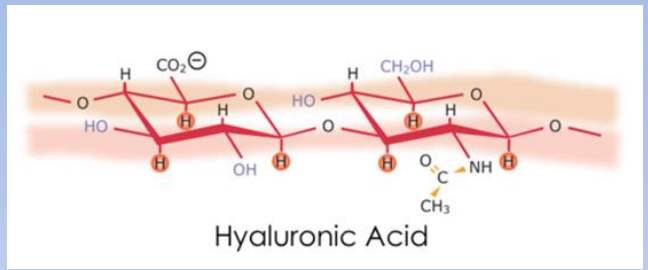
Gli acidi ialuronici non sono tutti uguali



Andrea Delle Sedie

Rheumatology Unit

University Hospital, Pisa, Italy

Hyaluronic acids …

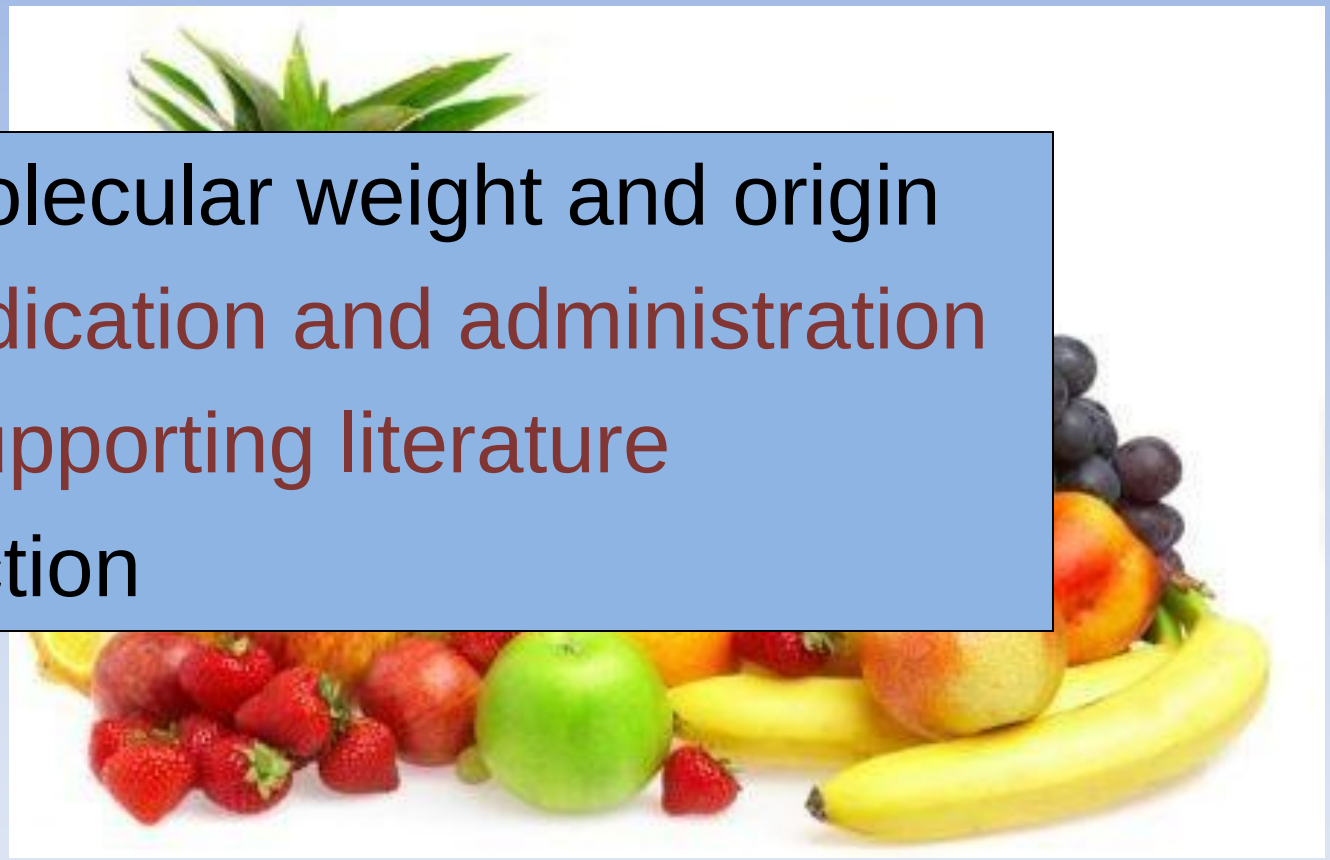
Domanda 1

Secondo voi gli acidi ialuronici sono realmente differenti tra loro?

- **Si, profondamente**
- **Non importa se sono diversi, il risultato è identico**
- **Non sono differenti**

HA: which are the differences

HA: which are the differences

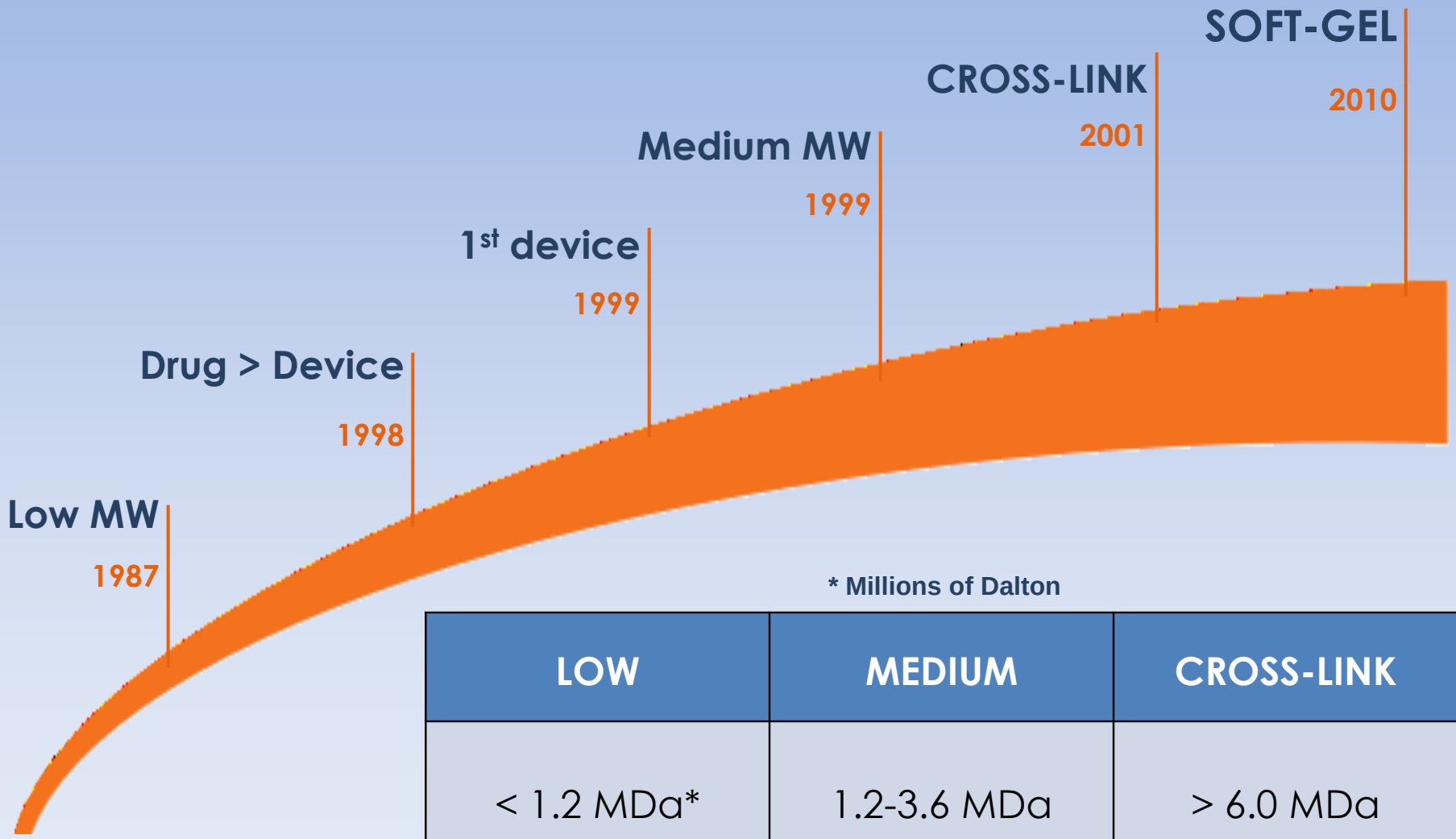


- Molecular weight and origin
- Indication and administration
- Supporting literature
- Action

HA: MW

MW: the evolution of the molecular weight

Increase in MW and decrease in the number of administrations…

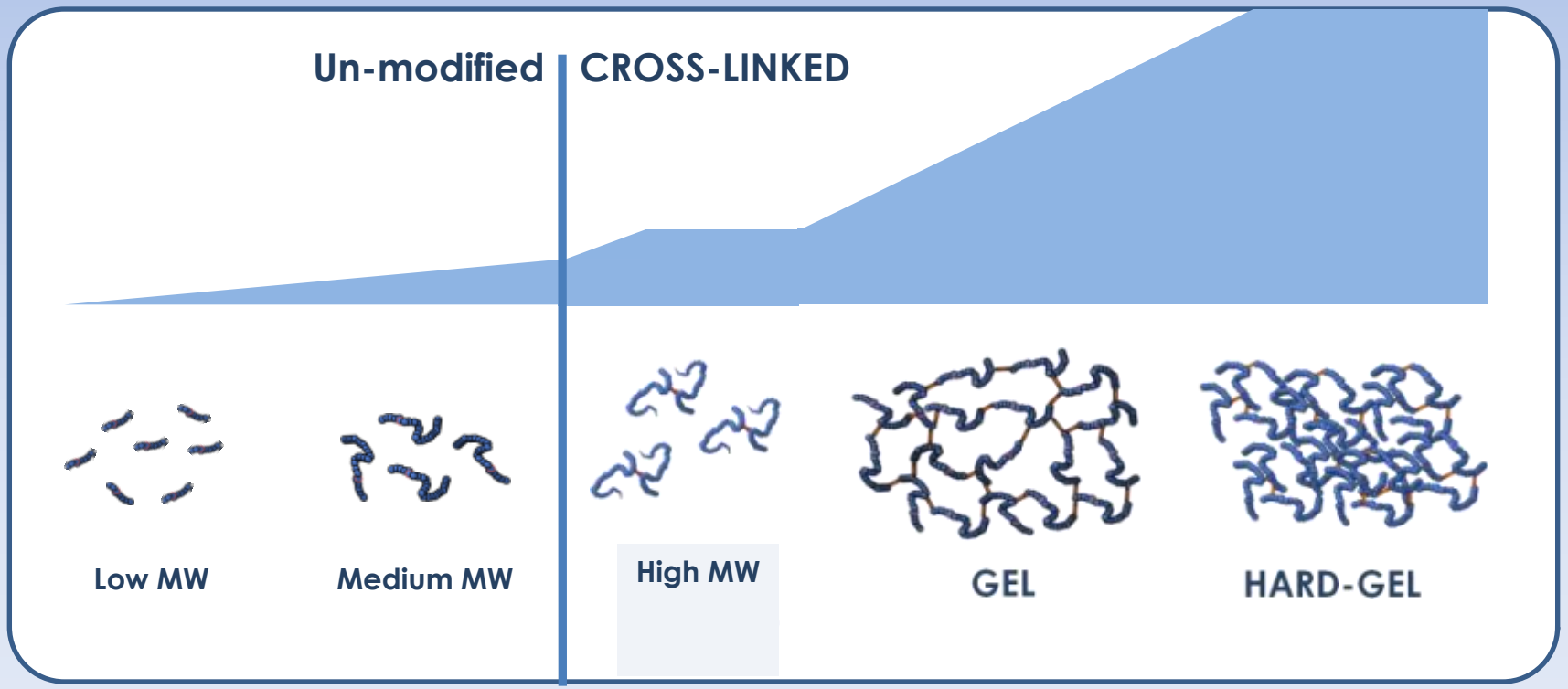


* Millions of Dalton

LOW	MEDIUM	CROSS-LINK
< 1.2 MDa*	1.2-3.6 MDa	> 6.0 MDa

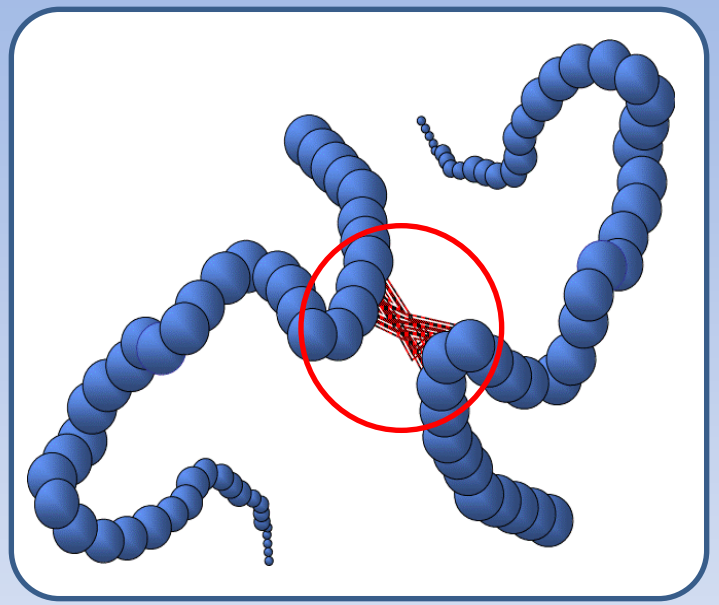
Why to increase the MW?

The increase of the MW is directly linked to the residing time of HA in the joint



Cross-link technology

It binds together un-modified HA chains using chemical bridges



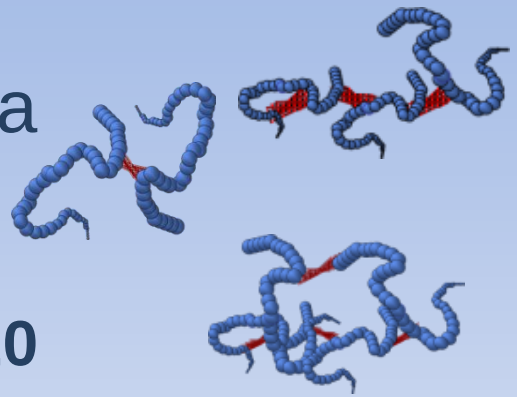
Increase MW

Increase the residing time in the joint

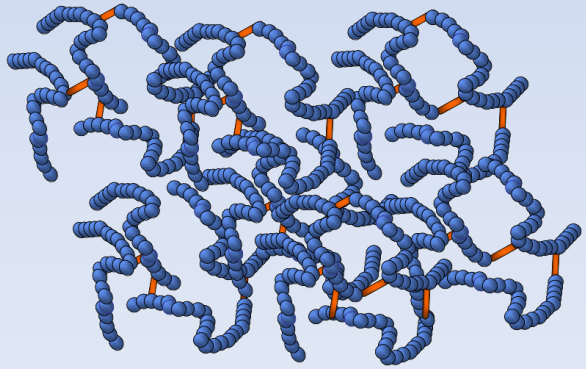
Increasing MW

Using the linking technique it is possible to create:

- HA molecules with a MW>$3.6x10^6$ Da (both liquid or fluid).



The first cross-linked product was **Hylan G-F 20** (*Synvisc)* ($6.0x10^6$ Da of MW)

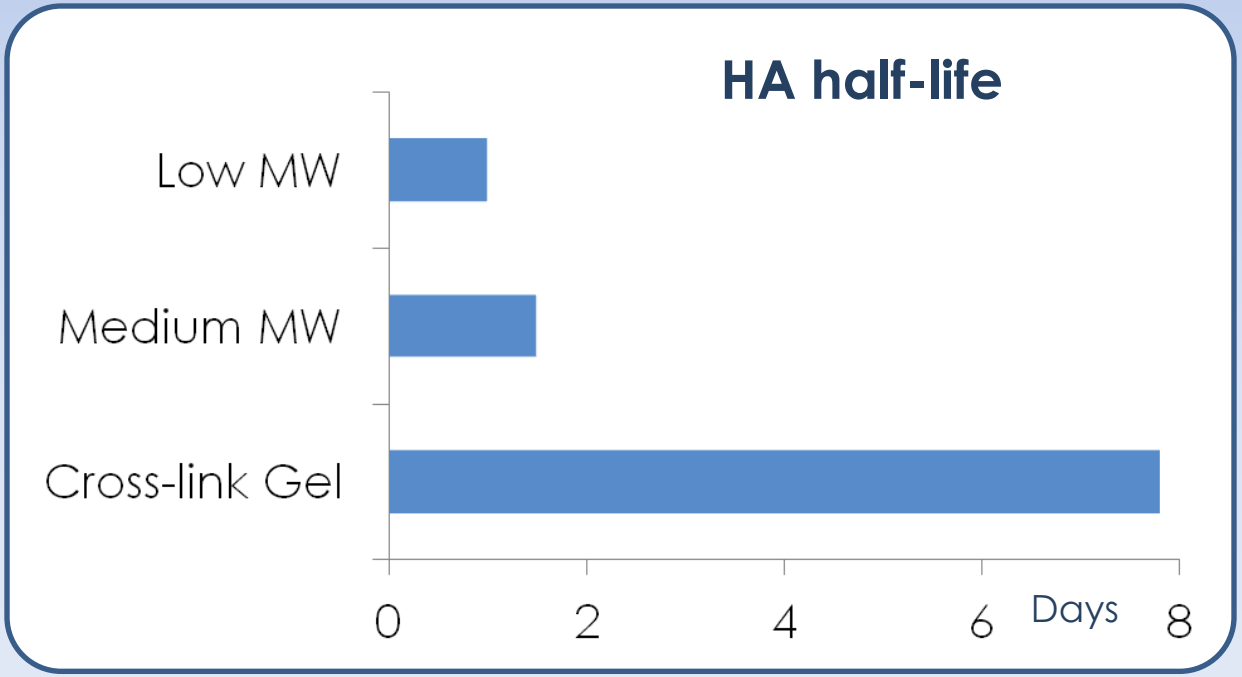


- 3-D network of HA (Gel)
  - HA changes its physical form from liquid or fluid to gel
  - being a gel it is not possible to refer to the HA using the concept of MW; it goes beyond the concept of MW

HA and its residing time in the joint

Cross-linked GEL has got an average half-life of 7.8 days (6.2 – 8.8):

- 4 times > medium MW
- 8 times > low MW



Differences among Branded Hyaluronic Acids in Italy, Part 1: Data from *In Vitro* and Animal Studies and Instructions for Use

Products MW	Number
low MW	**22**
medium MW	**23**
high MW	**3**
Not reported	**9**

It was not possible to perform a classification by molecular weight for three products, Jonexa, Durolane, and Hymovis, due to cross-linking molecular processes.

- *Jonexa is the result of the **combination of a medium molecular weight HA and Hylastan**, obtained by the cross-linking of HA with divinyl sulfone.*
- *Durolane is composed of a non-animal stabilized HA in **gel** formulation (NASHA)*
- *Hymovis is composed of **HYADD4** (sodium hyaluronate hexadecylamide)*

Origin of HA	number
rooster combs	5
biofermentation	50
Unknown (Artrosulfur HA and Structovia)	2

Migliore A et al, Clin Med Insights Arthritis Musculoskelet Disord 2016

Hylastan SGL-80

- Mix of:
  - 80% GEL **cross-link HA network** (divinilsulphone)
  - 20% 0,9-1,3 MDa LMW HA, liquid
- It acts like the healthy synovial fluid during mechanical stress(similar phase angle)
- It is indicated for the pain in knee OA
- Mono-somministration: 1 injection every 6 months

Differences among Branded Hyaluronic Acids in Italy, Part 1: Data from *In Vitro* and Animal Studies and Instructions for Use

Indications as reported on the leaflet of the hyaluronic acid brands merchandised in Italy for intra-articular use

TRADENAME	PAIN	REDUCED MOBILITY	OA	SYNOVIAL LIQUID SUBSTITUTION	NO TKR	POST TRAUMATIC	AFTER ARTHROSCOPY OR SURGERY
Arthrum®	0	0	1	0	1	1	0
Arthrum 2,5%®	1	0	1	0	1	1	0
Artrosulfur HA®	1	1	1	0	0	1	0
Artz®/Supartz®	0	0	1	0	0	0	0
Condrovisc®	0	0	1	0	0	1	0
Coxarthrum®	0	0	1	0	0	0	0
Durolane® (AF)	1	0	1	0	0	0	1
Euflexxa®	1	0	0	0	0	0	0
Fermathron S (AF)®	1	1	1	0	0	1	0
Go-On® (AF)	1	0	1				
Hyalart®	0	0	1				
Hyalgan®	0	0	1				
Hyalubrix®	0	0	1	1	0	0	0
Hya							
Hyl							
Ina							
Intr							
Jol							
Jor							
Kat							
Mo							
Orthovisc® (AF)	1	0	1	0	0	0	0
Ostenil®	1	1	1	0			
Ostenil® Plus	1	1	1	0			
Ostenil® mini	1	1	1	0			
Prolal®	1	0	0	0			
Promovia® (AF)	1	1	0	0			
RenehaVis®	1	1	0	0			
Rhizarthrum®	1	1	0	0			
Sinovial® (AF)	1	1	1	0			
SportVis®	1	1	0	0			
Structovial®	1	1	1	0			
Synocrom® (AF)	1	1	1	0			
Synolis® V-A	1	0	1	0			
Synvisc®	0	0	0	1			
Synvisc® One	0	0	0	1			
Yaral® (AF)	1	1	1	0			
Viscoplus®	1	1	0	0	0	0	0
Viscoplus gel®	1	1	1	0	0	0	0

Products	Pain	Reduced mobility	OA	Synovial liquid substitution	No TKR	Post traumatic	After arthroscopy or surgery
57	45	33	48	6	2	14	1

Curiously, some HA-based products… reported indication for OA, but not all of them. Some reported indication for joint pain relief, although they did not specify any joint alteration that might be inducing pain for which they are indicated and did not provide the related evidence. Again, some branded products reported to be indicated for SF temporary substitution or for the improvement of joint mobility, but no data regarding the cause of SF alterations or reduced joint mobility, such as OA or other conditions, were reported in the leaflet.

Migliore A et al, Clin Med Insights Arthritis Musculoskelet Disord 2016

Differences among Branded Hyaluronic Acids in Italy, Part 1: Data from *In Vitro* and Animal Studies and Instructions for Use

Joints: 15 for knee joint; 12 for big joints (such as shoulder, hip, ankle, elbow, and knee); 9 for small joints (such as carpometacarpal joints, metacarpophalangeal joints, temporomandibular joint, and other small joints).
For 15 products, it was impossible to gather data regarding which joint they are indicated for.

Products (N°)	Reported number of injections needed per cycle (N°)	Reported expected duration of effect
18	1	10/18
15	2-3	1/15
14	4-5	4/14
5	?	?

Similar products report an expected duration of effect that may vary from 3 to 12 months.

Brands reporting an expected duration of more than six months were combinations of HA with other substances.

Only Durolane, Ostenil, Synvisc, Orthovisc, Synolis VA, and Artz (Supartz) reported studies on their own products in the references of the leaflet, while Arthrum, Fermathron, and Go-on reported studies on generic HA

Differences among Branded Hyaluronic Acids in Italy, Part 1: Data from *In Vitro* and Animal Studies and Instructions for Use

TRADENAME	HYPERSENSITIVITY TO HA	SKIN INFECTION	JOINT INFECTION	JOINT INFLAMMATION	PREGNANCY/ BREAST FEEDING	VENOUS OR LYMPHATIC STASIS	HEPATHOPATHIES	CHILDREN	BLEEDING DISORDERS
Arthrum®	0	0	0	0	0	0	0	0	0
Arthrum 2,5%®	0	0	0	0	0	0	0	0	0
Artrosulfur HA®	0	1	1	1	0				
Artz®/Supartz®	1	0	0	0	1				
Condrovisc®	0	1	1	1	1				
Coxarthrum®	1	0	1	1	0				
Durolane® (AF)	0	1	0	0	1	0	0	1	0
Euflexxa®	1	1	1	0	1	0	0	0	0

Indications as reported on the leaflet of the hyaluronic acid brands merchandised in Italy for intra-articular use

Products	Hypersensitivity to HA	Skin infection	Joint infection	Joint inflammation	Pregnancy/ Breast feeding	Venous or limphatic stasis	Epathopathies	Children	Bleeding disorders
57	32	36	37	27	6	6	3	3	1

Intragel® (AF)	0	1	1	1	0	0	0	0	0
Jointex® (AF)	0	1	1	1	0	0	0	0	0
Jonexa®	1	1	1	0	0	1	0	0	0
Kartilage (AF)	1								
MonoVisc®	1								
Orthovisc® (AF)	1								
Ostenil® (AF)	1								
Proial®	1								
Promovia®	0								
RenehaVis®	1								
Rhizarthrum®	1								
Sinovial® (AF)	0								
SportVis®	1								
Structovial®	1								
Synocrom® (AF)	1								
Synolis® V-A	1								
Synvisc® (AF)	0								
Yaral® (AF)	0								
Viscoplus® (AF)	0								

The presence of infections in the site of injection or the presence of infectious arthritis should represent absolute contraindications to the use of IA HA, as already reported in literature.

Our analysis of the content of leaflets for various HAs marketed in Italy suggests that many reported indications and contraindications are arbitrary and not supported by scientific evidence, thus confounding the decision to prescribe the products. *Larger and brand-specific studies are necessary in order to understand and support the correct use of HA for IA injection and to guide clinicians in making a correctly targeted choice when prescribing an HA-based IA therapy.*

Migliore A et al, Clin Med Insights Arthritis Musculoskelet Disord 2016

HA: types of actions

Hyaluronic acid (HA): what and how

- **HA represents one of the most important component of human body and it is present almost in every tissue**

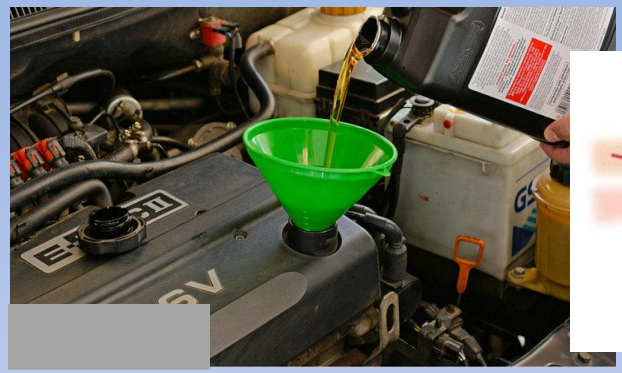
- **HA causes endogenous byosinthesis of HA and aggrecans by synoviocites and condrocites**

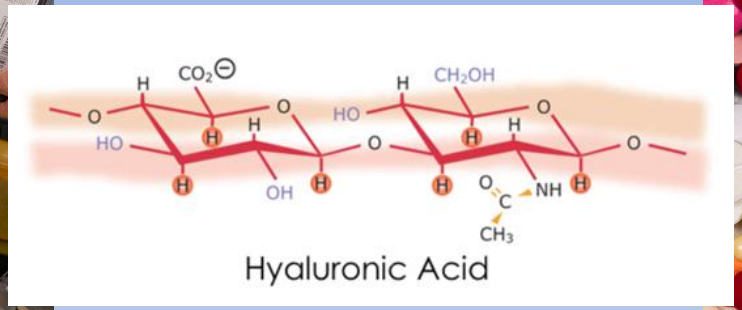
- **HA induces an anti-oxidant action reducing the amount of the oxygen free radicals**

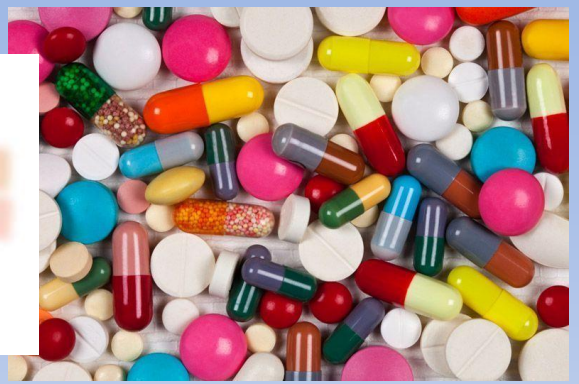
- **HMW HA protects the nociceptive nerve endings and decreases the stress transmetted by the movement of the nociceptors localised in the synovial membrane**

- **HA transports nutritive substances, cytokines etc… from the synovial membrane to the cartilage**

Biological activity and anti-inflammatory effect







The efficacy of the treatment, which lasts longer than the half-life of the exogenous HA, supports the hypothesis that the long-term effects are not only due to the restoration of the rheological properties.

Ghosh P. Clin Exp Rheumatol 1994
Kelly M.A. Am J Orthop 2004

Hyaluronic Acid Suppresses the Expression of Metalloproteinases in Osteoarthritic Cartilage Stimulated Simultaneously by Interleukin 1β and Mechanical Load

N°: osteochondral cylinders from 12 OA patients

- HA exhibits a pronounced suppressive effect on MMP-13
- Treatment with **HA resulted in a suppression of MMP-1** expression only at 1 mg/ml HA, while MMP-2 expression was not significantly affected by either HA concentration
- A more detailed analysis based on the K&L OA grade, showed a much greater degree of suppression of **MMP-13** expression in grade IV as compared to grade II OA

Pohlig F et al, PLoS One 2016

Is MW influencing the mechanism of action of HA?

***In vitro* (OA chondrocytes cultures) low and high MW HA present different biological behavior**

- HAs with a MW between 0.5-1.0 MDa are more effective in reducing inflammation
- Only LMW reduces the effects of IL-1 on the synthesis of NO and PGE2
- Both LMW and HMW HAs are able to reduce the apoptosis induced by NO

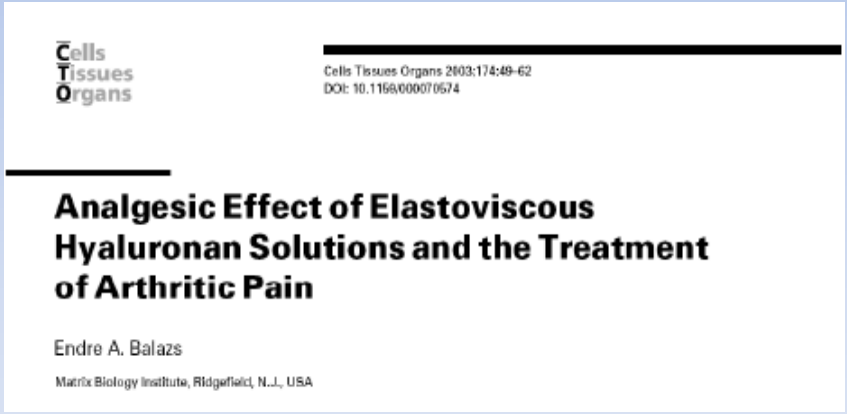
Maneiro E. et al. Clin Exp Rheumatol 2004

The comparison between LMW and cross-linked HA in early OA patients showed a greater efficacy of the cross-linked HA in reducing MMP-2 and MMP-9 (implicated in the degradation of cartilage matrix)

Hsieh Y, J of Orthop Res; 2007

The nociceptors stimulation in normal conditions and in the course of experimental acute arthritis is inversely proportional to the MW of the HA

Gomis A et al. Arthritis & Rheumatism 2004


Cells Tissues Organs

Cells Tissues Organs 2003;174:49–62
DOI: 10.1159/000070574

Analgesic Effect of Elastoviscous Hyaluronan Solutions and the Treatment of Arthritic Pain

Endre A. Balazs

Matrix Biology Institute, Ridgefield, N.J., USA

...the studies on the analgesic effect have demonstrated (both *in vitro* and in animal models) that the greater the elastoviscosity, the greater the analgesic effect

Balasz EA, Cell Tuissues Organ 2003

Chondroprotective effect of high-molecular-weight hyaluronic acid on osteoarthritic chondrocytes in a co-cultivation inflammation model with M1 macrophages

• HA increased the expression of cartilage-specific genes while catabolic-encoding genes exhibited lower expression levels than the control group. This positive effect of HA was also demonstrated by the measurement of pro-inflammatory cytokines, as their level decreased.

• **High-MW HA has a chondroprotective effect** in the present co-cultivation inflammation model, **as it decreases pro-inflammatory cytokines and increases anabolic factors**.

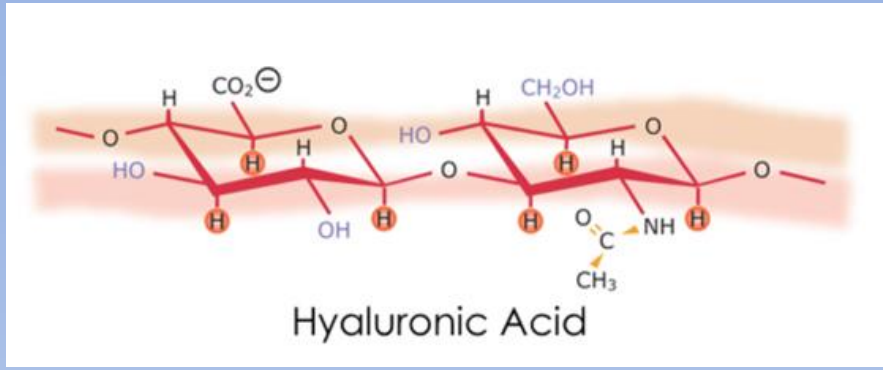
Bauer C et al, J Inflam (London) 2016

Hybrid complexes of high and low molecular weight: evaluation using an in vitro model of osteoarthritis

- AIM: to assess the anti-inflammatory effect of H/L-HA hybrid complexes (SINOVIAL-HL®) in comparison with HA at high (H-HA) and low MW (L-HA) separately used, through the evaluation of specific biomarkers involved in cartilage degradation and correlated to osteoarthritis (TNF-α, IL-6 mRNA and COMP-2) in human chondrocytes.

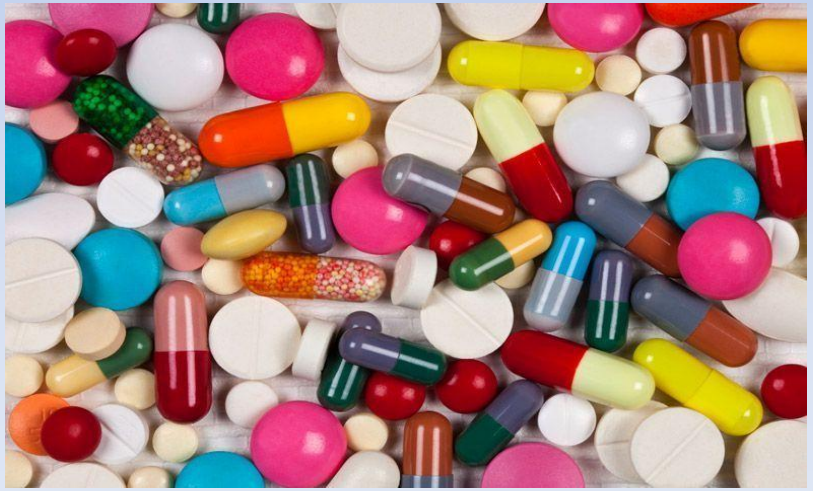
- RESULTS: H/L-HA significantly reduced inflammation biomarkers respect to both L-HA or H-HA separately considered at transcriptional and protein level.

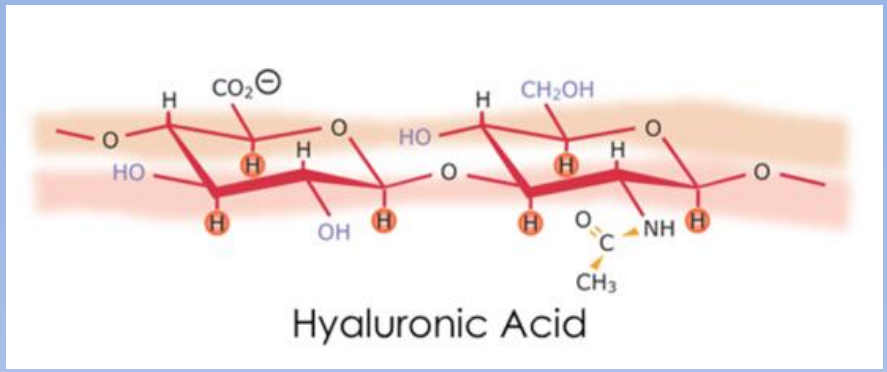
Stellavato A et al, J Biol Requl Homeost Agents 2016



Viscosupplementation

Viscoinduction





Viscosupplementation

Viscosupplementation:

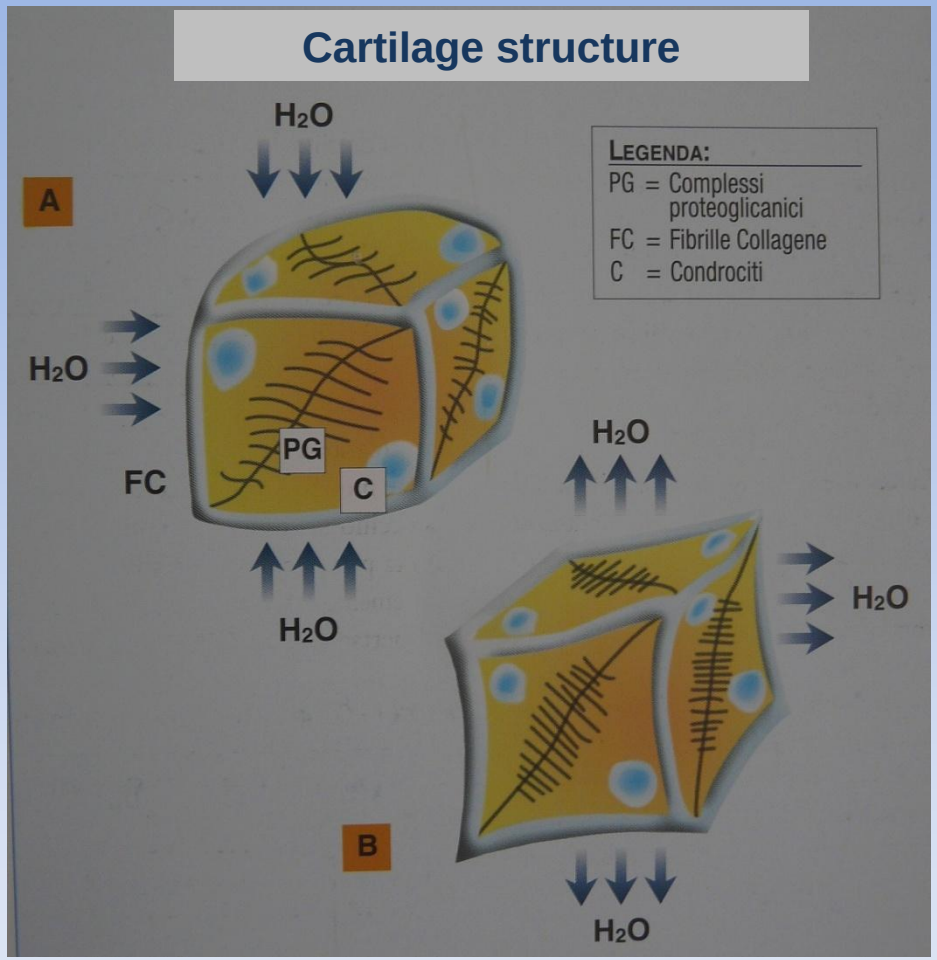
The term “viscosupplementation” indicates the mechanical action of joint lubrication. It is the restoration of homeostasis and the rheological properties (that are viscosity and elasticity) of a pathological synovial fluid, restoring the normal viscoelastic conditions.

It represents the temporary replacement of synovial fluid.

> **Cross-linked HA restore** the environmental conditions of the healthy synovial fluid and the joint functions determining the **production of a synovial fluid rheologically healthy and of HMW HA**

Bagga et al, J Rheumatol 2006

Synovial liquid & cartilage in healthy subject and OA



- Usually, when the cartilage is under pressure the water is expelled from the extracellular matrix (B), coming back when the load is finished (A), due to the proteoglycans negative charges
- As the years pass, the decrease in HA concentration and MW, determines a decrease in the synovial fluid viscoelasticity

➢ 18-27 yy:	MW= 5 MDa,	elasticity= 117 Pa,	viscosity= 45 Pa
➢ 52-78 yy:	MW= -	elasticity= 18,9 Pa,	viscosity= 10,1 Pa
➢ OA	MW= 1,9 MDa,	elasticity= 1,9 Pa,	viscosity= 1,4 Pa

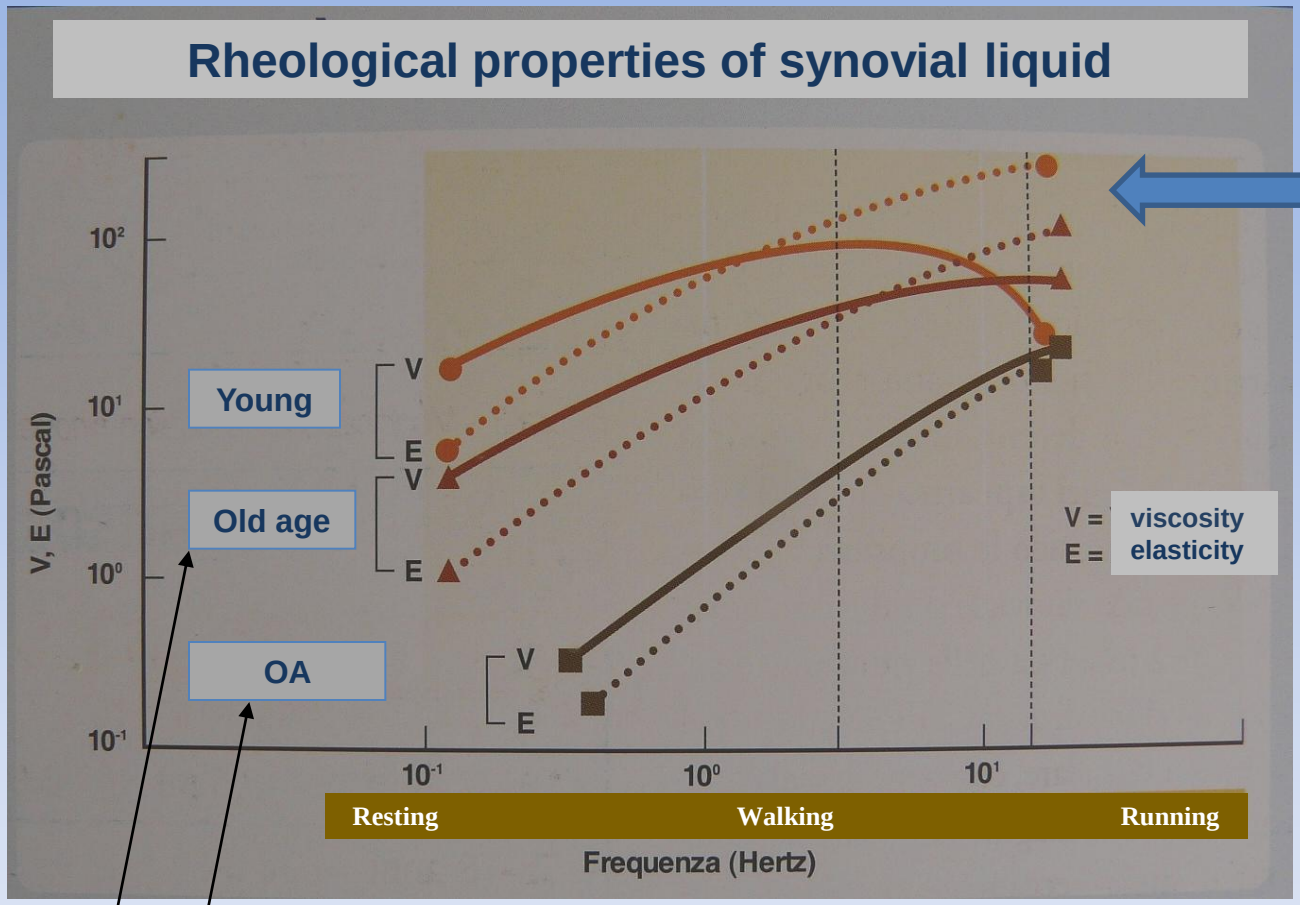
Hyaluronic acid (HA): what and how

• **HA ensures a protective action at a joint level (absorbing mechanical stress) due to viscosity and elasticity**

• **<u>Viscosity</u>: it is a measure of a fluid or semifluid's resistance to flow**. It describes the internal friction of a moving fluid. A fluid with low viscosity flows easily because its molecular makeup results in very little friction when it is in motion *(with a progressive decrease of the strenght while going in the deeper layer).* It protects the tissue absorbing the shock.

• **<u>Elasticity</u>: it is the ability of HA chains to deform, under an external stress, and to return to its original form giving back the energy previously stored as elastic energy**

Hyaluronic acid (HA): what and how



As the frequency increases, synovial fluid changes its behavior from viscous to elastic

Rheology is the science of deformation and flow.
Solids, liquids, and all materials whose behavior is intermediate between solids and liquid is that if we apply a stress or load on any of them they will deform or strain.

When the concentration or molecular weight of HA decrease, the viscoelastic protection is not assured.

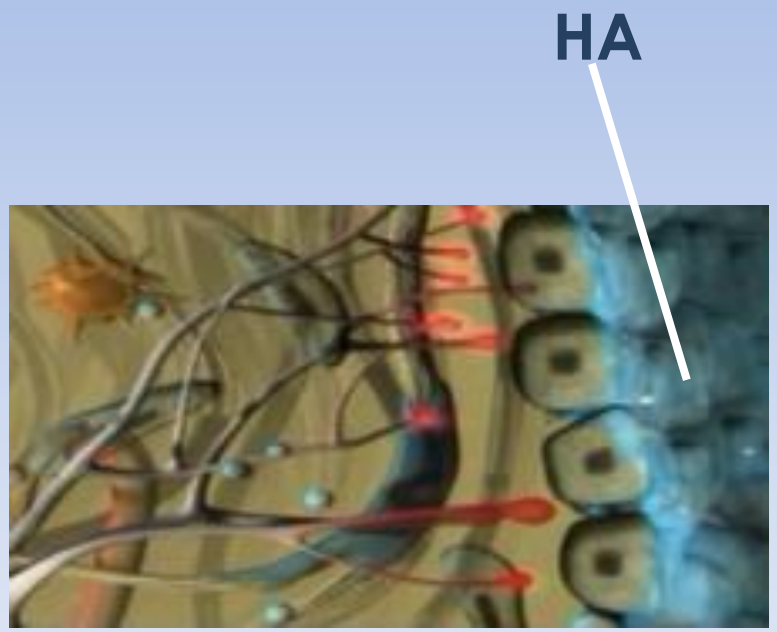
As the age increases, or in case of OA, synovial fluid lose its optimal rheological properties (with a prevalence of elasticity over viscosity only for higher frequencies) with respect to the healthy knee, providing less stress protection even for lower frequencies.

Tucciarone A. OsteoArtrosi.eu 2010

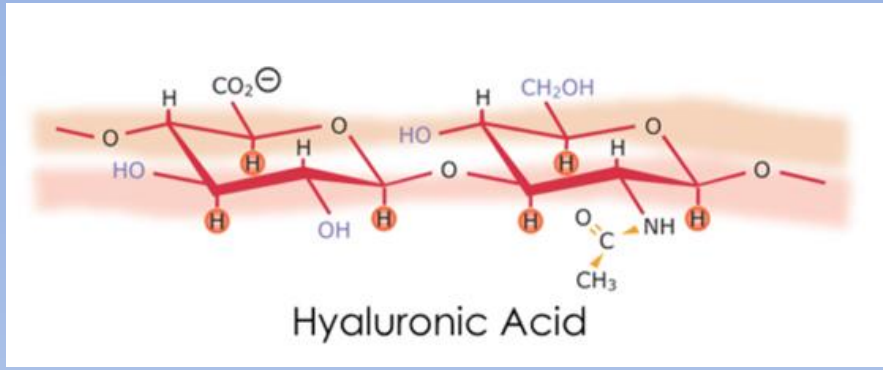
VISCOSUPPLEMENTATION:

Pain control (analgesic effect)

cross-linked HA, differently from not cross-linked HA, creates a sort of insulating protective barrier (“pad effect”) that «switch-off» the nociceptive afferent fibers localised in the joint capsule



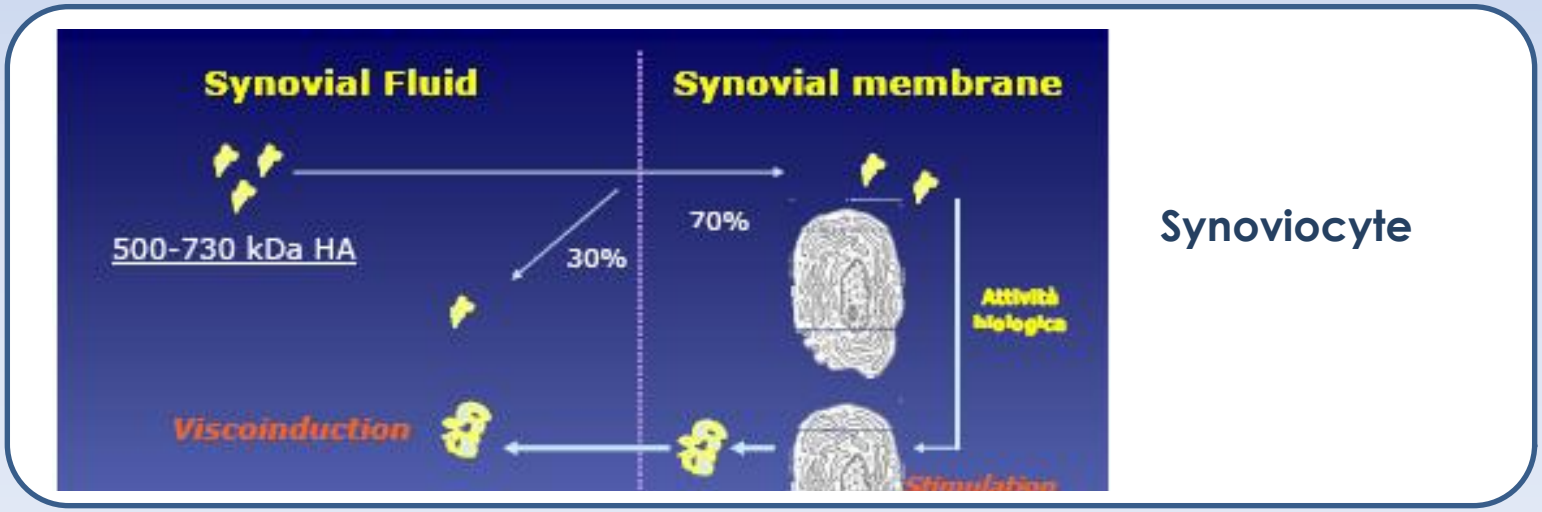
Gomis et al, Arthritis Rheum 2004



Viscoinduction

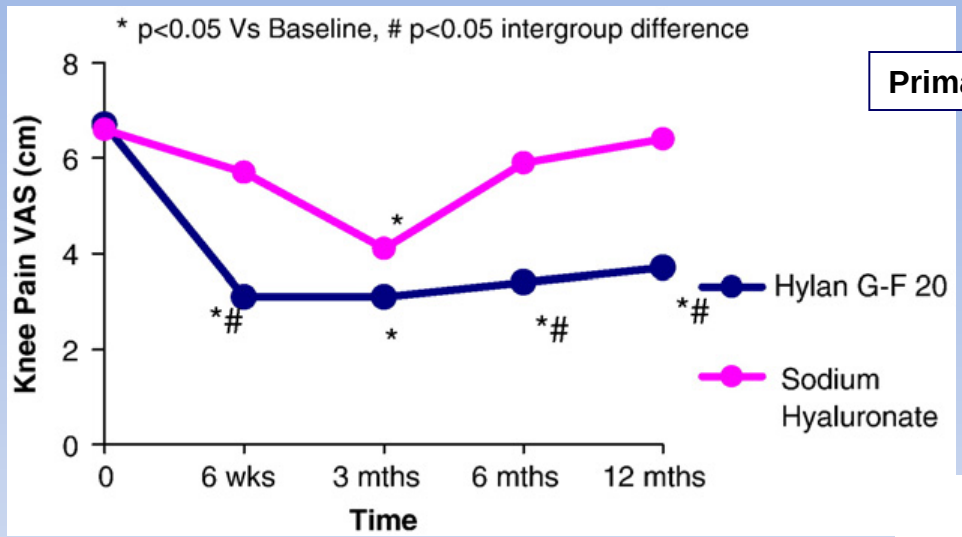
VISCO-INDUCTION: biological activity of LMW HA?

The term "visco-induction" indicates the LMW HA ability to cross the synovial membrane restoring synovial cells metabolism and so, normalyizing the biosynthesis of endogenous HA. The optimal interaction between HA molecules and the specific receptors (CD44, ICAM-1, RAHMM) seems to be obtained only for MW in a specific range between 0.5-4x10^6 DA.



What literature is telling us…

Efficacy of Hylan G-F 20 and Sodium Hyaluronate in the treatment of OA of the knee — A prospective randomized clinical trial

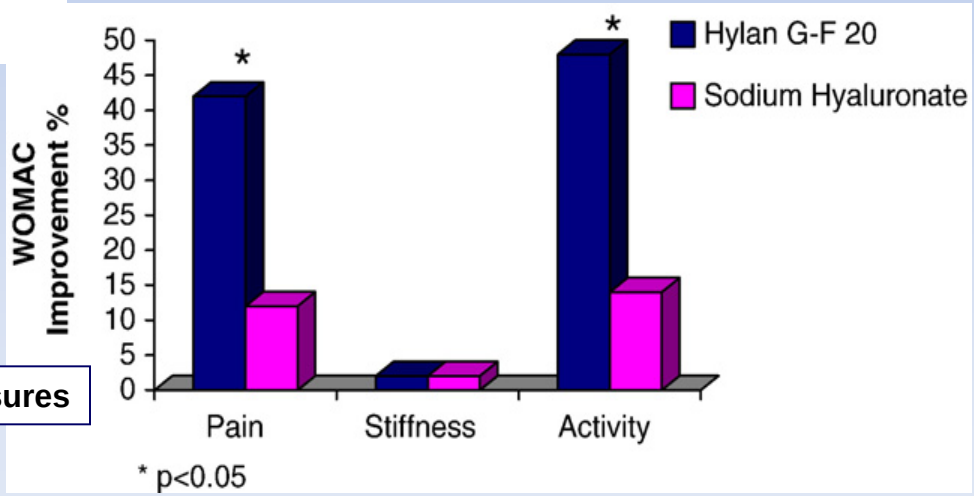


Primary outcome measure

Significant difference between groups at weeks 6 (p=0.001) that remains significant up to 12 months (p=0.01), even if it is absent at the 3-months point.

Reduction of paracetamol intake at 6 (p=0.01) and 12 months (p=0.03)

Secondary outcome measures



Hylan G-F 20 significantly better:

- WOMAC pain at 3 (p=0.02), 6 (p=0.01) and 12 months (p=0.007)
- WOMAC physical domains at 6 (p=0.02) and 12 months (p=0.004)

Raman R et al, The knee 2008

Hylan G-F 20 Versus Low Molecular Weight Hyaluronic Acids for Knee Osteoarthritis: A Meta-Analysis

OBJECTIVE: To compare the effectiveness and safety of intra-articular injection of hylan G-F 20 and LMWHA in the treatment of knee joint OA.

METHODS: A comprehensive search of the literature up to February 2016 was performed; multiple databases were searched with 'Synvisc' or 'hylan' or 'hyaluronan' as free word terms. The pain-related outcomes and treatment-related adverse events from intent-to-treat analyzed studies were pooled for meta-analysis; other functional outcomes were included in the qualitative analysis.

RESULTS: 20 trials (**3034 pts and 3153 knees**). The pooled pain-related outcomes at 2 to 3 months reached a statistically significant difference in favor of hylan G-F 20 (p= 0.02), and the significance still existed with exclusion (in order to eliminate heterogeneity) of the three studies that most favored hylan G-F 20 (p= 0.03). No significant difference was reached for other group and subgroup analyses or treatment-related adverse events.

CONCLUSION: According to the current results, limited evidence showed a **superior effect favoring hylan G-F 20 over LMWHA in the period from 2 to 3 months post-injection for pain-related outcomes**. There was no evidence of increased risk of treatment-related adverse events for hylan G-F 20 injections.

Zhao H et al, BioDrugs 2016

A multi-centre, open label, long-term follow-up study to evaluate the benefits of a new viscoelastic hydrogel (Hymovis®) in the treatment of knee osteoarthritis

Methods: prospective, multi-center, open label, phase III clinical study. Two intra-articular injections (3 mL; 8 mg/mL HYADD® 4) on day 0 and 7 and again after 6 months. Follow-up for 52 weeks. N=50 (>40 yrs with knee OA). WOMAC, JSW, OMERACT OARSI responder criteria, EQ-5D, rescue medication consumption.

Endpoint: WOMAC pain at 52 weeks.

Results: Pain when walking on a flat surface (WOMAC A1 score) significantly improves at 52 wks vs baseline. WOMAC stiffness, physical function and total score significantly improve since 3 months after treatment (up to the end of the study). X-ray knee OA progression: 26% of patients. 88% of pts responder to the therapy classified as per OMERACT-OARSI criteria. The EQ-5D increased significantly vs baseline (at each study time point).

Conclusions: Hymovis® progressively alleviate the knee pain since the first treatment cycle (maintained up to one year after the treatment start) with improve of all the scores considered. Hymovis® is effective and safe in symptomatic treatment of painful knee OA.

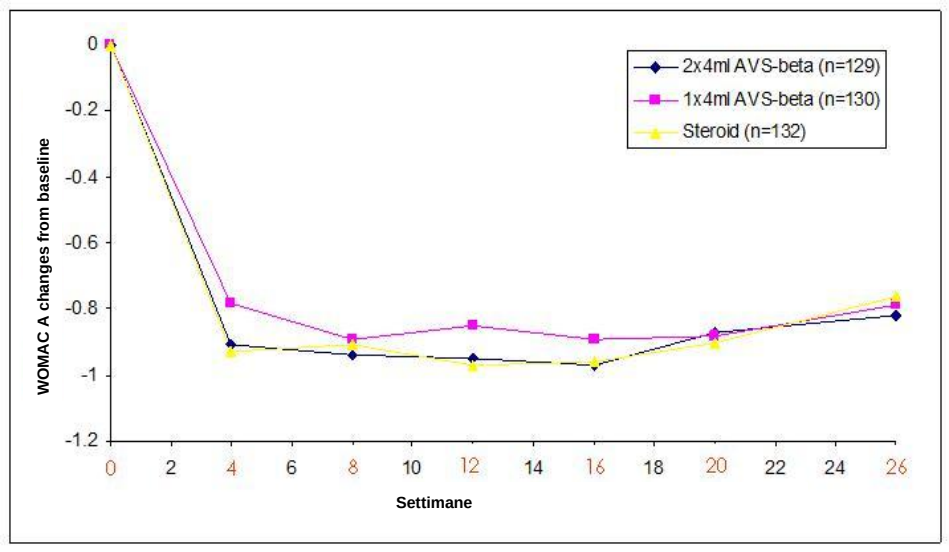
Benazzo F et al, Eur Rev Med Pharmacol Sci 2016

Safety and efficacy of intra-articular Hylastan SGL-80 in patients with symptomatic osteoarthritis (OA) of the knee

Aim: To compare the efficacy and safety of Hylastan SGL-80 to GC

Methods: 391 pts with OA of the knee (grade II-III KL) were divided into 3 groups:
A. Hylastan SGL-80 4 ml, 2 injections at 2 weeks apart
B. Hylastan SGL-80 4 ml, 1 injection
C. Methylprednisolone acetate 1 ml, 1 injection
Duration: 26 weeks
End-point: reduction in pain (WOMAC-A)

Results: There was a statistically significant difference *vs* baseline at 26 weeks in the 3 groups ($p<0.0001$). No statistically significant difference between the two Hylastan SGL-80 groups and GC.



Conclusions

A single injection of Hylastan SGL-80, reducing pain at 26 weeks, represents a possible alternative to multiple injections.

Conrozier T et al. Ann Rheum Dis 2010; 69(Suppl3): 271

Safety and efficacy of intra-articular Hylastan SGL-80 in patients with symptomatic osteoarthritis (OA) of the knee – follow-up

Methods

201 patients (who had a positive response to the first treatment) were retreated and divided into 2 groups:

A. Hylastan SGL-80 4 ml, 2 injections at 2 weeks apart

B. Hylastan SGL-80 4 ml, 1 injections

Duration: 26 weeks

Endpoint: reduction in pain (WOMAC-A)

Results

There was a statistically significant difference *vs* baseline values at 26 weeks in both the 2 groups ($p<0.0002$ and 0.006). No statistically significant difference between the two groups.

Conclusions

Retreatment with Hylastan SGL-80 reduces the pain for a further 26 weeks. The double dose increases temporary AEs (swelling, pain and stiffness).

CONCLUSIONS

Hyaluronic acids are not all alike

- *different origins, composition and indications/number of injections*
- *some properties of HA are common*
- *differences in MW/structure are responsible for different mechanisms of action*
- *large SLR supports different clinical results*


Thanks...

Hypothesis…

Initial OA → **Low-medium MW**

Long standing OA → **High MW/Cross links**

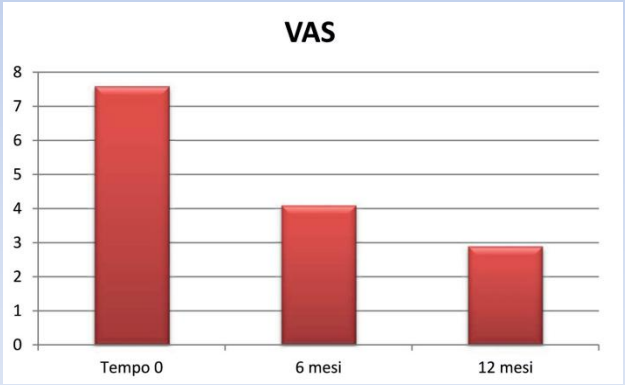
Observational study on the efficacy and safety of administration of cross-linked hyaluronic acid on hip osteoarthritis. Follow up at 12 months

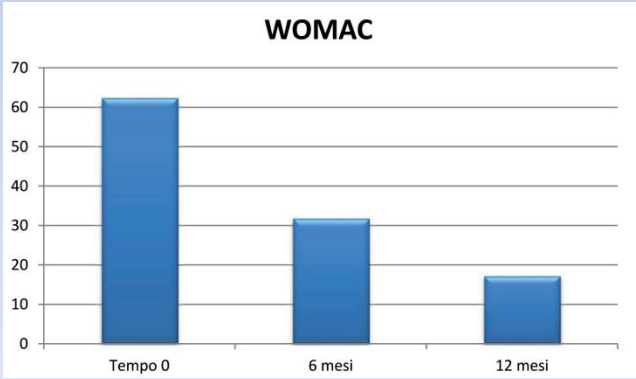
Aim of the study: to evaluate efficacy and safety of hylastan SGL-80 administration in patients affected by hip osteoarthritis in clinical practice

Methods: Open, non-controlled, prospective study

- All pts were treated with Hylastan SGL-80 US-guided infiltration at 0, 1 and 6 months
- All patients were treated for 15 days with either naproxen or etoricoxib before the injection
- VAS and WOMAC were performed at 0, 6 and 12 months and compared to baseline
- In case of synovial joint effusion or ileum-psoas bursitis, US-guided arthrocentesis was performed
- Hip injection was performed using either anterosuperior (according to Migliore-Tormenta technique) or antero-inferior access

Results: N= 30 pts (12 with primary OA); all with Kellgren-Lawrence grade I-II





Conclusions:

- Hylastan SGL-80 injection results in positive effect in pts with hip OA in terms of compliance and safety even in pts presenting synovitis
- Efficacy seems to be inversely related to the grade of disease (and influenced by the presence of synovitis
- The most responsive pts are those with less severe radiological grade of disease

Wolenski L et al. ISIAT 2013

Clinical and cost outcomes from different hyaluronic acid treatments in patients with knee osteoarthritis: evidence from a US health plan claims database

OBJECTIVE: To compare disease-specific costs and risk of TKR among patients receiving different HA treatments in a commercially insured cohort of patients with knee OA in the USA.
METHOD: Retrospective analyses using IMS Health's PharMetrics Plus Health Plan Claims Database were conducted by identifying knee OA patients with claims indicating initiation of HA treatment at an 'index date' during the selection period (2007-2010). Patients were required to be continuously enrolled in the database for 12 months preindex to 36 months postindex. A generalized linear model (GLM) with a gamma distribution and log-link function was used to model aggregate patient-based changes in disease-specific costs. A Cox proportional hazards model (PHM) was used to model the risk of TKR. Both multivariate models included covariates such as age, gender, comorbidities, and preindex healthcare costs.
RESULTS: 50,389 patients with HA treatment for knee OA were identified. 18,217 (36.2%) patients were treated with HA products indicated for five injections per treatment course (Supartz and Hyalgan). The remainder were treated with HA products indicated for fewer than five injections per treatment course, with 20,518 patients (40.7%) receiving Synvisc; 6,263 (12.4%), Euflexxa; and 5,391 (10.7%), Orthovisc. Synvisc- and Orthovisc-injected patients had greater disease-specific costs compared to Supartz/Hyalgan (9.0%, $p<0.0001$ and 6.8%, $p=0.0050$, respectively). Hazard ratios (HRs) showed a significantly higher risk of TKR for patients receiving Synvisc compared to Supartz/Hyalgan (HR=1.069, $p=0.0009$). **Patients treated with Supartz/Hyalgan, Euflexxa, and Orthovisc had longer delays to TKR than those treated with Synvisc**.
CONCLUSION: Analysis of administrative claims data provides real-world evidence that meaningful differences exist among some HA products in disease-specific cost and time to knee replacement surgery.

Dasa V et al, Drugs Context 2016

Hyaluronan concentration and size distribution in human knee synovial fluid: variations with age and cartilage degeneration

BACKGROUND: One potential mechanism for early superficial cartilage wear in normal joints is alteration of the lubricant content and quality of synovial fluid. The purpose of this study was to determine if the concentration and quality of the lubricant, hyaluronan, in synovial fluid: (1) was similar in left and right knees; (2) exhibited similar age-associated trends, whether collected postmortem or antemortem; and (3) varied with age and grade of joint degeneration.

METHODS: Human synovial fluid of donors (23-91 yrs) without OA was analyzed for the concentrations of protein, hyaluronan, and hyaluronan in the MW ranges of 2.5-7 MDa, 1-2.5 MDa, 0.5-1 MDa, and 0.03-0.5 MDa. Similarity of data between left and right knees was assessed by reduced major axis regression, paired t-test, and Bland-Altman analysis. The effect of antemortem versus postmortem collection on biochemical properties was assessed for age-matched samples by unpaired t-test. The relationships between age, joint grade, and each biochemical component were assessed by regression analysis.

RESULTS: Joint grade and the concentrations of protein, hyaluronan, and hyaluronan in the molecular weight ranges of 2.5-7 MDa, 1-2.5 MDa, and 0.5-1 MDa in human synovial fluid showed good agreement between left and right knees and were similar between age-matched patient and cadaver knee joints. There was an age-associated decrease in overall joint grade (-15 %/decade) and concentrations of hyaluronan (-10.5 %/decade), and hyaluronan in the molecular weight ranges of 2.5-7 MDa (-9.4 %/decade), 1-2.5 MDa (-11.3 %/decade), 0.5-1 Mda (-12.5 %/decade), and 0.03-0.5 MDa (-13.0 %/decade). **Hyaluronan concentration and quality was more strongly associated with age than with joint grade**.

CONCLUSIONS: The age-related increase in cartilage wear in non-osteoarthritic joints may be related to the altered hyaluronan content and quality of synovial fluid.

Temple-Wong MM et al, Arthritis Res Ther. 2016

A Systematic Study of the Effect of Different Molecular Weights of Hyaluronic Acid on Mesenchymal Stromal Cell-Mediated Immunomodulation

• MSCs from 3 independent donors were analyzed for changes in the levels of 19 selected transcripts involved in HA signaling (CD44, TLR4, ICAM1, NFKBIA), immunomodulation (COX2, IDO, TSG6, TGFβ, HGF, PD-L1 and PD-L2), trophic activity (HGF, IL6), angiogenesis (VEGFA and CXCL8), proliferation (CYCLIND1), chondrogenesis (SOX9, ACAN, TGF-B), joint lubrication (PRG4) and catabolism (MMP3). **No significant change in MSC gene expression upon exposure to HAs of different MWs was seen.**

• **hHA significantly increased the proliferation of activated PBL**

• *high MW HAs have higher viscosities and are eliminated more slowly than lower MW HAs from the joints, providing increased biomechanical relief and prolonged interaction with joint components*

• *High MW HAs are almost impermeable to most membrane barriers such as the skin, but the catabolic components within the joint eventually degrade HA allowing it to diffuse out. While crosslinking HA creates larger molecules which are more resistant to degradation, thus remaining longer within joints, our experiments were restricted to analyzing aqueous solutions of different MWs of native HA.*

MSCs: mesenchymal stromal cells
PBMC: peripheral blood mononuclear cells
PBL: peripheral blood lymphocytes

Gómez-Aristizábal A et al, PLoS One 2016