100, Italy; [2]Department of Public Health, Experimental and Forensic Medicine, Unit of Human and Clinical Nutrition, University of Pavia, Pavia 27100, Italy; [3]Endocrinology and Nutrition Unit, Azienda di Servizi alla Persona ''Istituto Santa Margherita'', University of Pavia, Pavia 27100, Italy; [4]Department of Biology, College of Science, University of Bahrain, Sakhir 32038, Bahrain; [5]Research and Development Unit, Milan 20139, Italy

Corresponding author: Gabriella Peroni. Email: gabriella.peroni01@universitadipavia.it

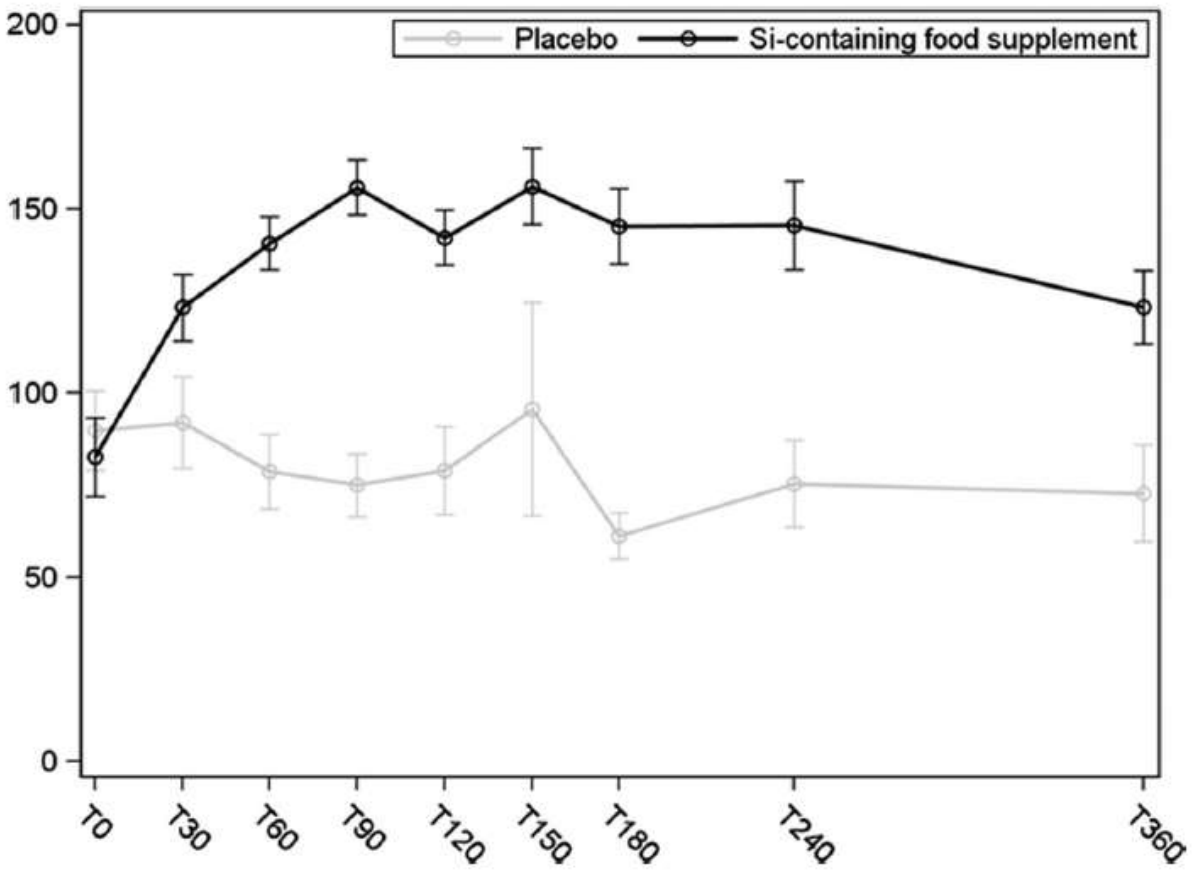
Silicon: A neglected micronutrient essential for bone health



The inhibition of NF-κB results in activation of Runx2, the master transcription factor necessary for osteoblast precursor differentiation. This deactivation of NF-κB also inhibits the expression of NFATc1, the key transcription gene for osteoclast precursor differentiation. Thus, Si(OH)4 can stimulate osteoblast differentiation and inhibit osteoclast differentiation by antagonizing NF-κB activation via miR-146a, which implies a potential role in bone remodeling.

Experimental Biology and Medicine 2021; 246: 1500–1511. DOI: 10.1177/1535370221997072

Mol. Nutr. Food Res. 2015, *59*, 1584–1589



Biodisponibilità del silico e del silicio bioattivato

International Journal of
Molecular Sciences

MDPI

Review

Nutraceutical Approach to Chronic Osteoarthritis: From Molecular Research to Clinical Evidence

Alessandro Colletti [1,2] and Arrigo F. G. Cicero [2,3,*]

Int. J. Mol. Sci. **2021**, 22, 12920. https://doi.org/10.3390/ijms222312920

Nutraceuticals have been often tested in advanced stages of diseases where they are often (and logically) less useful!

RCTs are sometimes underpowered …

But there is an interesting literature … from suggestive to solid !!!

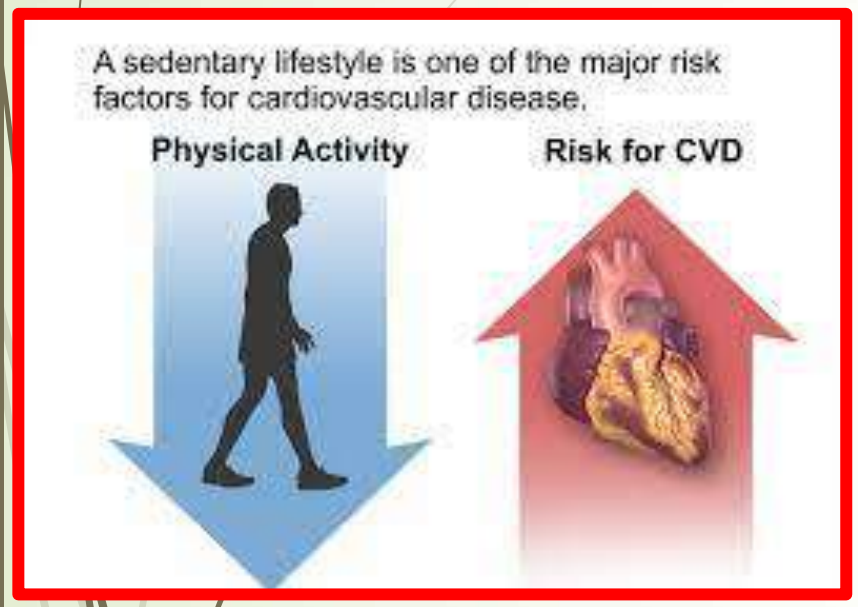
Glucosamine sulphate and OA: the results of a meta-analysis of 31 RCTs

Compared to placebo, glucosamine showed a significant improvement with unstandardized mean differences (UMD) in:

- Total WOMAC: -2.49 (95%CI -4.14, -0.83)
- Pain WOMAC: -0.75 (95% CI: -1.18, -0.32)
- Function WOMAC: -4.78 (95% CI: -5.96, -3.59)
- Lequesne score: -1.03 (95% CI: -1.34, -0.72)

Eur J Med Res. 2015;20:24.

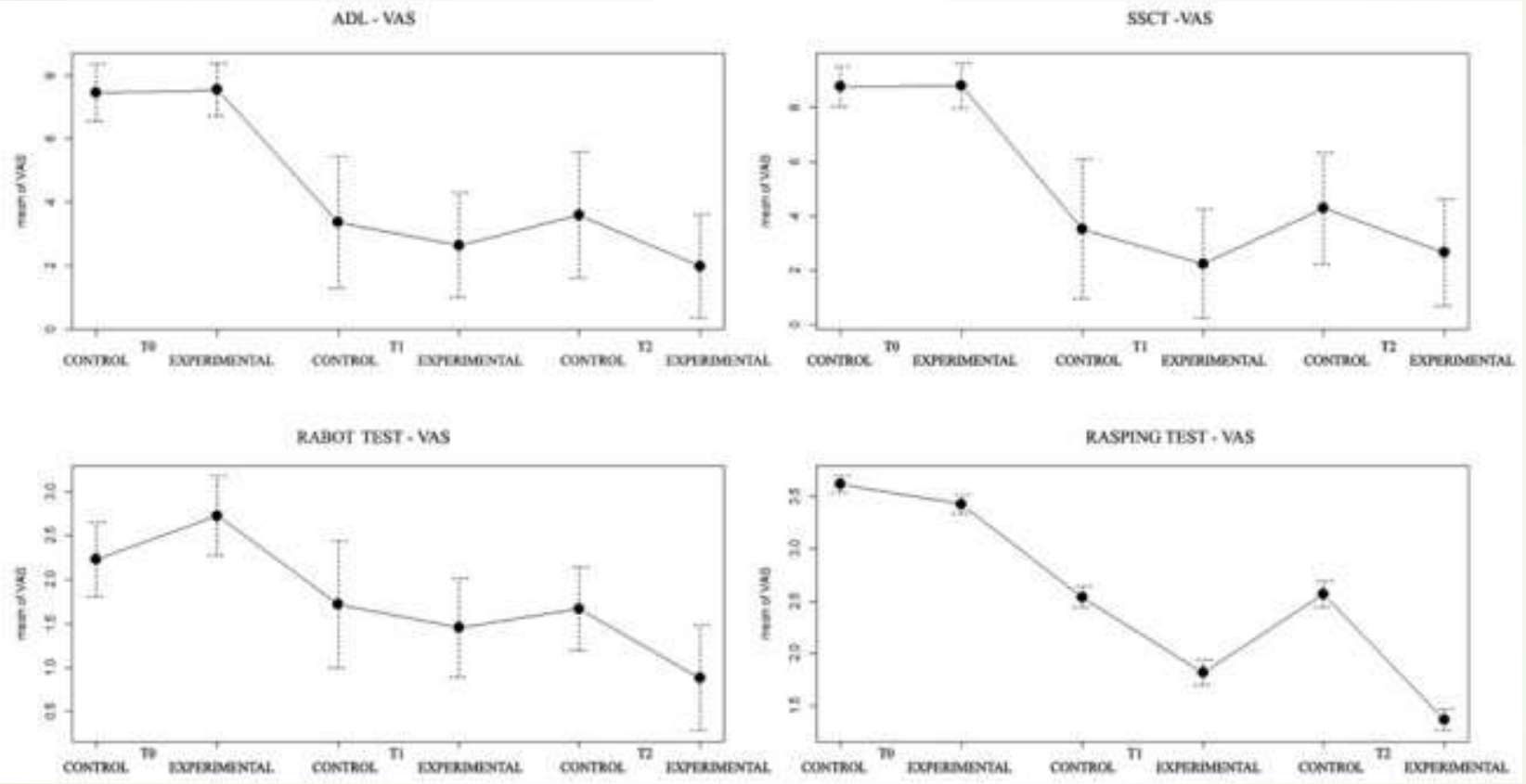
Association of habitual glucosamine use with risk of CV disease



- Participants: **466 039** participants without CVD at baseline.
- Results: During a median follow-up of 7 years, there were 10 204 incident CVDs, 3060 CVD deaths, 5745 CHD events, and 3263 strokes.
- After adjustment for age, sex, body mass index, race, lifestyle factors, dietary intakes, drug use, and other supplement use, glucosamine use was associated with a significantly lower risk of **total CVD events** (HR **0.85**, 95%CI 0.80 to 0.90), **CVD death** (**0.78**, 0.70 to 0.87), **CHD** (**0.82**, 0.76 to 0.88), and **stroke** (**0.91**, 0.83 to 1.00).

BMJ 2019;365:l1628

The synergic use of the High Power Laser Therapy and Glucosamine sulfate in Knee osteoarthritis: A RCT



Acta Biomed. 2021;92(3):e2021237.

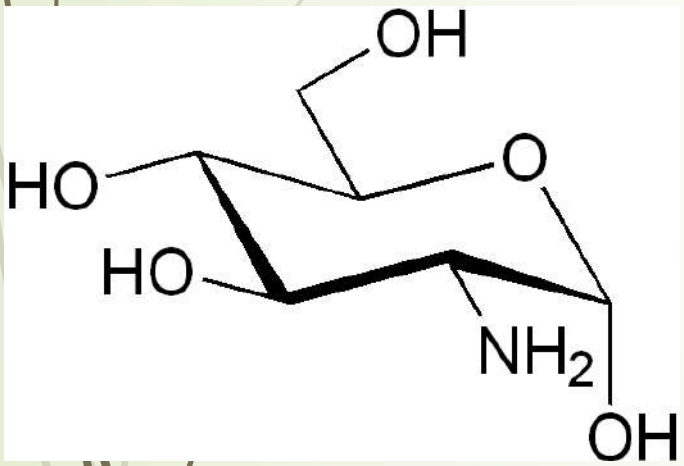
The VAS was utilized to evaluate the intensity of pain perceived by the patient (a 10 cm line, from 0 or "no pain" to 10 "severe pain"): (1) during the activities of daily living (ADL), (2) during Standardized Stair Climbing Task (SSCT), (3) during the patellar grind evaluation (Rabot test) (18) and the Zohlen's sign or Rasping test (4). Evaluations were performed at the first visit (T0), after the end of treatment (T1) and at 6 months (T2).

Condroitin sulphate and OA: the results of a meta-analysis of 43 RCTs

- Participants treated with chondroitin achieved statistically significantly and clinically meaningful better pain scores (0–100) in studies less than 6 months than those given placebo with an absolute risk difference of 10% lower (95%CI 15% to 6%); NNT = 5 (95% CI, 3 to 8)
- In studies >6 months, the absolute risk difference for pain was 9% lower (95% CI 18 to 0)
- For the WOMAC MCII Pain subscale outcome, a reduction in knee pain by 20% was achieved by 53/100 in the chondroitin group versus 47/100 in the placebo group, an absolute risk difference of 6% (95% CI 1 to 11), (RR 1.12, 95% CI 1.01 to 1.24).
- Differences in Lequesne's index (composite of pain, function and disability) statistically significantly favoured chondroitin as compared with placebo in studies <6 months, with an absolute risk difference of 8% lower (95% CI 12 to 5)
- Loss of minimum joint space width in the chondroitin group was statistically significantly less than in the placebo group, with a relative risk difference of 4.7% less (95%CI 1.6 to 7.8).
- Chondroitin did not result in statistically significant numbers of adverse events or withdrawals due to adverse events compared with placebo or another drug.

Cochrane Database Syst Rev. 2015 Jan 28;1:CD005614.

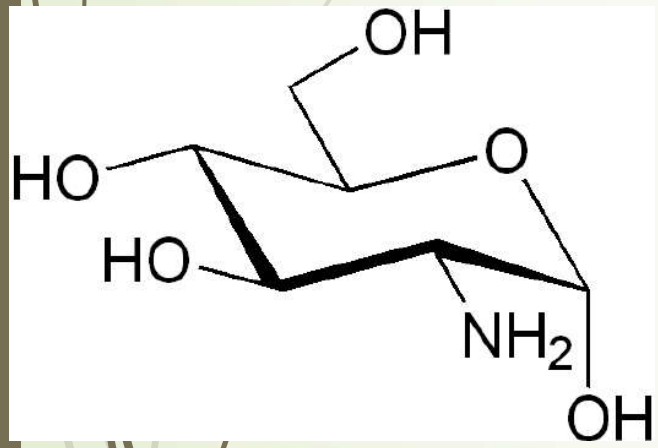
Glucosamine sulphate and OA: level of evidence



B: Knee osteoarthritis
Evidence supports the use of glucosamine sulfate taken by mouth to treat knee osteoarthritis.
B: **Osteoarthritis (general)**
Several studies have found that glucosamine may benefit osteoarthritis in other body parts, aside from the knee. However, there is less evidence to support this compared to knee osteoarthritis. Knee osteoarthritis appears to respond better than other joints to any treatment.

B= Good scientific evidence for this use

Condroitin sulphate and OA: level of evidence



A: Osteoarthritis (general)
Chondroitin sulfate is considered a promising treatment for osteoarthritis. It is most often used to treat osteoarthritis of the finger, knee, hip joints, low back, and facial joints. Research has mostly focused on knee osteoarthritis, with fewer studies conducted on other joints. Clinical trials suggest that chondroitin may have significant effects when compared to placebo.

A: **Osteoarthritis (knee)**
Chondroitin sulfate is considered a promising treatment for osteoarthritis of the knee. It is also most often used to treat osteoarthritis of the finger, hip joints, low back, and facial joints. Clinical trials suggest that chondroitin may have significant effects when compared to placebo.

A= Strong scientific evidence for this use

Absolute treatment effects (change from baseline) for pain and function: a meta-analysis of 54 trials including 16427 patients

Treatment	Pain (SMD)	Pian (WOMAC 0-10)	Function (SMD)	Function (WOMAC 0-10)
Celecoxib	-1.09 (-1.23, -0.96)	-2.73 (-3.08,-2.40)	-0.94 (-1.06, -0.82)	-1.97 (-2.23,-1.72)
Glucosamine	-0.85 (-1.05, -0.65)	-2.13 (-2.63,-1.63)	-0.56 (-0.78, -0.35)	-1.18 (-1.64,-0.74)
Chondroitin	-1.02 (-1.31, -0.74)	-2.55 (-3.28,-1.85)	-0.87 (-1.19, -0.54)	-1.83 (-2.50,-1.13)
glucosamine + chondroitin	-1.00 (-1.66, -0.34)	-2.50 (-4.15,-0.85)	-1.66 (-2.45, -0.86)	-3.49 (-5.15,-1.81)

Zeng C et al. Sci Rep. 2015;5:16827.

Comparisons of trials and results

Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) (2010)

- 662 subjects, Rx follow-up: 2 years
- Over 2 years, no treatment achieved a clinically important difference in WOMAC pain or function as compared with placebo. However, glucosamine and celecoxib showed beneficial but not significant trends.
- Use of Glucosamine hydrochloride in advanced OA stage, t.i.d.

Long Term Evaluation of Glucosamine Sulfate Study (LEGS) (2014)

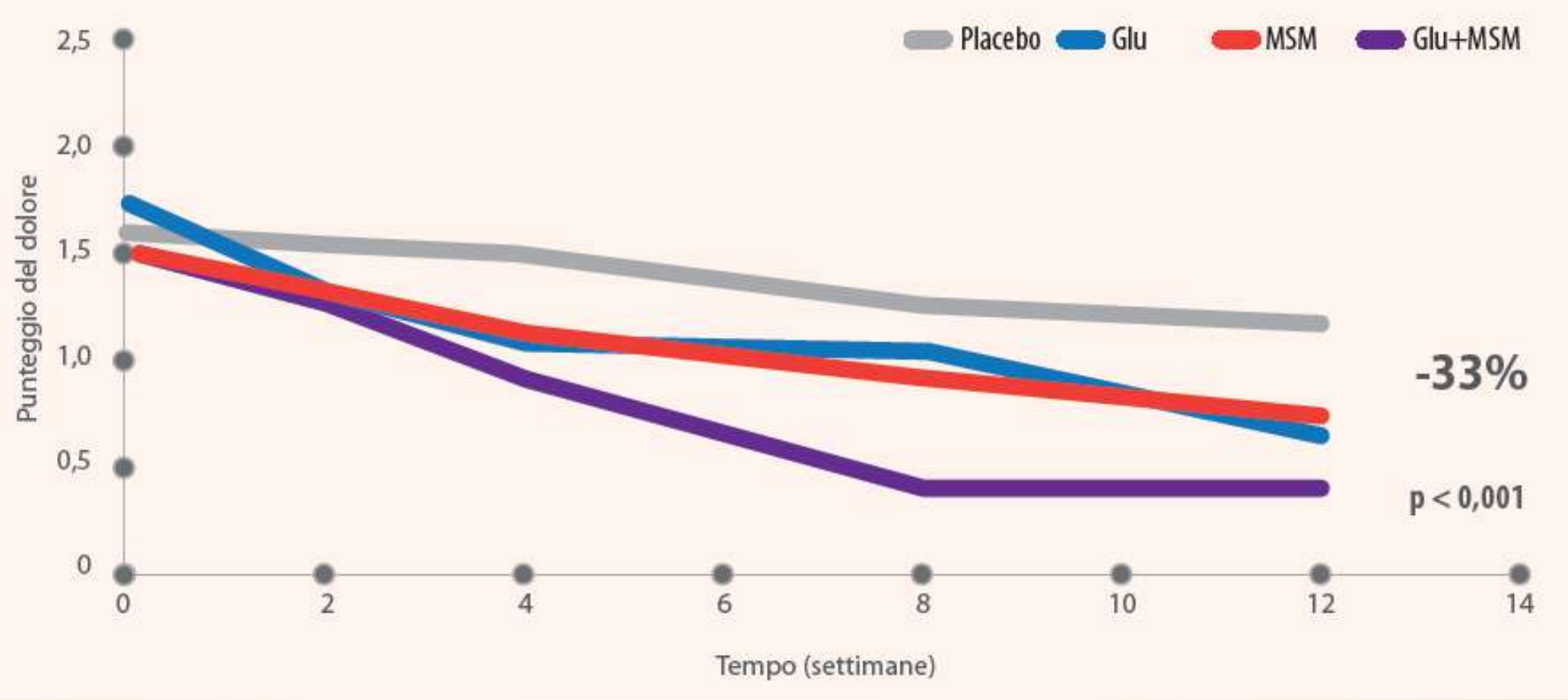
- 605 subjects, Rx follow-up: 2 years
- No significant differences were found in the amount of joint space narrowing in people taking glucosamine sulphate or chondroitin alone, compared with placebo, u.i.d.
- However, people taking the combination of glucosamine and chondroitin had about half the amount of joint space narrowing compared with those taking placebo (a difference of 0.10 mm, p=0.046).

MSM: effect on knee osteoarthritis

	MSM (n = 25)			Placebo (n = 25)				Significance for between group differences at follow-ups	
	6 weeks	12 weeks	Difference 0-12 wk [CI]	6 weeks	12 weeks	Difference 0-12 wk [CI]	Between group difference [CI]	0-6 wks	0-12 wks
WOMAC									
Pain	35.5 ± 26.1	34.0 ± 24.5	-9.0 ± 24.0 [-18.9, 0.9]	47.1 ± 26.6	49.4 ± 20.8	3.5 ± 19.3 [-4.5, 11.5]	12.4 [0.0, 24.8]	0.20	0.05*
Stiffness	39.2 ± 31.0	36.0 ± 26.2	-11.7 ± 30.7 [-24.3, 1.0]	52.9 ± 30.4	58.5 ± 24.2	15.5 ± 35.8 [0.7, 30.3]	27.2 [8.2, 46.2]	0.03*	0.01*
Function	36.6 ± 23.7	33.1 ± 23.1	-7.7 ± 19.3 [-15.8, 0.3]	46.2 ± 25.1	54.3 ± 21.1	6.9 ± 17.0 [0.1, 13.9]	14.6 [4.3, 25.0]	0.51	0.01*
Total	36.6 ± 23.9	33.3 ± 22.5	-8.4 ± 17.8 [-15.8, -1.1]	47.2 ± 24.5	53.5 ± 20.3	6.5 ± 17.0 [0.5, 13.5]	15.0 [5.1, 24.9]	0.26	0.00*
ALF	36.5 ± 16.6	36.9 ± 20.7	-6.8 ± 10.3 [-11.0, -2.5]	32.2 ± 10.6	33.9 ± 10.9	0.8 ± 4.9 [-1.2, 2.8]	7.6 [2.9, 12.2]	0.02*	0.00*
SF-36	59.8 ± 19.7	62.2 ± 20.3	8.1 ± 21.8 [-0.8, 17.1]	61.1 ± 16.2	54.5 ± 15.4	-3.4 ± 14.6 [-9.5, 2.6]	-11.6 [-22.1, -1.0]	0.52	0.03*
VAS	3.30 ± 2.8	3.61 ± 2.9	-0.2 ± 3.2 [-1.5, 1.1]	5.22 ± 2.9	5.16 ± 2.22	0.6 ± 2.7 [-0.6, 1.7]	0.7 [-0.9, 2.4]	0.18	0.38

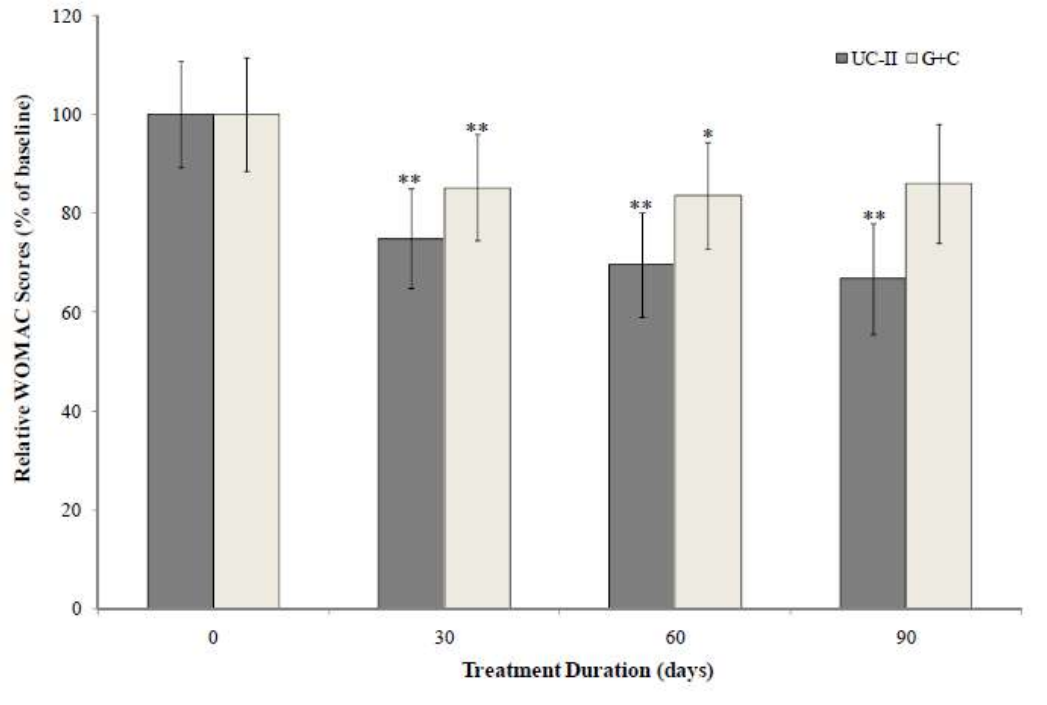
BMC Complement Altern Med. 2011 Jun 27;11:50.

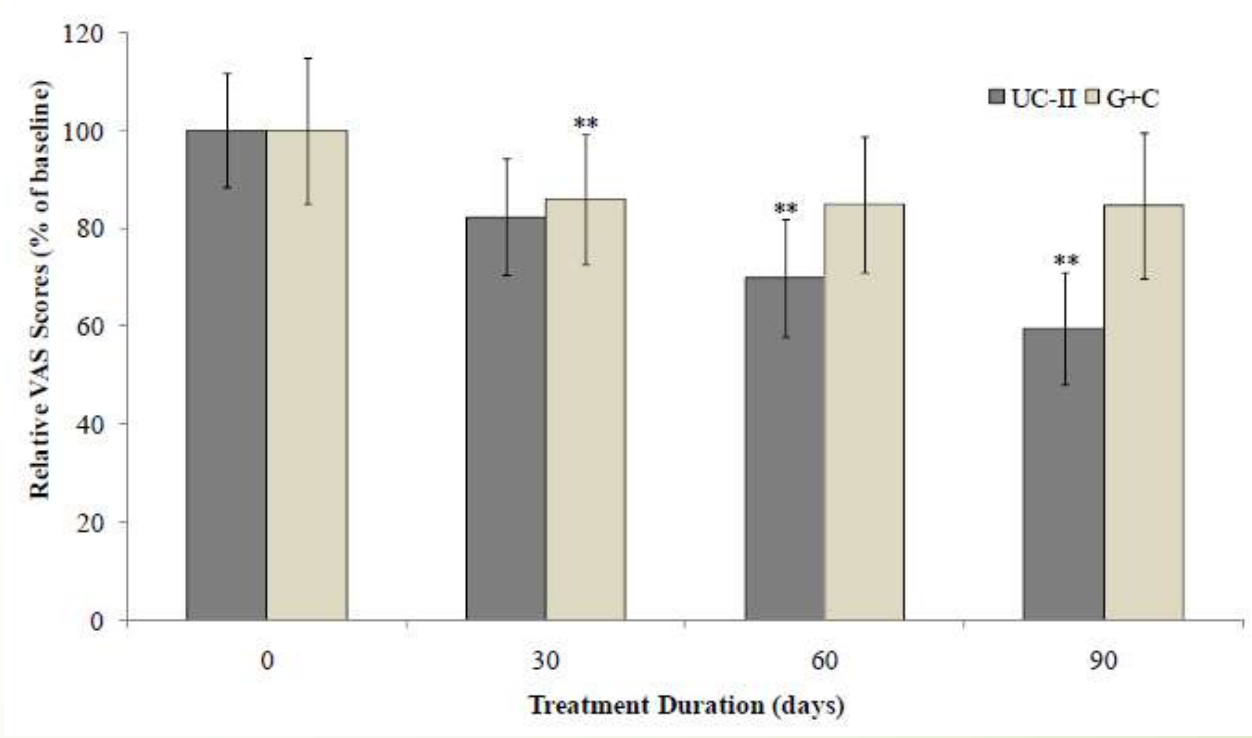
118 patients with mild-to-moderate knee OA randomized to glucosamine 500 mg t.i.d. vs. MSM 500 mg t.i.d. vs. glucosamine + MSM t.i.d. vs. placebo 500 mg t.i.d.



Usha PR et al. Clin Drug Invest 2004;24:353-363

Efficacy of undenatured type II collagen in the treatment of osteoarthritis of the knee: an RCT

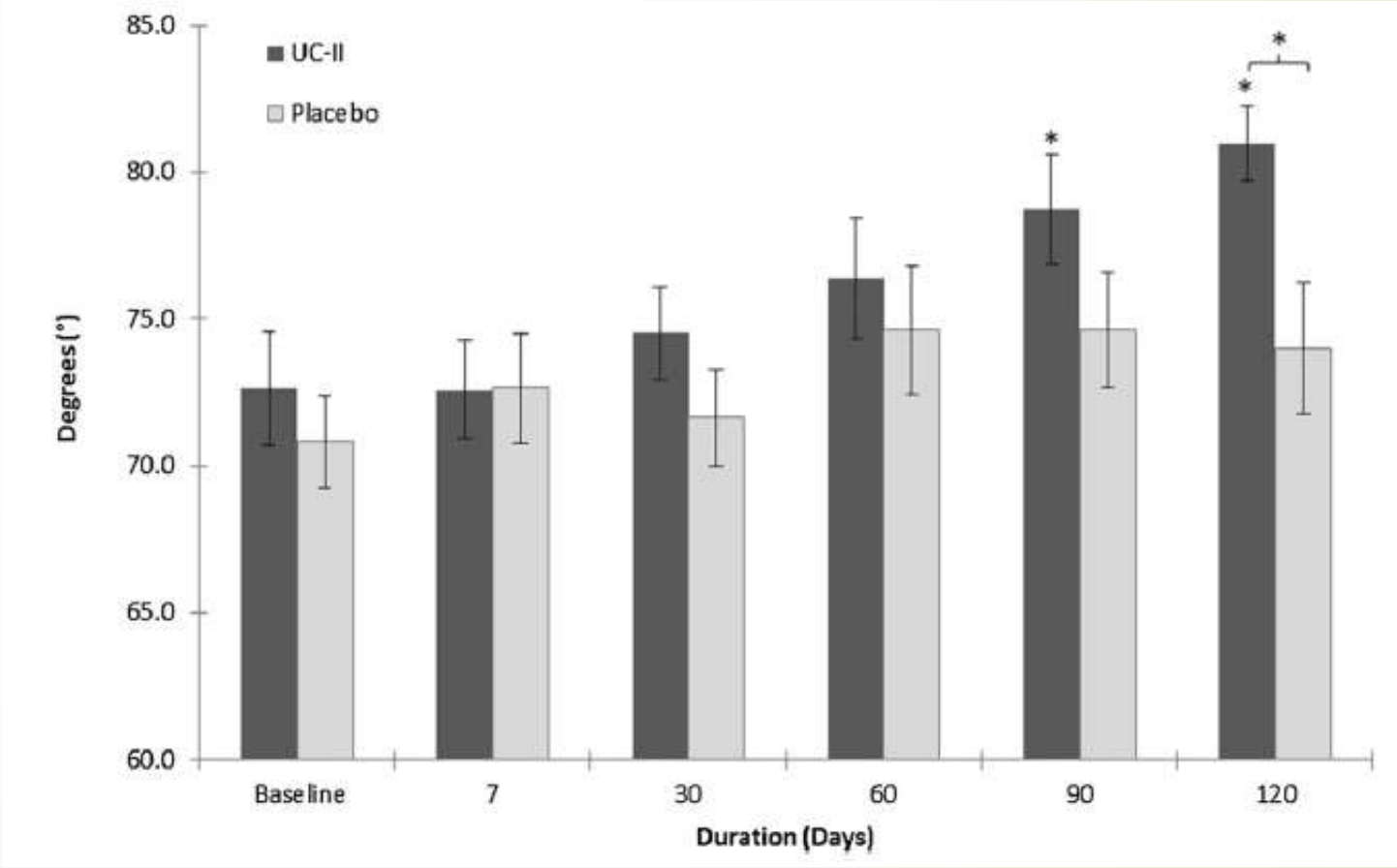




Int. J. Med. Sci. 2009, 6

Undenatured type II collagen (UC-II®) for joint support: an RCT in healthy volunteers

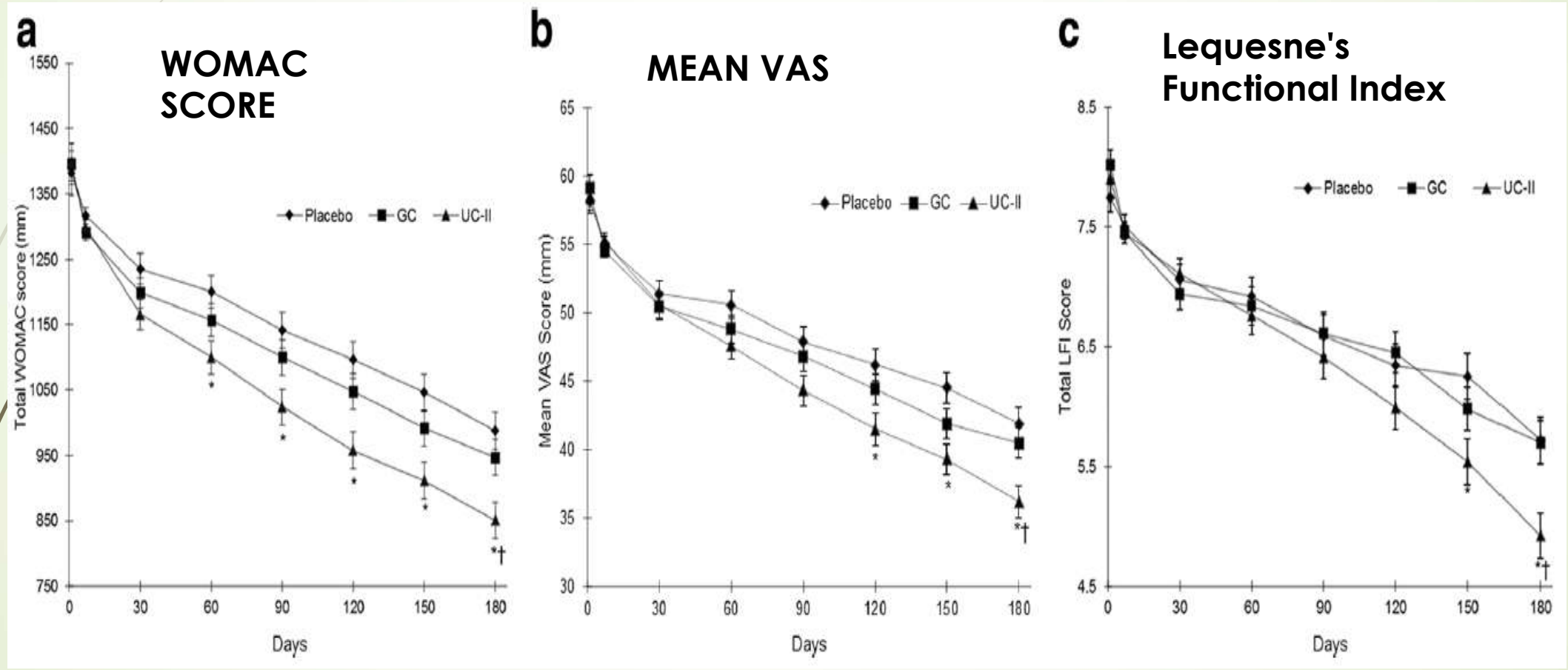
Knee extension as measured by goniometry



Lugo et al. J Int Soc Sports Nutr 2013;10:48

Efficacy of an undenatured type II collagen supplement in modulating knee osteoarthritis symptoms: a multicenter RCT

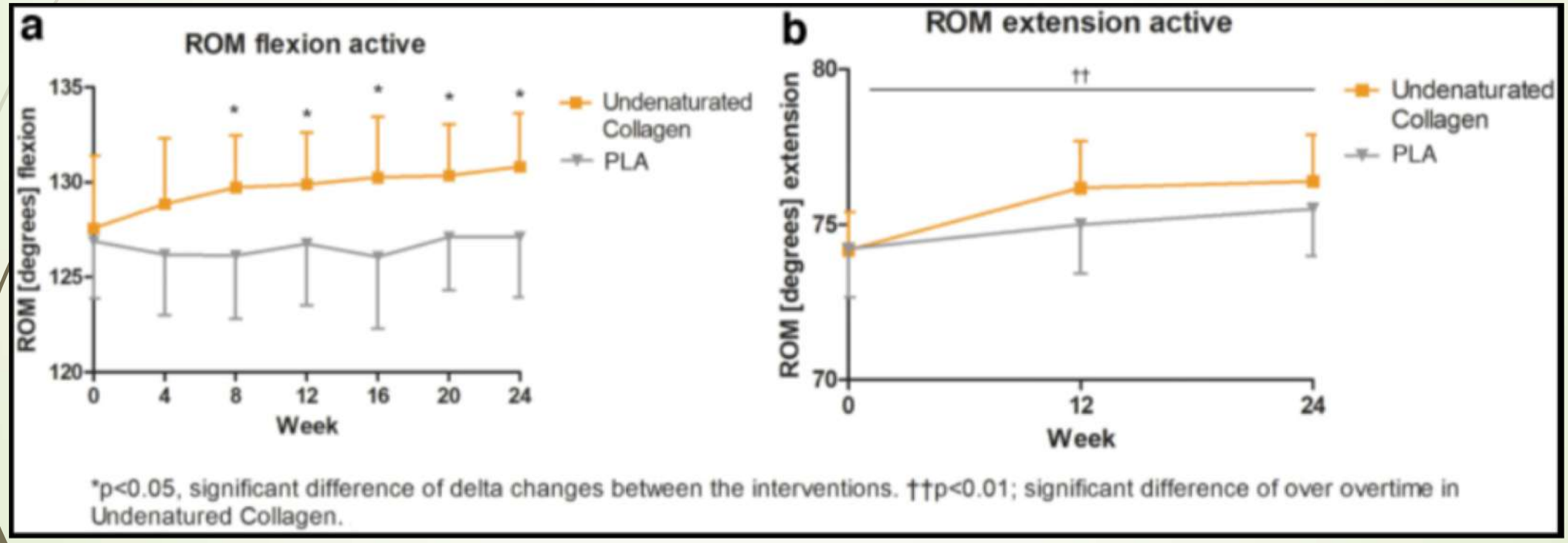
N. 199; Placebo vs. Gluco/Condro (1500/1200 mg) vs. Collagen II (40 mg)



Lugo et al. Nutrition J. 2016;15:14

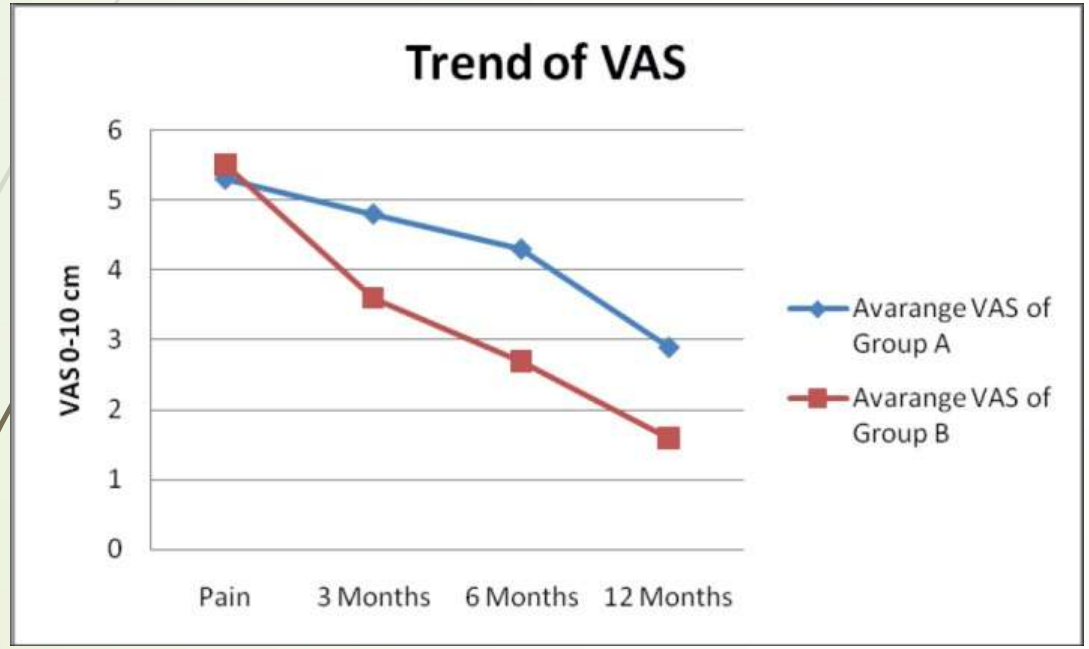
Randomized Controlled Trial > J Integr Complement Med. 2022 Jun;28(6):540-548.
doi: 10.1089/jicm.2021.0365. Epub 2022 Apr 4.

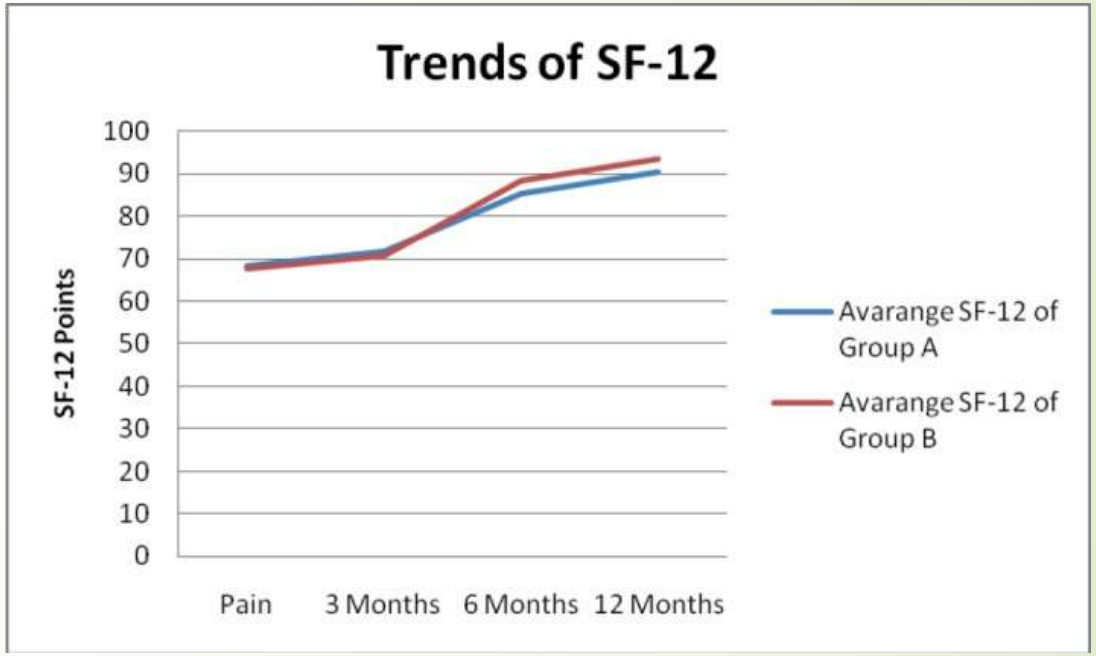
UC-II Undenatured Type II Collagen for Knee Joint Flexibility: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Study



*p<0.05, significant difference of delta changes between the interventions. ††p<0.01; significant difference of over overtime in Undenatured Collagen.

Collagen Peptide and Hyaluronic acid vs. Collagen Peptide and Hyaluronic acid+ Vitamin C





Med Arch. 2019 Jun;73(3):173-177.

Effects of oral jaluronic acid on pain in Knee OA: a clinical trial

	Oralvisc ($n = 21$)		Placebo ($n = 19$)	
	Baseline	3 months	Baseline	3 months
VAS	HA 0.18[a]	4.06 ± 0.53[b]*	6.18 ± 0.21	5.84 ± 0.50
WOMAC pain	8.81 ± 0.67[a]	5.75 ± 0.90[b]*	8.05 ± 0.77	8.16 ± 0.73
WOMAC total	40.29 ± 2.55[a]	27.62 ± 4.38[b]*	40.53 ± 3.40	39.58 ± 3.97

Oral ???

– 30% !!! ???

Rheumatol Int. 2015;35(1):43-52.

diseases

MDPI

Article

Short-Term Effect of a New Oral Sodium Hyaluronate Formulation on Knee Osteoarthritis: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial

Arrigo F. G. Cicero [1,*], Nicolò Girolimetto [2], Crescenzio Bentivenga [1], Elisa Grandi [1], Federica Fogacci [1] and Claudio Borghi [1]

Table 1. Changes in VAS-p, WOMAC (and related subscales) indexes, Lequesne functional index (LFI) and knee extension ROM in the enrolled subjects during the trial.

	FS-HA (*n*: 30)			Placebo (*n*: 30)		
	T0	T28	T56	T0	T28	T56
VAS-p (mean ± SD)	6.7 ± 1.0	5.5 * ± 0.9	4.1 *,° ± 0.6	6.4 ± 1.1	5.9 ± 1.2	6.0 ± 1.3
Pain WOMAC (mean ± SD)	9.6 ± 1.2	9.0 * ± 1.2	8.8 *,° ± 0.9	9.3 ± 1.4	9.1 ± 1.2	9.3 ± 1.1
Function WOMAC (mean ± SD)	22.8 ± 2.4	22.1 ± 2.5	20.3 ± 1.9 *	23.1 ± 2.7	22.9 ± 2.8	22.7 ± 2.1
Total WOMAC (mean ± SD)	40.3 ± 3.8	36.8 * ± 4.3	33.9 *,° ± 4.1	40.5 ± 3.8	39.3 ± 4.1	38.9 ± 4.4
Lequesne Functional Index (mean ± SD)	6.5 ± 0.9	6.3 ± 1.0	6.1 * ± 1.1	6.7 ± 1.1	6.5 ± 1.0	6.5 ± 1.2
Extension ROM (mean ± SD)	86 ± 11	88 ± 12	91 ± 15 *	85 ± 13	84 ± 11	82 ± 13

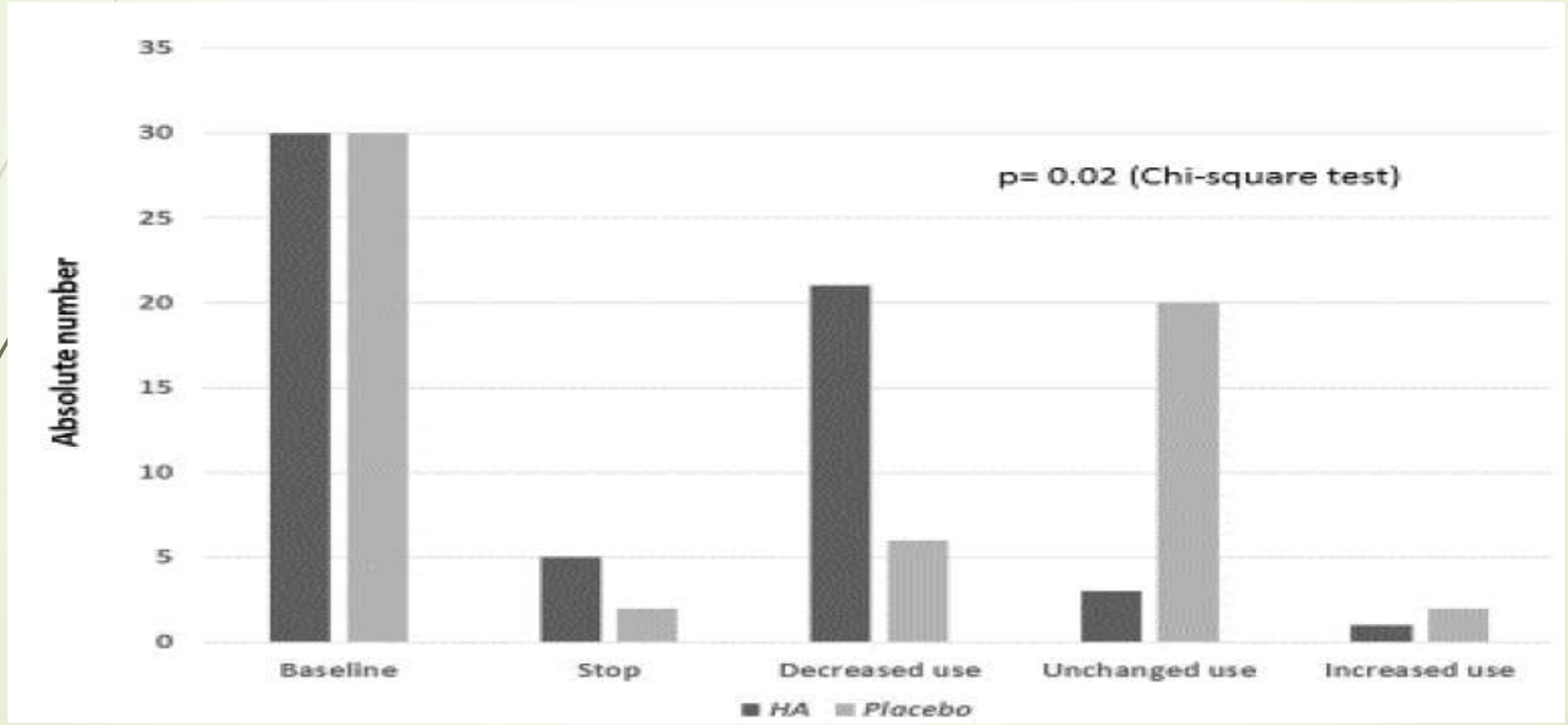
diseases

MDPI

Article

Short-Term Effect of a New Oral Sodium Hyaluronate Formulation on Knee Osteoarthritis: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial

Arrigo F. G. Cicero [1,*], Nicolò Girolimetto [2], Crescenzio Bentivenga [1], Elisa Grandi [1], Federica Fogacci [1] and Claudio Borghi [1]

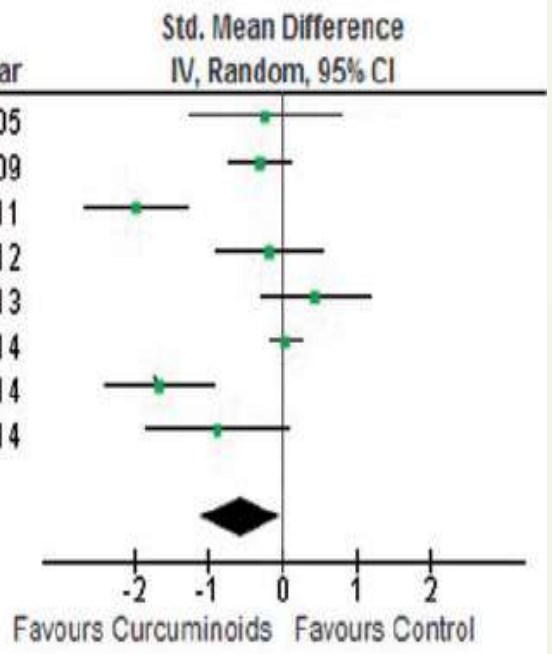


Analgesic Efficacy of Curcuminoids in Clinical Practice: A Systematic Review and Meta-Analysis of RCTs

Study or Subgroup	Curcuminoids Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Durgaprasad et al.	0.31	1.89	8	0.72	1.33	7	10.1%	-0.23 [-1.25, 0.79]	2005
Kuptniratsaikul et al.	-2.6	2.41	45	-1.9	2.13	46	14.4%	-0.31 [-0.72, 0.11]	2009
Agarwal et al.	-30.6	10.51	25	-8.44	11.6	25	12.6%	-1.97 [-2.66, -1.29]	2011
Chandran and Goel	-42.96	23.46	15	-39.08	17.45	15	12.3%	-0.18 [-0.90, 0.53]	2012
Ryan et al.	4.64	4.98	14	2.87	2.72	16	12.3%	0.44 [-0.29, 1.16]	2013
Kuptniratsaikul et al.	3.25	2.11	171	3.17	1.98	160	15.4%	0.04 [-0.18, 0.25]	2014
Panahi et al.	-30.02	16.24	19	-2.85	16.11	21	12.3%	-1.65 [-2.37, -0.92]	2014
Drobnic et al.	23.3	7.9	9	30.6	7.9	10	10.6%	-0.88 [-1.84, 0.07]	2014
Total (95% CI)			306			300	100.0%	-0.57 [-1.11, -0.03]	

Heterogeneity: $Tau^2 = 0.48$; $Chi^2 = 50.51$, $df = 7$ ($P < 0.00001$); $I^2 = 86\%$

Test for overall effect: $Z = 2.08$ ($P = 0.04$)



Forest plot detailing standardized mean difference and 95%CI for the impact of curcuminoid supplementation on the severity of pain.

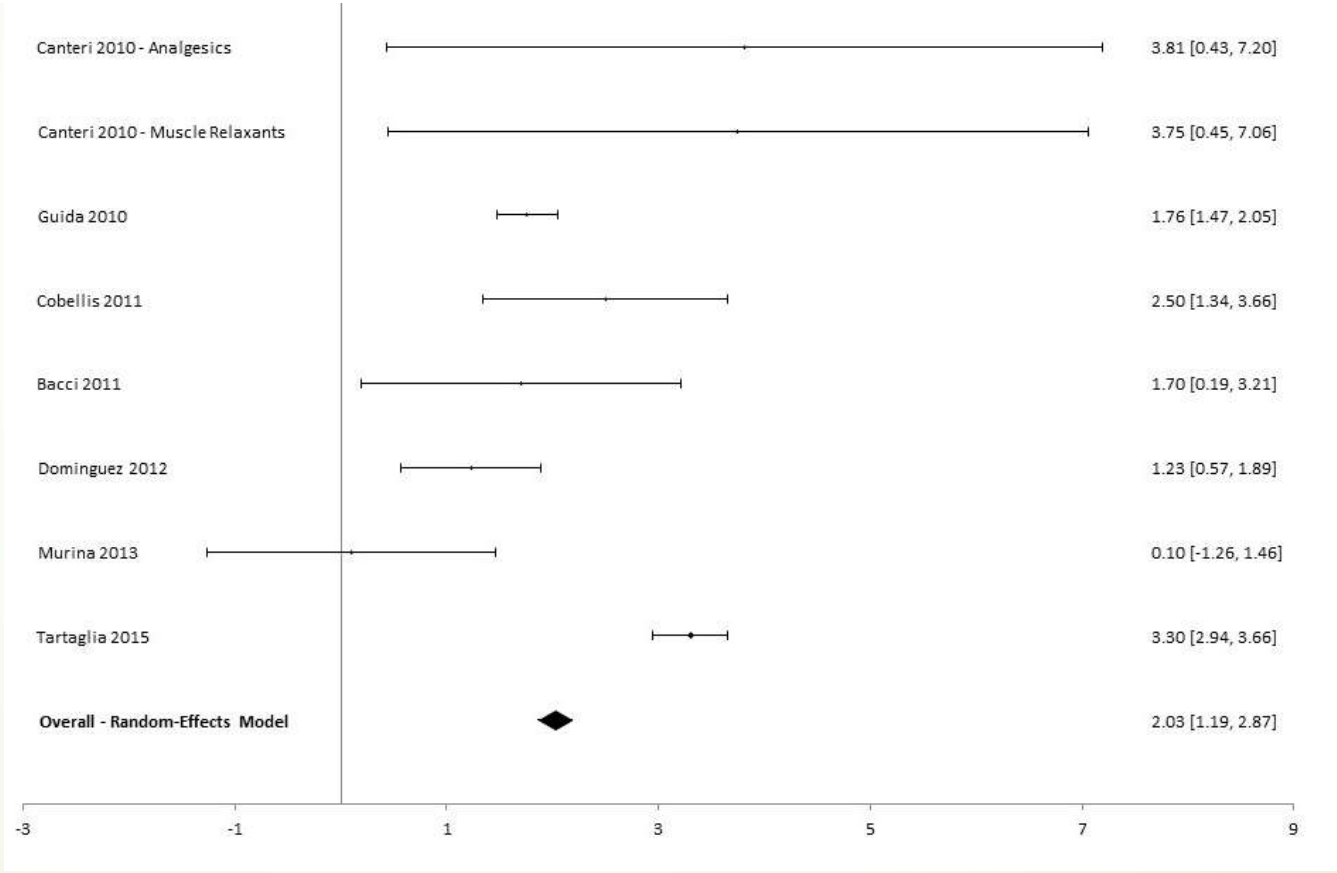
Pain Medicine 2015

Pain Physician 2017; 20:353-362 • ISSN 1533-3159

Systematic Review

Efficacy of Palmitoylethanolamide for Pain: A Meta-Analysis

10 studies including data from 786 patients who received PEA and 512 controls



***Pain Physician* 2017;20: 353-62**

Conclusioni

- Alcuni nutraceutici hanno dimostrato effetti preventivi e/o di rallentare l'evoluzione di patologie osteoarticolari croniche
- La tollerabilità è usualmente alta
- I trattamenti devono essere cronici e continuativi