XX Congresso Nazionale
Società Italiana di Chirurgia
Ambulatoriale e Day Surgery

PRP e MSc nel trattamento della Gonartrosi

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Cos'è il PRP

PRP (Platlet-Rich-Plasma): derivato ematico che contiene una concentrazione piastrinica superiore a quella del sangue intero. (almeno 200% della concentrazione di piastrine del sangue periferico)

	Costi	Concentrazione	Leucociti
1. **Filtrazione sanguigna e piastrinoferesi**	↑	↑	↓
2. **Centrifugazione a «single spinning»**	↓	↑ max 3 volte	↑
3. **Centrifugazione a «double spinning»**	↑	↑ max 8 volte	↑

Tipi di PRP

4 sono i principali PRP: ***P-PRP, L-PRP, P-PRF/PRFM, L-PRF***

1. **(P-PRP)** Pure PRP: assenza di leucociti, elevata concentrazione di piastrine e fattori di crescita, basso contenuto di fibrina (prodotto per piastrinoferesi)
   - Soluzione liquida
   - Forma gelificata

2. **(L-PRP)** Leukocite Rich PRP: maggiore concentrazione di piastrine rispetto al P-PRP e fattori di crescita, presenza di leucociti, basso contenuto di fibrina (centrifugazione double spin)
   - Soluzione liquida
   - Forma gelificata

Tipi di PRP

3. **(P-PRF/PRFM)** Pure platelet rich fibrin/Platlets Rich Fibrin Matrix: scaffold di fibrina con elevata concentrazione di piastrine, basso contenuto di leucociti (doppia centrifugazione low speed e high speed + $CaCl_2$)
   - Forma gelificata/solida (non infiltrabile)

4. **(L-PRF)** Leukocyte platelet rich fibrin: scaffold di fibrina ad elevata concentrazione di piastrine ed elevato numero di leucociti (centrifugazione singola senza anticoagulante ed attivatore della fibrina)
   - Forma gelificata/solida (non infiltrabile)

Dohan Ehrenfest et l. 2014

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Fattori di crescita e loro ruolo

Table 1. Summary of the effect of growth factors on chondrocytes/cartilage, synovium, and mesenchymal stem cells in vitro and in vivo

Growth factor	Chondrocytes/cartilage	Synovium	Mesenchymal stem cell	References
TGF-β1	Stimulates synthesis of ECM Decreases catabolic activity of IL-1 and MMPs	Causes synovial proliferation and fibrosis Induces chemotaxis of inflammatory leukocytes to synovium Induction of osteophyte formation	Increases proliferation and ECM production ulates collagen type 1 gene expression	7, 8, 27, 47, 89, 92
BMP-2	Stimulates synthesis of ECM Partial reversal of dedifferentiated phenotype in OA Increased ECM turnover (increased aggrecan degradation)	Presumed role in maturation of osteophytes Multiple injections lead to synovial fibrosis Stimulates synovial thickening in experimental OA	Increases proliferation and ECM production Downregulates collagen type 1 gene expression	10, 27, 38, 47, 92
BMP-7	Stimulates ECM synthesis Decreases cartilage degradation through decreasing activity/ expression of numerous ILs and MMPs	Decreases expression of MMPs and aggrecanase Does not appear to caus formation or synovial fibrosis	Inhibits cell proliferation Inconsistent ability to induce chondrogenesis Potentiates chondrogenic differentiation with TGF-βs resulting in increased ECM synthesis and decreasing collagen type 1 compared with TGF-β alone	5, 40, 65, 81, 82
IGF-I	Stimulates ECM synthesis Decreases matrix catabolism except in aged and OA cartilage	Protective effect on synovium resulting in decrease and decreased evidence of chronic inflammation	Stimulates cell proliferation s expression of ECM Additive effect when combined with TGF-β	29, 52, 67, 96
FGF-2	Decreases aggrecanase activity Antagonizes PG synthesis Upregulates MMPs	Induces synovial proliferation Inflammatory and indu osteophyte formation when used alone	Increases PG synthesis s cell proliferation	24, 41, 64, 87
FGF-18	Increases chondrocyte proliferation and stimulates ECM in vitro and in injured joints but not in normal joints	Induces synovial thickening Enlargement of chondrophytes in experimental OA		24, 25, 66
PDGF	No adverse effect in normal joints	No adverse effect in normal joints	Induces proliferation	43, 57

TGF-β1 = transforming growth factor-β1; BMP = bone morphogenetic protein; IGF-I = insulin growth factor I; FGF = fibroblast growth factor; PDGF = platelet-derived growth factor; ECM = extracellular matrix; IL = interleukin; MMP = matrix metalloproteinase; OA = osteoarthritis; PG = proteoglycan.

Fortier et al. 2011

Indicazioni all'uso del PRP

Linee guida internazionali univoche non esistono!

Marmotti et al. 2014

Esistono però evidenze sulle condizioni nelle quali il PRP risulta più efficace sul decorso della malattia:

- Paziente giovane
- Basso grado di condropatia (Kellgren-Lawrence 0-3)
- No coinvolgimento del compartimento rotuleo
- Basso BMI

Kon et al. 2013

Jang et al. 2013

Halpern et al. 2012

Risultati Studi preclinici

Studi preclinici su modelli cellulari umani/animali hanno dimostrato:

- Aumento dei marker antiinfiammatori

Osterman et al. 2015

- Stimolazione della proliferazione condrocitaria

Akeda et al. 20006

- Aumento della deposizione di collagene e proteoglicani

Akeda et al. 20006

- Preservazione del fenotipo condrocitario

Zhu et al. 2013

Risultati - PRP

TABLE 2: Case series concerning PRP intra-articular injections for cartilage pathology.

PRP and intra-articular injections for cartilage pathology: case series

Authors	Year	Number of cases (age and range in y)	Study	Level of evidence	Type of PRP	Procedure and observations	Clinical results
Sampson et al. [68]	2010	14 (age 18–87)	Case series	IV	L-PRP	3 L-PRP injections at 4-week interval;	Improvement at 52 weeks from baseline in Brittberg-Peterson VAS for Pain—resting, Pain—moving, and Pain—bent knee and in KOOS for Pain and Symptom Relief.
Kon et al. [70]	2010	91 (age 24–82)	Case series	IV	L-PRP	3 L-PRP injections at 3-week interval; before the injection: Ca-chloride was added to activate platelets; knee articular damage: grades 0–4 of Kellgren-Lawrence scale.	Improvement at 6 and 12 months from baseline in IKDC, objective and subjective, and EQ VAS; tendency of worsening between 6 and 12 months.
Wang-Saegusa et al. [69]	2011	261 (mean age 48 ± 17)	Case series	IV	P-PRP	PRGF obtained following Anitua's technique; 3 injections at 2-week interval.	Improvement at 6 months from baseline in VAS pain score, Lequesne Index, SF-36 physical, WOMAC Index for pain, stiffness and functional capacity.
Filardo et al. [71]	2011	90 (age 24–82)	Case series	IV	L-PRP	3 L-PRP injections at 3-week interval; before the injection: Ca-chloride was added to activate platelets; knee articular damage: grades 0–4 of Kellgren-Lawrence scale.	Improvement at 24 months from baseline in IKDC, objective and subjective, and EQ VAS; worsening of all scores between 12 and 24 months.
Napolitano et al. [72]	2012	27 (age 18–81)	Case series	IV	L-PRP	3 infiltrations of PRP at weekly intervals; calcium gluconate 10% was added; knee articular damage: chondropathy (Outerbridge 1-2), grades 1–3 of Kellgren-Lawrence scale.	Improvement at 6 months from baseline in Numerical Rating Scale (NRS) for subjective measurement of pain and the WOMAC index for patients with knee arthritis and cartilage disease.
Gobbi et al. [74]	2012	50 (age 32–60)	Case series	IV	L-PRP	2 infiltrations of PRP at 1 month interval; articular damage: grades 1–3 of Kellgren-Lawrence scale.	Improvement at 6 and 12 months from baseline in VAS for pain, IKDC subjective and objective score, KOOS Tegner and Marx scores.
Sánchez et al. [80]	2012	40 (age 33–84)	Case series	IV	P-PRF	3 infiltrations of PRP at weekly intervals; Calcium chloride was added; hip articular damage: Tonnis 2-3.	Improvement at 6 months from baseline in VAS, WOMAC Index, and the Harris pain subscale; no significant changes in pain scores between the 6- to 7-week and 6-month time points.
Torrero et al. [73]	2012	30 (age 18–65)	Case series	IV	L-PRP	Single intra-articular injection of PRP; knee articular damage: chondropathy (Outerbridge 1–3).	Improvement at 6 months from baseline in VAS and KOOS.

TABLE 2: Continued.

PRP and intra-articular injections for cartilage pathology: case series

Authors	Year	Number of cases (age and range in y)	Study	Level of evidence	Type of PRP	Procedure and observations	Clinical results
Jang et al. [77]	2013	90 (age 32–85)	Case series	IV	L-PRP	PRP obtained through Magellan Autologous Platelet Separator; knee articular damage: Kellgren-Lawrence Grade 1–3.	Improvement at 6 months from baseline in VAS and IKDC score; worsening from 6 to 12 months; negative correlation with age, Kellgren-Lawrence grade and presence of patellofemoral joint degeneration.
Raeissadat et al. [76]	2013	60 (mean age 57 ± 9)	Case series	IV	L-PRP	2 L-PRP injections at 4-week interval; no exogenous activation; knee articular damage: grades 1–4 of Kellgren-Lawrence scale.	Improvement at 6 months from baseline in WOMAC Index and the native (Farsi) edition of the SF-36 questionnaire (physical and mental).
Halpern et al. [75]	2013	15 (mean age 54 age 30–70)	Case series	IV	P-PRF	1 PRP injection (Cascade system); knee articular damage: grades 0–2 of Kellgren-Lawrence scale.	Improvement at 12 months from baseline in VAS and WOMAC Index.
Gobbi et al. [79]	2014	119 (age 40–65)	Case series	IV	P-PRP	3 PRP injections at a monthly interval; articular damage: Kellgren-Lawrence Grade 1-2; 50 cases received a second cycle at the completion of 1 year.	Improvement at 24 months from baseline in VAS, KOOS, Tegner and Marx scores; tendency of worsening from 12 to 24 months; at 18 months, greater improvement in patients who received the second cycle.
Mangone et al. [78]	2014	72 (age 52–82)	Case series	IV	L-PRP	3 L-PRP injections at 3-week interval; knee articular damage: Kellgren-Lawrence Grade 2-3.	Improvement at 12 months from baseline in WOMAC index , VAS at rest, and VAS in movement; WOMAC index improved only in the first 3 months.

y = years; PRP = Platelet-Rich Plasma; P-PRP = Pure PRP, with a low content of leukocyte; L-PRP = Leukocyte rich PRP; P-PRF = Pure Platelet-Rich Fibrin.

Marmotti et al. 2014

Risultati <u>congruenti</u>:

- Miglioramento Dolore
- Miglioramento Rigidità
- Miglioramento Funzionalità

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Risultati Studi Comparativi

Table 3: Comparative studies concerning PRP intra-articular injections for cartilage pathology.

PRP and intra-articular injections for cartilage pathology: comparative studies

Authors	Year	Number of cases (age and range in y)	Study	Level of evidence	Type of PRP	Procedure and observations	Clinical results
Sánchez et al. [81]	2008	30 (mean age 63 ± 8)	Observational retrospective cohort study	III	P-PRP	3 PRGF injections at 1-week interval; control group: HMW-HA (30 pts); knee articular damage: Ahlbäck grades 1–4.	Better improvement of PRGF group at 5 weeks in WOMAC index.
Kon et al. [82]	2011	50 (age 30–81)	Prospective comparative study	II	L-PRP	3 L-PRP injections at 2-week interval; before the injection: Ca-chloride was added to activate platelets; control group: HMW-HA (50 pts), LMW-HA (50 pts); knee articular damage: grades 0–4 of Kellgren-Lawrence scale.	Better improvement of PRP group at 6 months in IKDC and EQ VAS scores; better results in subgroup of patients with cartilage degeneration; worsening from 2 to 6 months subgroup in patients with advanced OA; no difference between PRP and control groups in patients over 50 years.
Li et al. [83]	2011	15 (age 36–76)	Randomized prospective study	II	L-PRP	3 PRP injections at 3-week interval; before the injection: Ca-chloride was added to activate platelets; control group: sodium hyaluronate (LMW-HA) (15 pts).	No difference in IKDC score, WOMAC score, and Lequesne index between 2 groups within 4 months; better improvement of PRP group at 6 months.
Filardo et al. [67]	2012	54 (mean age 55; age 18–80)	Randomized double blind prospective comparative study	I	L-PRP	3 L-PRP injections at 1-week interval; control group: HMW-HA (55 pts); knee articular damage: grades 0–4 of Kellgren-Lawrence scale.	Improvement at 12 months from baseline in IKDC, KOOS, EQ-VAS, and Tegner for both groups; no differences between PRP group and controls; trend toward better results for the PRP group in patients with less degenerated joints.
Spaková et al. [84]	2012	60 (mean age 53 ± 12)	Prospective cohort study	II	L-PRP	3 PRP injections; control group: HA.	Better improvement of PRP group at 6 months in Numerical Rating Scale (NRS) and the WOMAC index.
Sánchez et al. [86]	2012	79 (mean age 60 ± 8)	Randomized controlled trial	I	P-PRP	3 P-PRP injections at 1-week interval; control group: HMW-HA (74 pts); knee articular damage: Ahlbäck grade I–III.	Better improvement of PRP group at 24 weeks in the percentage of patients having a 50% decrease in WOMAC pain subscale; trend toward better improvement (not significant) of PRP group in scores on the WOMAC subscales for stiffness and physical function, in Lequesne index, in the percentage of OMERACT-OARSI responders, and in the amount of acetaminophen in mg/day.
Cerza et al. [85]	2012	60 (mean age 66 ± 11)	Randomized controlled trial	I	P-PRP	4 PRP injections at 1-week interval; control group: LMW-HA (60 pts).	Better improvement of PRP group at 24 weeks in WOMAC scores; no correlation with the grade of gonarthrosis.
Mei-Dan et al. [92]	2012	15 (mean age 43 ± 18)	Randomized controlled trial	II	P-PRP	3 PRGF injections at 2-week interval; control group: HMW-HA (15 lesions; 1-week interval); ankle articular damage: Ferkel grade 1–3 osteochondral lesions.	Better improvement of PRP group at 28 weeks in AOFAS Ankle-Hindfoot Scale (AHFS), VAS for pain, stiffness, and function, subjective global function scores.
Vaquerizo et al. [87]	2013	48 (age 62 ± 7)	Randomized controlled trial	I	P-PRP	3 P-PRP injections at 1-week interval; control group: HMW-HA (48 pts; 1 single injection); knee articular damage: grades 2–4 of Kellgren-Lawrence scale.	Better improvement of PRP group at 48 weeks in WOMAC index, Lequesne index and OMERACT-OARSI responders.
Say et al. [88]	2013	45 (mean age 55)	Prospective study	II	P-PRP	1 P-PRP injections; control group: HA (45 pts; 3 injections at 1-week interval).	Better improvement of PRP group at 6 months in KOOS and VAS for pain.
Patel et al. [89]	2013	52 (group A; age 33–80) 50 (group B; age 34–70)	Randomized controlled trial	I	P-PRP	Group A (52 knees): single injection of PRP; group B (50 knees): 2 injections of PRP at 3-week interval; group C (46 knees): single injection of normal saline; knee articular damage: Ahlbäck grade I-II.	Better improvement of PRP groups at 6 months in WOMAC, VAS and overall satisfaction with the procedure; no difference between group A and B; slight worsening from 3 to 6 months.
Hart et al. [90]	2013	50 (age 31–75)	Randomized controlled trial	I	P-PRP	9 PRP injections during 1 year; control group (50 pts): 1% mesocain; knee articular damage: Grade II (fibrillation), Grade III (fissuring and fragmentation, but no bone exposed).	Better improvement of PRP groups at 12 months in Lysholm, Tegner, IKDC, and Cincinnati scores.
Battaglia et al. [91]	2013	50 (age 25–76)	Randomized controlled trial	I	L-PRP	3 PRP injections at 1-week interval; control group: HMW-HA (50 pts); hip articular damage: grades 2–4 of Kellgren-Lawrence scale.	No difference at 12 months between the groups in Harris Hip Score (HHS), NSAID consumption and VAS.

y = years; PRP = Platelet-Rich Plasma; P-PRP = Pure PRP, with a low content of leukocyte; L-PRP = Leukocyte rich PRP; P-PRF = Pure Platelet-Rich Fibrin; LMWHA = Low Molecular Weight Hyaluronic Acid; HMW-HA = High Molecular Weight Hyaluronic Acid; pts = patients; PRGF = "Preparation Rich In Growth Factors" or Plasma-Rich Growth Factors or Platelet Rich Growth Factor with a very low/absent content of leukocytes.

Risultati contrastanti

Improveme

No

2014

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Vantaggi e Svantaggi

- x Lieve gonfiore e sensazione di calore nelle ore-giorni seguenti l'infiltrazione
- x Effetto temporaneo (max 1 anno)
- x Basse *level of evidence* (Case series)
- x Selezione accurata del paziente
- x Letteratura non univoca con risultati contrastanti

- Prodotto autologo
- No controindicazioni a cicli ripetuti
- Risultati incoraggianti sulla degenerazione cartilaginea
- Maggiore efficacia e durata su dolore e funzione rispetto ad HA e placebo

Am J Sports Med. 2015 May 7. pii: 0363546515582027. [Epub ahead of print]

Platelet-Rich Plasma Intra-articular Knee Injections Show No Superiority Versus Viscosupplementation: A Randomized Controlled Trial.

Filardo G[1], Di Matteo B[2], Di Martino A[1], Merli ML[1], Cenacchi A[3], Fornasari P[3], Marcacci M[1], Kon E[4].

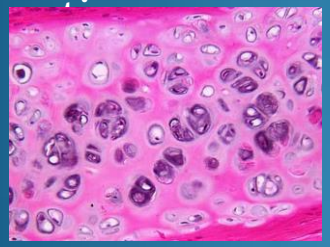
L'ultima frontiera: le MScs

MSc:

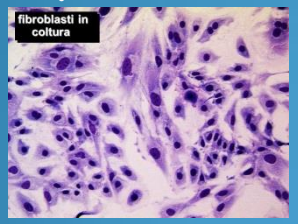
cellula staminale adulta, immatura ed indifferenziata, pluripotente

Tessuto connettivale

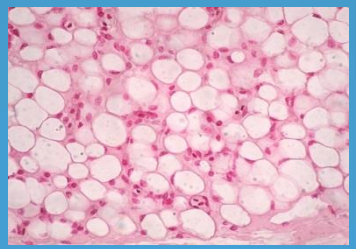
Condroci



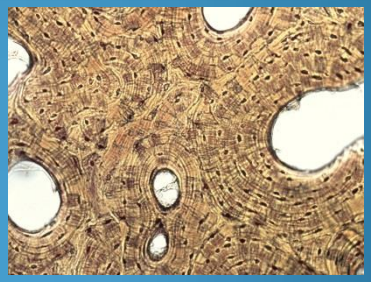
Fibroblast



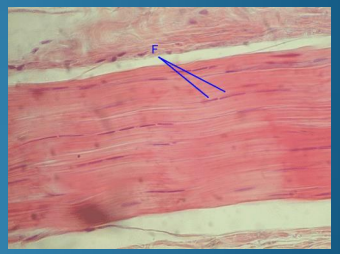
Adipociti



Osteoblasti



Tenociti



L'ultima frontiera: le MScs

Origine:

- Midollo osseo
- Sangue periferico
- Tessuto adiposo
- Fluido articolare
- Sangue del cordone ombelicale
- Placenta

Funzione:

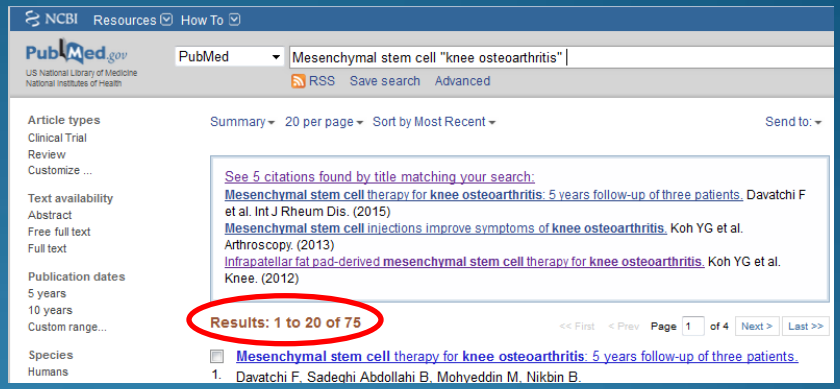
- Immunomodulatoria
- Riparativa
- Antinfiammatoria

Bernardo et al. 2009

L'ultima frontiera: le MScs

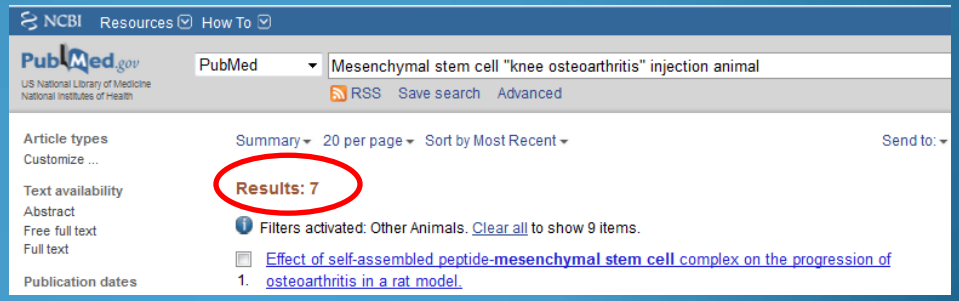
Stato dell'arte

Pochi studi (sviluppi solo negli ultimi 10-12 anni -> 2003)



Molti studi sono relativi a scaffold con MSC e non a terapia infiltrativa

Quasi il 50% studi su modello animale

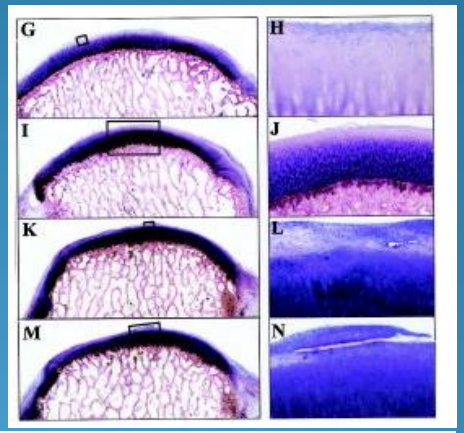


L'ultima frontiera: le MScs

Studi animali

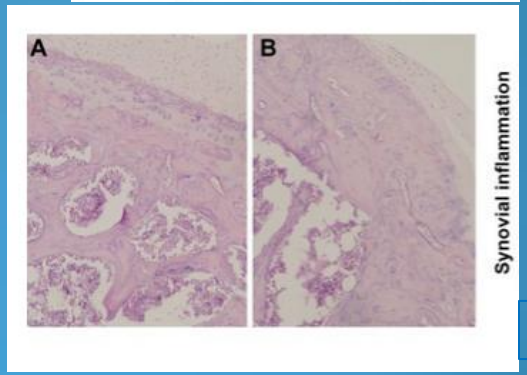
I pochi studi animali Risultati Incoraggianti

- Diminuzione citochine proinfiammatorie e delle MMP → Minor danno alla cartilagine
- Minor sclerosi subcondrale



Murphy et al. 2003

- Minor infiammazione sinoviale



Kim et al. 2014

L'ultima frontiera: le MScs

Studi su Uomo

Pochissimi studi Basse *Level of evidence*

Author	*Year*	*Lev of Evidence*	*Procedura*	*Risultato clinico*
Centeno et al.	2008	V	1 paziente, infiltrazione singola di Msc, valutazione ROM, VAS, MRI	Miglioramento di tutti gli indici (VAS, ROM, MRI)
Varma et al.	2010	III	50 pazienti, 25 debriment, 25 debriment +MSC, valutazione VAS, KOOS, Qualità di vita	Miglioramento VAS, KOOS e qualità di vita ad un anno
Koh et al.	2012	III	50 pazienti, 25debriment + PRP + MSc, 25 debriment + PRP. Valutazione VAS, Lisholm e Tegner score	No reazioni avverse, debriment + PRP + MSc miglioramento a breve termine. No differenze a fine follow up
Emadedin et al.	2012	IV	6 pazienti, Kellgren-Lawrence 3-4, valutazione VAS, funzionalità, distanza percorsa, RM T2 pre e post	Miglioramento di tutti gli indici a 6 mesi, ritorno ai livelli basali ad un anno
Koh et al.	2013	IV	18 pazienti, infiltrazione di PRP e MSc, valutazione VAS, WOMAC, Lisholm RMN T2 pre e post (MOCART)	Miglioramento VAS, WOMAC e Lisholm e MOCART . Correlazione positiva tra MOCART e n° cellule iniettate

L'ultima frontiera: le MScs

Studi su Uomo

Author	*Year*	*Lev of Evidence*	*Procedura*	*Risultato clinico*
Orozco et al.	2013	IV	12 pazienti, infiltrazione di MSc, valutazione dolore, disabilità, qualità di vita e qualità cartilaginea in RMN T2	Miglioramento di tutti gli indici, riduzione del 27% delle aree povere di cartilagine, miglioramento della qualità cartilaginea in 11/12 pazienti
Wong et al.	2013	III	56 pazienti, 28 infiltrazione con HA, 28 infiltrazione con HA + PRP. Valutazione IKDC, Lisholm e Tegner score, MOCART	Miglioramento significativo di tutti gli indici nel gruppo trattato con MSc+HA
Jo et al.	2014	IV	18 pazienti, infiltrazione con MSc, valutazione dose, sicurezza, WOMAC, valutazione radiologica, artroscopica e istologica	Migliore alta concentrazione, no eventi avversi, miglioramento scala WOMAC e diminuzione del dolore, diminuzione difetto cartilagineo e aumento dello spessore cartilagineo, ispessimento cartilagineo di tipo simil ialino
Davatchi et al.	2015	IV	3 pazienti, Kellgren Lawrence 3-4, infiltrazione con MSc, valutazione distanza di cammino, salire le scale, dolore, crepitio patellare contrattura in flessione e VAS (alto grado)	A 5 anni di follow up miglioramento di tutti gli indici, il ginocchio trattato risulta meno danneggiato del ginocchio controlaterale

L'ultima frontiera: le MScs

Indicazioni?

<u>Ad oggi siamo ancora in fase preliminare, non esistono indicazioni al trattamento con MSc</u>

Punti a favore

Risultati incoraggianti:

- Miglioramento della qualità cartilginea (RM T2 ed istologica)
- Diminuzione indici di flogosi
- Diminuzione sclerosi subcondrale
- Miglioramento della qualità di vita
- Miglioramento indici clinici

Punti a sfavore

- x Potenziale oncogenico delle MSc
- x Pochi studi che saggiano la sicurezza
- x Pochi studi e di bassa qualità *(Level of Evidence IV)*
- x Non c'è univocità nella scelta delle MSC da utilizzare (Midollo? Tessuto adiposo?)
- x Non c'è univocità nella formulazione (MSC+HA, MSC+PRP, MSC)

Discussione

Siamo ancora in una **fase pioneristica**:

Il **PRP** offre per ora le maggiori evidenze in termini di sicurezza, rigenerazione cartilaginea, gestione del dolore e disabilità.

Nonostante ciò servono ulteriori studi per confermare/smentire i risultati contrastanti presenti in letteratura.

Le **MSc** rappresentano la prospettiva futura con risultati molto incoraggianti nella gestione della gonartrosi. Tuttavia occorrono studi ulteriori e di qualità per meglio comprendere il tipo di cellule staminali (midollo osseo vs tessuto adiposo), il profilo di sicurezza, la concentrazione, il regime di infiltrazioni e le conferme dei promettenti risultati in vitro.

Take Home Messages

PRP

Risultati incoraggianti:

- Aumento marker antiinfiammatori
- Aumento deposizione di collagene e proteoglicani
- Stimolazione proliferazione condrocitaria
- Miglioramento qualità di vita
- Miglioramento dolore
- Miglioramento della funzionalità

MSc

Risultati incoraggianti:

- Miglioramento della qualità cartilginea istologica e radiologica
- Diminuzione indici di flogosi
- Diminuzione sclerosi subcondrale
- Miglioramento della qualità di vita
- Miglioramento della funzionalità

Tuttavia la strada verso conoscenze approfondite è ancora lunga ed in salita.....

Grazie per l’attenzione…