



Fatores locais que alteram o reparo

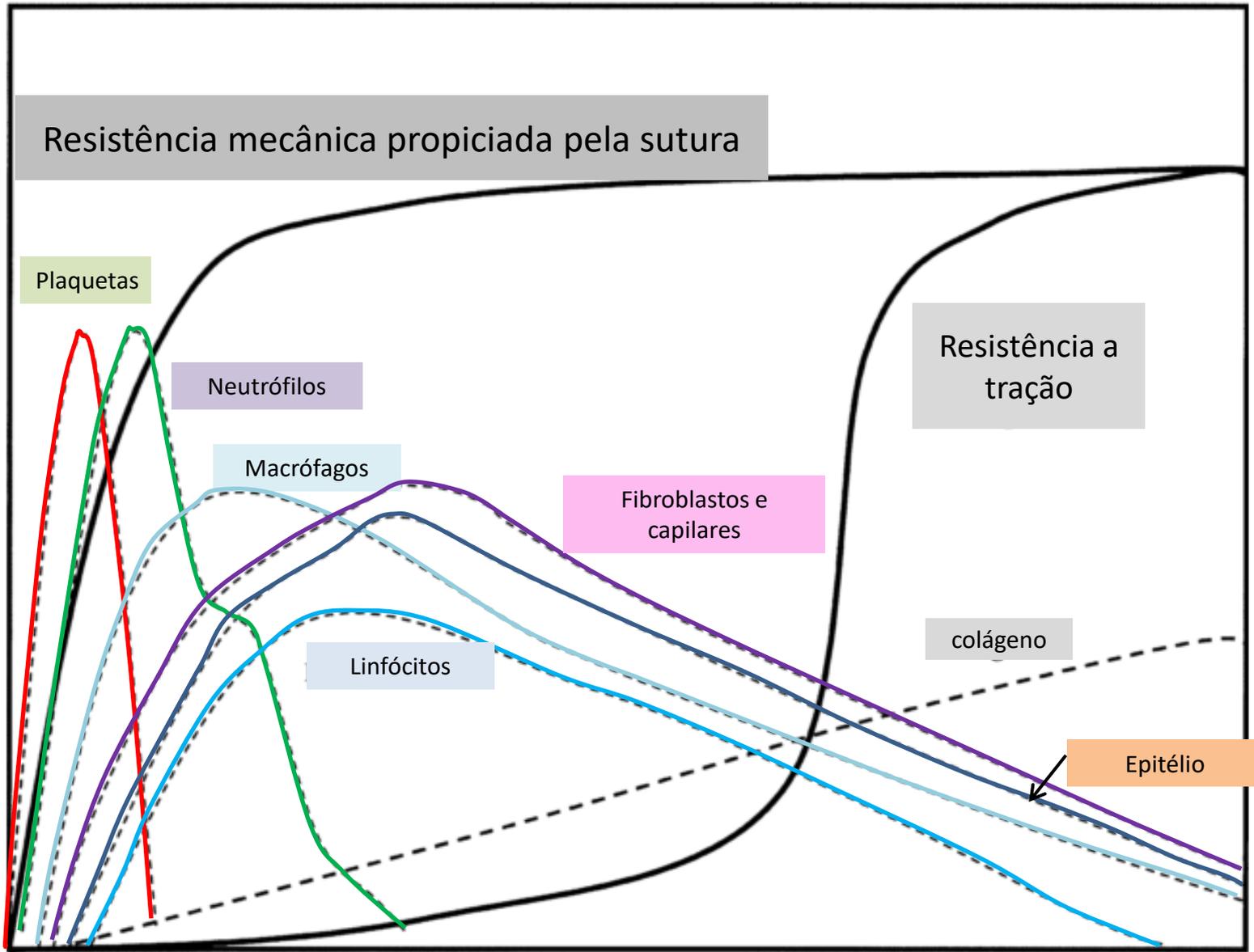
Luciana Corrêa



Fatores locais que alteram o reparo

- Regularização das bordas da ferida
- Distância entre as bordas da ferida
- Estabilização das bordas da ferida – sutura
- Infecção secundária
- Presença de corpos estranhos
- Vascularização e oxigenação

Importância da sutura/imobilização



Oxigenação e hipóxia

HIPÓXIA

Transitória
e inicial

Estimula a proliferação fibroblástica

Estimula a proliferação endotelial – vascularização

Estimula a proliferação epitelial

HIPÓXIA

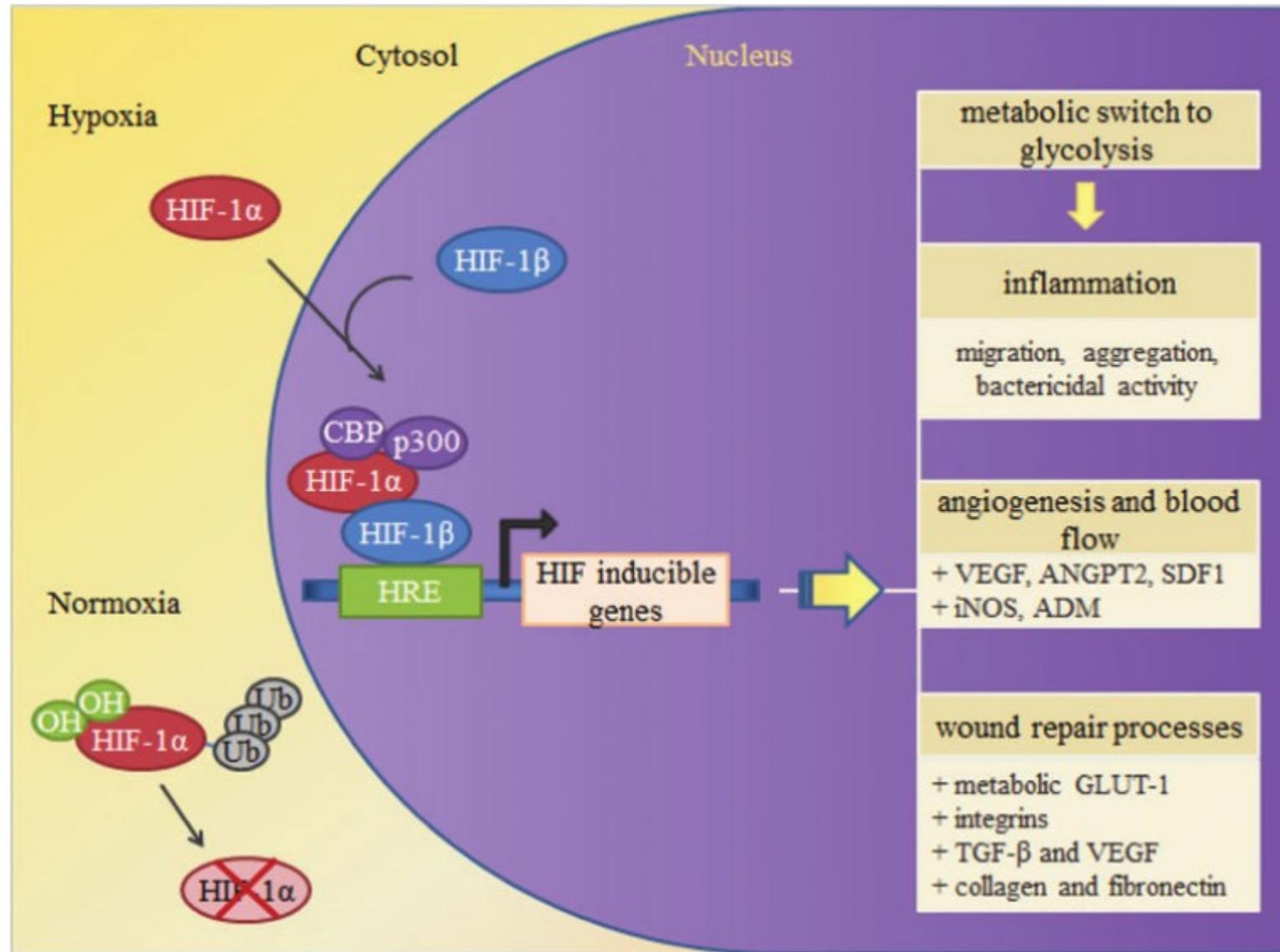
Intensa
e permanente

Inibe a formação de colágeno do tipo I

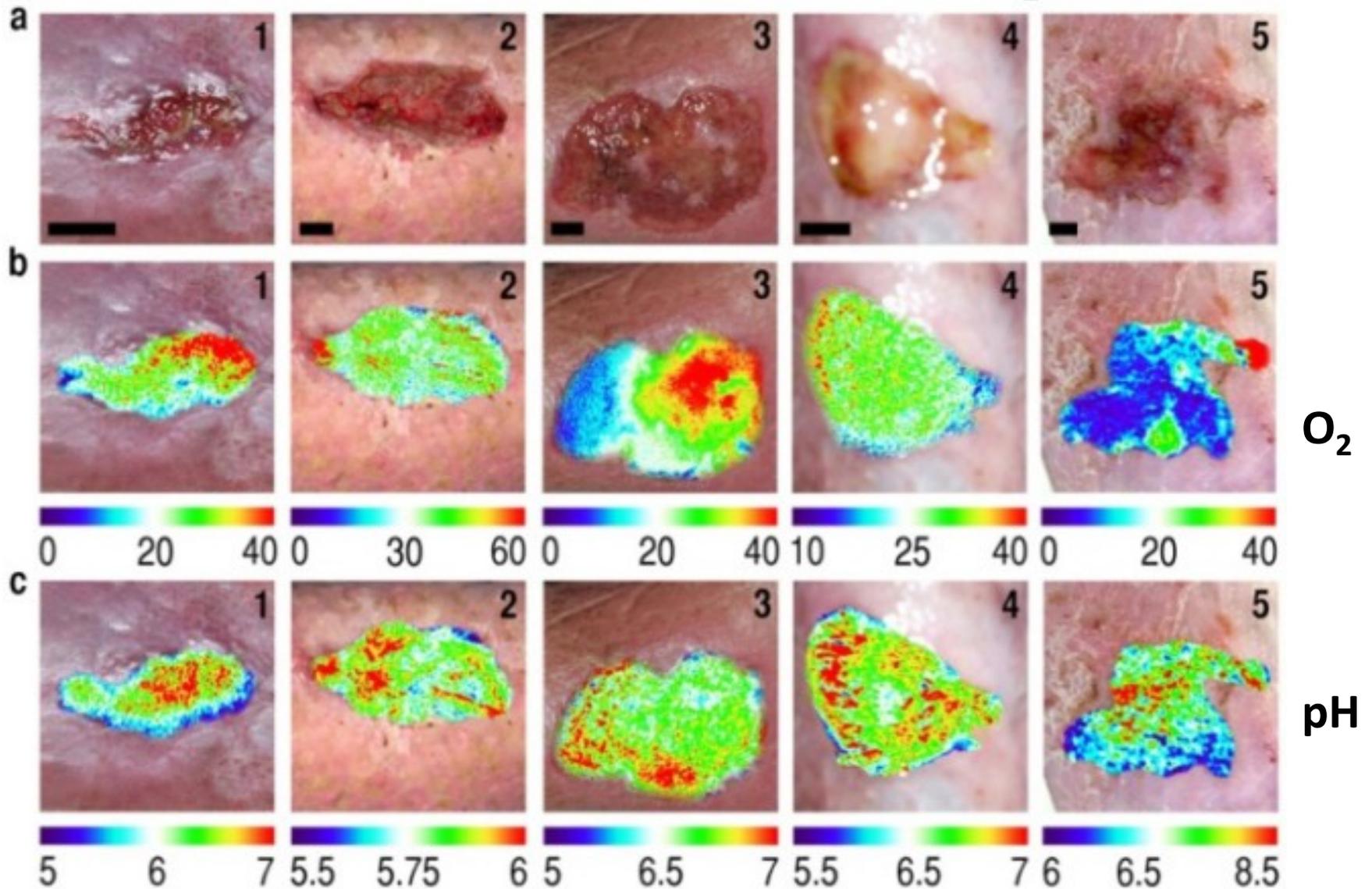
Inibe o crescimento epitelial no centro da ferida

Inibe a diferenciação em miofibroblasto

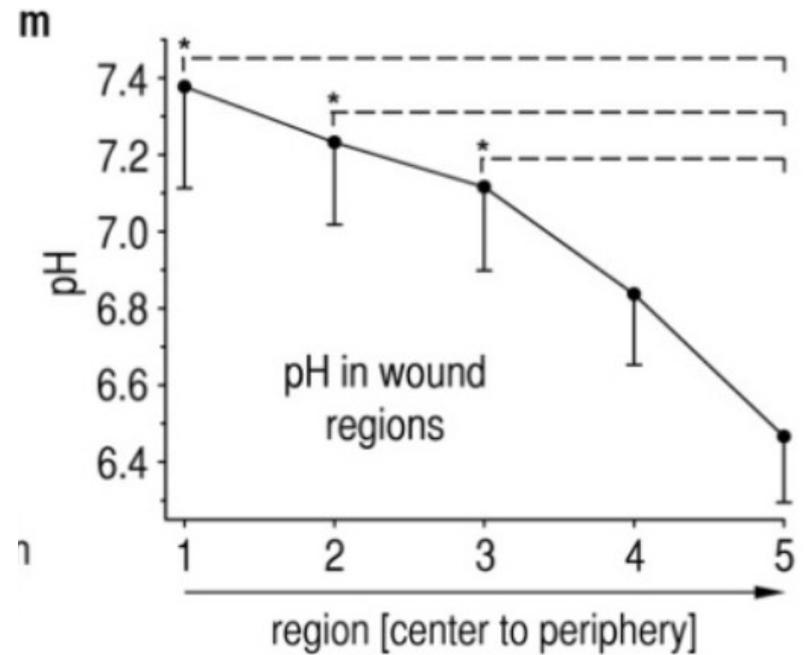
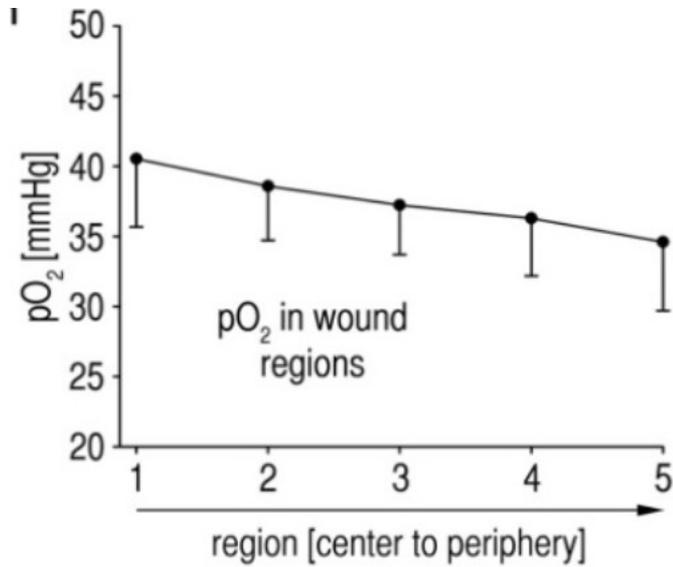
Oxigenação e hipóxia – fator induzível por hipóxia 1 (HIF1)



Oxigenação e pH em feridas crônicas

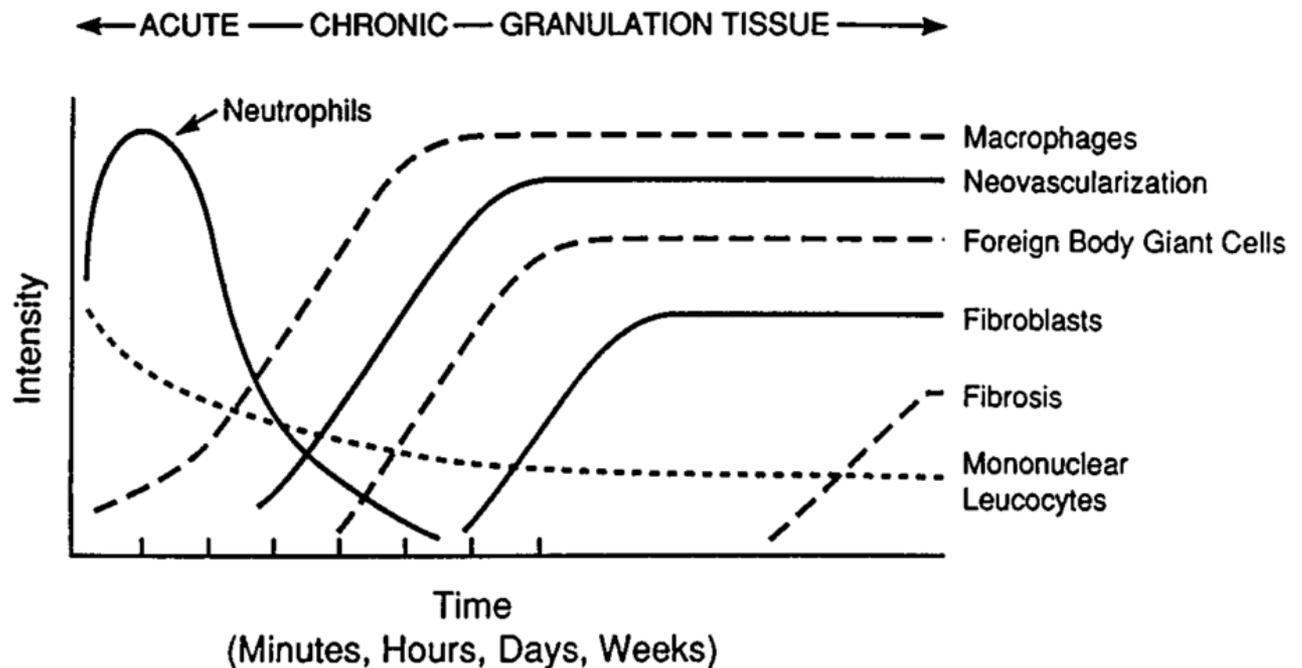


Oxigenação e pH em feridas crônicas



Reação do tecido a biomateriais

1. Injúria
2. Reação do biomaterial com componentes do coágulo
3. Formação de matriz extracelular provisória
4. Inflamação aguda – imunidade inata
5. Inflamação crônica – imunidade adaptativa
6. Formação do tecido de granulação
7. Formação de corpo estranho
8. Fibrose / encapsulamento



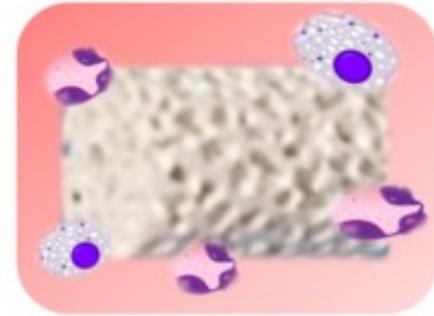
Reação do tecido a biomateriais



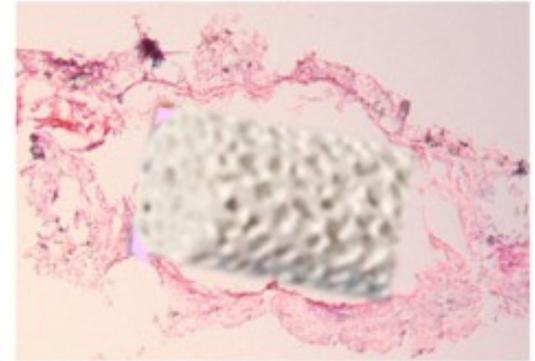
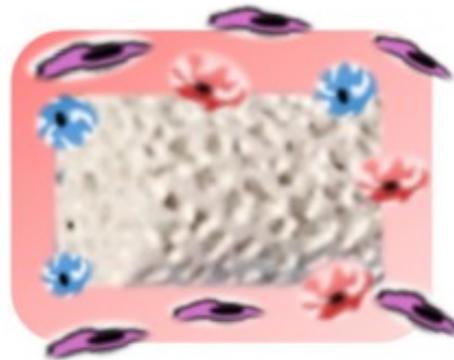
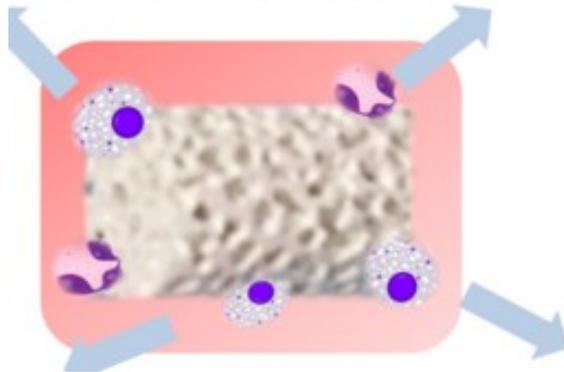
Release of cytokines and chemokines from cells (1-5 days)



Recruitment of tissue repair cells (5-15 days)

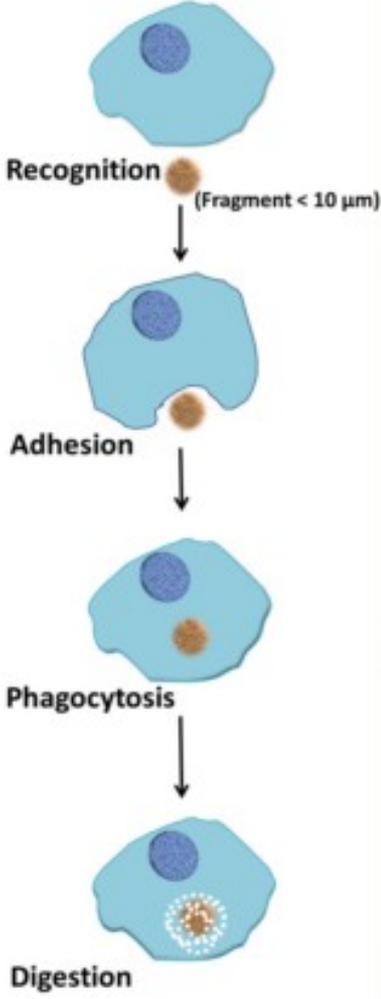


Fibrous encapsulation and granulation tissue formation (3-4 weeks)

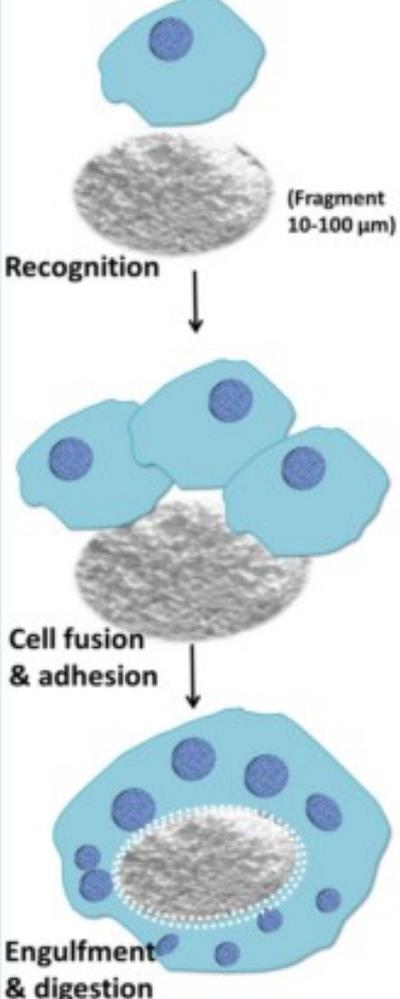


Reação de corpo estranho

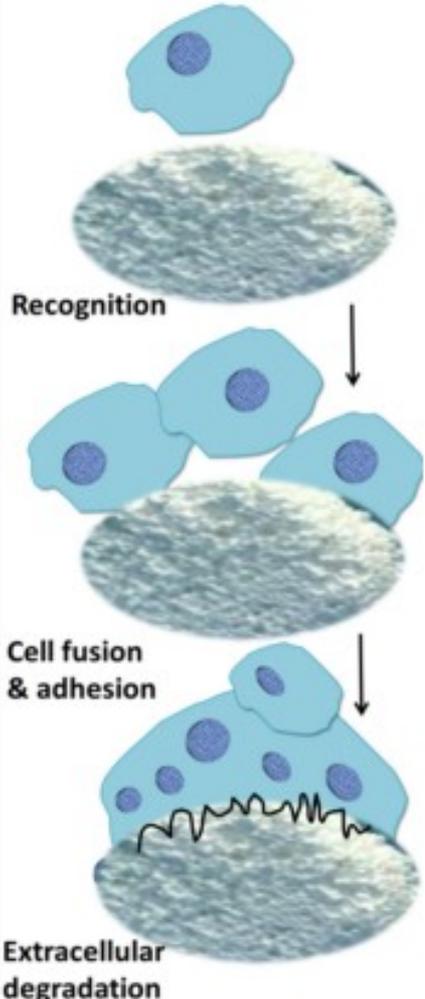
Macrophage Mediated Phagocytosis



Giant Cell Mediated Engulfment



Extracellular Degradation

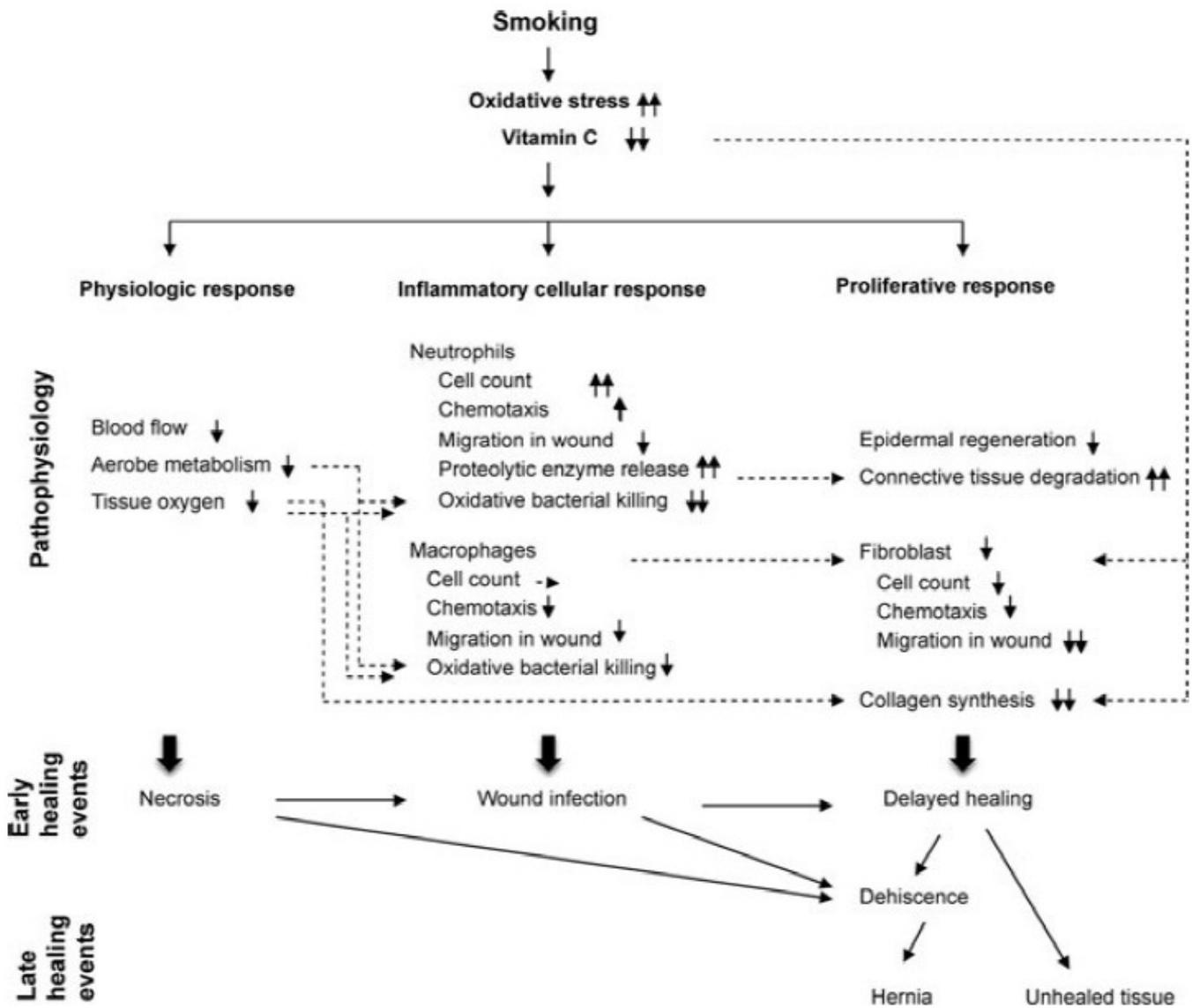




Fatores sistêmicos que alteram o reparo

Luciana Corrêa

Fumo e reparo tecidual



Diabetes e reparo tecidual

Deficiências na microcirculação (redução do tamanho dos capilares, arteriolesclerose, espessamento da membrana basal)

Má distribuição do fluxo sanguíneo, com redução da vasodilatação devido a neuropatia periférica

Redução da migração leucocitária, predispondo a infecção

Alteração do balanço entre metaloproteinases e atividade proteolítica, com redução do remodelamento da matriz extracelular

Redução da resposta fibroblástica a fatores de crescimento (ex. TGF- β)

Redução da produção de citocinas por macrófagos

Redução da proliferação e migração de queratinócitos

Agentes quimioterápicos e reparo ósseo

Table 2 Chemotherapeutic agents' effect on fracture healing

Year/study	Model used	Drug	Outcome
1983/Burchardt ¹⁵	Dogs	Doxorubicin and Methotrexate	<ul style="list-style-type: none"> • Decrease of bone formation
1983/Sommer-Tsilenis ¹¹²	Rats	Cyclophosphamide	<ul style="list-style-type: none"> • Inhibition of collagen formation • Delayed mineralisation
1984/Nilsson ⁸⁸	Rats	Methotrexate	<ul style="list-style-type: none"> • Inhibition of bone formation
1984/Friedlaender ³⁷	Rats	Doxorubicin and Methotrexate	<ul style="list-style-type: none"> • Diminished bone formation • The number of osteoblasts and osteoclasts was unaffected
1992/Khoo ⁶⁸	Rabbits	Doxorubicin	<ul style="list-style-type: none"> • Impairment of bone healing
2001/Hausman ⁵⁴	Rats	TNP-470	<ul style="list-style-type: none"> • Result resembles atrophic non-union • Suppressed callus and woven bone
2001/Hazan ⁵⁵	Humans	na	<ul style="list-style-type: none"> • High increase of non-union rates
2001/Subasi ¹¹⁵	Rabbits	Methotrexate (osteosarcoma regimen)	<ul style="list-style-type: none"> • This regimen had no effect on distraction osteogenesis
2003/Gravel ⁴⁷	Goats	Doxorubicine	<ul style="list-style-type: none"> • No effect on distraction osteogenesis
2004/Li ⁷⁵	In vitro (MSCs)	Arsenic trioxide, Busulphan, Cyclophosphamide, Methotrexate, Cytarabine, Etoposide, Dexametasone, Vincristine, Paclitaxel	<ul style="list-style-type: none"> • Variability of affection • Paclitaxel, vincristine, etoposide and cytarabine had higher degree of affection
2004/Tortolani ¹¹⁷	Rabbits	Doxorubicin	<ul style="list-style-type: none"> • Inhibition of spinal fusion

na: not available.

Corticóides e reparo ósseo

Table 3 The effect of steroids on fracture healing

Year/study	Model used	Drug	Outcome
1951/Blunt ¹³	Rabbits	Cortisone	• Decreased callus formation
1951/Sissons ¹¹¹	Rabbits	Cortisone	• Retardation of healing • Abnormal histological appearance
1952/Key ⁶⁷	Rats	Cortisone	• No inhibitory effect encountered
1964/Weiss ¹²⁴	Rats	Cortisone	• No inhibitory effect encountered
1966/Murakami ⁸⁶	Guinea pigs	Cortisone	• Retardation of bone healing
1972/Ehrlich ^{31,32}	Rats	Prednisone	• Inhibition of collagens synthesis
1986/Sato ¹⁰⁶	Rats	Dexamethasone	• Retardation of mineralisation
1992/Hogevold ⁵⁸	Rats	Methylprednisolone	• No inhibitory effect encountered
2000/Waters ¹²²	Rabbits	Prednisone	• Lower callus size and mineral content • Chronic administration resulted in weaker bone
2001/Sawin ¹⁰⁷	Rabbits	Dexamethasone	• Inhibition of bone graft incorporation in spinal fusion
2002/Luppen ⁷⁸	Rabbits	Prednisolone	• 25% lower callus area and 55% inhibition of torsional strength
2005/Aslan ⁶	Rats	Prednisone	• No inhibitory effect encountered

A administração aguda de corticóides em humanos não acarreta prejuízo no reparo ósseo

Corticóides e reparo tecidual em geral

Table 2 Effect of chronic corticosteroid administration on wound healing in humans

Study (Ref)	N	Equivalent dose (mg/day of prednisone)	Duration	Wound complication rate (control %)
Numerous Diseases				
Green, 1965 ⁶¹	38	10.8 ± 7	1 day–13 mo	29 (NR)
Engquist et al, 1974 ⁶⁰	100	18 pts: <10 74 pts: >10	19 pts: <1 yr 73 pts: >1 yr	44 (22)
Reding et al, 1990 ⁶²	55	51 (15–480)	18 mo	13 (2)
Rheumatoid Arthritis				
Popert & Davis, 1958 ⁶⁸	15	12.4 ± 3	25 ± 16 mo	20
Garner et al, 1973 ⁶⁵	100	2.5–15	Variable	71 (25)
Escalante & Beardmore, 1995 ⁶⁶	204	6.4 ± 2.2	NR	15.9
Jain et al, 2002 ⁶⁷	30	8.8 (4.25–20)	NR	3.3 (9.5)
Inflammatory Bowel Disease				
Price, 1968 ⁷⁴	80	NR	NR	15 (40)
Knudsen et al, 1976 ⁷²	41	>40	NR; >2 mo	66 (27)
Allsop & Lee, 1978 ⁶⁹	162	>20	NR	31
Post et al, 1991 ⁷³	265	NR	NR; preoperative	19 (7)*
Ziv et al, 1996 ⁷⁵	361	169 pts: >20 192 pts: <20	NR; >1 mo	8 (6) 12 (6)
Brewer et al, 2003 ⁷⁰	219	73 pts: >20 146 pts: <20	NR NR	18 (11) 12 (11)

N is the number of patients or the number of operations from each study in the experimental group. Dose is adjusted for equivalent doses of prednisone (1 = 1 mg/day prednisone). Duration refers to the number of months that patients took corticosteroids preoperatively. Wound complication rate is defined as disruption, persistent drainage, dehiscence, infection, or wound failure. In cases where no control group was included, there are no parenthetical numbers provided. *Indicates there was a statistically significant difference in complication rates between the experimental and control groups.

NR = not reported; pts = patients.

A administração crônica, mas não a aguda, de corticóides em humanos acarreta prejuízo no reparo

Corticóides e cirurgia odontológica

Table 5. SELECTED ARTICLES IN ORAL SURGERY (CORTICOSTEROID ADMINISTRATION AND INFECTION)

Study	Randomized- Controlled Trial	Jaw Arch	Infections in CS Group	Subjects in CS Group	Infections in Control Group	Subjects in Control Group	Mean Age (yr)	Original Steroid Used	Original Dose (mg)	Method of Delivery	Time of Steroid Delivery
Esen et al, ⁴⁹ 1999	Yes	Mand	0	20	0	20	22	Methylprednisolone sodium succinate	125	IV	Preop
Holland, ⁵⁷ 1987	Yes	Mand	0	20	0	20	23.4	Methylprednisolone	40	IV	Preop
Milles et al, ⁵⁸ 1993	Yes	Max/mand	0	11	1	11	24	Methylprednisolone	20	IV	Preop
Skjelbred and Løkken, ⁵² 1982	Yes	Max/mand	0	24	0	24	24	Betamethasone	9	IM	Preop
Skjelbred and Løkken, ⁵³ 1982	Yes	Max/mand	0	12	0	12	23	Betamethasone	9	IM	Postop
Neupert et al, ⁶³ 1992	Yes	Max/mand	2	60	2	60	18-24	Dexamethasone	4	IV	Preop
Baxendale et al, ⁵⁹ 1993	Yes	Max/mand	0	25	0	25	22.8	Dexamethasone	8	Oral	Preop
Schmelseizen and Frölich, ⁶⁰ 1989	Yes	Max/mand	5	26	3	25	18	Dexamethasone	6	Oral	Preop + postop
Pedersen, ⁶⁹ 1985	Yes	Mand	0	30	0	30	22	Dexamethasone	4	IM	Preop

Abbreviations: CS, corticosteroid; IM, intramuscular; IV, intravenous; mand, mandibular teeth surgically removed; max, maxillary teeth surgically removed; postop, postoperative; preop, preoperative.

NOTE. Table lists the number of infections in the CS versus control groups in various clinical oral surgery trials, in which a CS was administered. All studies were randomized, double-blind studies tested against placebo (saline).

Dan, Thygesen, and Pinbolt. *Corticosteroids in Oral/Orthognathic Surgery*. *J Oral Maxillofac Surg* 2010.

O uso de corticóides em período que antecede a cirurgia oral menor ou a cirurgia ortognática não aumentou o risco de infecção e de atraso no reparo tecidual

Antibióticos e reparo ósseo

Table 4 The effect of antibiotics on fracture healing

Year/Study	Model used	Drug	Outcome
1971/Gudmundson ⁴⁹	Mice	Oxytetracycline	<ul style="list-style-type: none">• No significant effect
1996/Mont ⁸³	In vitro	Ciprofloxacin	<ul style="list-style-type: none">• Inhibition of cellular proliferation• No effect on proteoglycans synthesis, morphology and stain pattern
2000/Huddleston ⁶⁰	Rats	Ciprofloxacin	<ul style="list-style-type: none">• Decreased torsional strength and stiffness• Alternations of cartilage morphology
2002/Alkan ³	Rats	Doxycycline	<ul style="list-style-type: none">• No effect
2002/Lamparter ⁷²	Rats	Doxycycline	<ul style="list-style-type: none">• Inhibition of matrix metalloproteinases
2003/Perry ⁹²	Rats	Levofloxacin and Trovafloxacin	<ul style="list-style-type: none">• Decrease in strength• Inferior quality of callus
2004/Kim ⁶⁹	Rats	Gentamicin and Tetracycline	<ul style="list-style-type: none">• Decreased bone formation
2004/Haleem ⁵³	Rats	Gentamicin and Vancomycin	<ul style="list-style-type: none">• No effect encountered
2005/Tuncay ¹¹⁸	Rats	Norfloxacin, Ofloxacin, Pefloxacin and Ciproxacin	<ul style="list-style-type: none">• Retardation of healing occurred in all fluoroquinolone treated animals• Differences in terms of healing inhibition were encountered

Os antibióticos têm efeito direto sobre a cartilagem, interferindo na ossificação endocondral e nos centros de crescimento

Anticoagulantes e reparo ósseo

Table 5 The effect of anticoagulants on fracture healing

Year/study	Model used	Drug	Outcome
1955/Stinchfield ¹¹³	Rabbits and dogs	Heparin and Dicumarol	<ul style="list-style-type: none">• Delayed healing• Fibrous accumulation in callus
1996/Muir ⁸⁴	Rats	Heparin	<ul style="list-style-type: none">• Decreased rates of bone formation• Increased rates of resorption
1997/Muir ⁸⁵	Rats	Heparin and LMWH	<ul style="list-style-type: none">• LMWH has milder effect on bone formation
2000/Street ¹¹⁴	Rabbits	LMWH	<ul style="list-style-type: none">• Retardation of bone healing
2002/Kock ⁷⁰	Rabbits	Heparin and LMWH	<ul style="list-style-type: none">• Heparin impaired the filling of bore holes whilst LMWH had no effect

LMWH: low-molecular-weight heparin.

A heparina parece diminuir o volume do trabeculado ósseo de forma irreversível

NSAIDs e reparo tecidual em geral

Table 1 Summary of relevant studies

Drug	Animal studies	Human studies	Quality of evidence	Summary of effects
Soft tissue healing				
Indomethacin	3	0	Inconclusive	No detrimental effect
Piroxicam	2	0	Inconclusive	No detrimental effect
Celecoxib	2	0	Inconclusive	No detrimental effect
Soft tissue to bone healing				
Indomethacin	2	0	Strong	Decreased biomechanical strength of healing tendon
Celecoxib	2	0	Strong	Decreased biomechanical strength of healing tendon
Bone healing				
Indomethacin	12	1	Strong	Impairs bone healing
Diclofenac	4	0	Weak	Impairs bone healing
Ibuprofen	3	0	Inconclusive	No detrimental effect
Piroxicam	1	1	Strong	No detrimental effect
Ketorolac	4	1	Weak	No detrimental effect
Celecoxib	6	0	Inconclusive	Possible detrimental effect

Quality of evidence: Inconclusive: mixed results. <70 % of studies. Weak: majority of studies in agreement with one result. >70 % of studies. Strong: overwhelming evidence of one result. >85 % of studies

NSAIDs parecem não interferir no reparo de tecidos moles, mas de tecido ósseo sim (ex. indometacina)

Table 6 The effect of NSAIDs on fracture healing

Year/study	Model used	Drug	Outcome
1979/Sudmann ¹¹⁶	Rabbits	Indomethacin	<ul style="list-style-type: none"> • Inhibition of haversian remodelling
1982/Elves ³⁴	Rats	Indomethacin	<ul style="list-style-type: none"> • No effect on repairing drill holes • Higher effect on older animals • Histological evidence of increased fibrous accumulation with decrease of osteogenesis and remodelling
1988/Davis ²³	Humans	Fluriprophen	<ul style="list-style-type: none"> • No effect on Colles' fracture
1990/Keller ⁶⁵	Rabbits	Indomethacin	<ul style="list-style-type: none"> • Effect depends on the extent of trauma
1993/Adolphson ²	Humans	Piroxicam	<ul style="list-style-type: none"> • No effect on Colles' fracture
1998/Reikeraas ¹⁰⁰	Rats	Ketorolac Trom. and Indomethacin	<ul style="list-style-type: none"> • Ketorolac Tromethamine had no effect on healing of rat osteotomy whilst indomethacin impaired healing
1998/Glassman ⁴³	Humans	Ketorolac	<ul style="list-style-type: none"> • High rate of non-union in spinal fusion
1999/Sell ¹⁰⁸	In vitro	Diclofenac	<ul style="list-style-type: none"> • MSCs proliferation decreased by 18% and osteoblastic proliferation by 2.5%
1999/Wumig ¹²⁶	Humans	Indomethacin	<ul style="list-style-type: none"> • No effect on prosthetic loosening after cementless hip arthroplasty
2000/Gianroudis ⁴¹	Humans	Ibuprophen and Diclofenac	<ul style="list-style-type: none"> • Increased risk for non-union
2003/Beck ⁹	Rats	Diclofenac	<ul style="list-style-type: none"> • Impaired bone healing, low bending stiffness and bone strength
2002/Long ⁷⁷	Rabbits	Celecoxib	<ul style="list-style-type: none"> • No effect on spinal fusion
2003/Gerstenfeld ⁴⁰	Rats	Ketorolac, Parecoxib	<ul style="list-style-type: none"> • Cox-2 selective parecoxib has small effect on delaying fracture healing • Ketorolac had the highest effect
2003/Giordano ⁴²	Rats	Tenoxicam	<ul style="list-style-type: none"> • Delays in bone healing occurred
2003/Riew ¹⁰⁴	Rabbits	Indomethacin	<ul style="list-style-type: none"> • Inhibition in early phase of healing
2004/Brown ¹⁴	Rat	Celecoxib	<ul style="list-style-type: none"> • No effect on fracture healing
2004/Goodman ⁴⁴	Rabbits	Rofecoxib	<ul style="list-style-type: none"> • Less bone ingrowth • Lower effect if given short-term
2005/Reuben ¹⁰¹	Humans	Celecoxib, Rofecoxib and Ketorolac	<ul style="list-style-type: none"> • Celecoxib, rofecoxib and low dose of ketorolac had no effect on spinal fusion • High dose of ketorolac increased the rate of non-union
2005/Reuben ¹⁰²	Human	Celecoxib	<ul style="list-style-type: none"> • Short-term administration had no effect on spinal fusion
2005/Endo ³⁵	Rats	Etodolac	<ul style="list-style-type: none"> • Bone healing was impaired.
2005/Persson ⁹³	Rats	Indomethacin	<ul style="list-style-type: none"> • The drug inhibited bone formation in heterotopic demineralised allogeneic bone matrix but had no effect on autografts
2006/Pountos ⁹⁶	In vitro	Diclofenac, Ketorolac, Parecoxib, Ketoprofen, Piroxicam, Meloxicam and Lomoxicam	<ul style="list-style-type: none"> • No effect on MSCs proliferation when cellular medium was supplemented with expected plasma concentrations. • Negative effect encountered when toxic concentrations used (over 100 µg/ml). • NSAIDs in plasma concentrations had no effect on osteogenesis
2006/Krischak ⁷¹	Rats	Diclofenac	<ul style="list-style-type: none"> • Impairment of callus maturation
2006/Leonelli ⁷⁴	Rats	Rofecoxib and Ibuprophen	<ul style="list-style-type: none"> • Non-union in 65% of rofecoxib treated and 17.6% of ibuprophen treated rats

NSAIDs e reparo ósseo

Indometacina e diclofenaco interferem no processo de reparo ósseo