Mucoviscidose et conséquences osseuses
Conséquences de la maladie et des traitements, surveillance

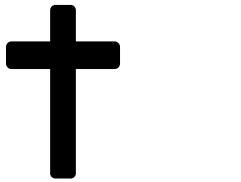
Dr François ROBIN

MCU-PH Service Rhumatologie

CHU Rennes

Quelques généralités nécessaires

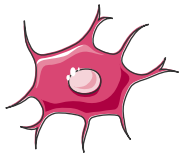
Les acteurs cellulaires du métabolisme osseux



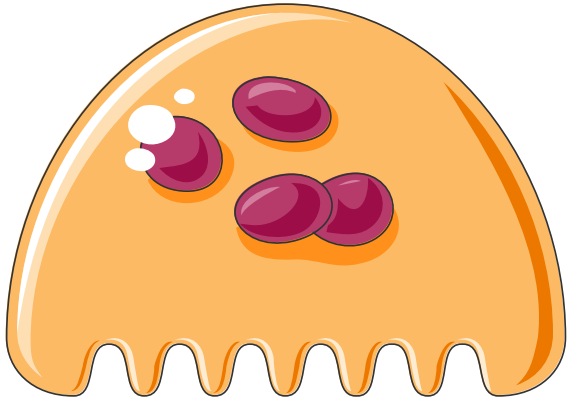
Apoptose

Cellules bordantes

Ostéoblaste mature



Ostéocyte mature



Ostéoclaste mature

Bilezikian JP, 1re éd. Wiley. 2018.
Bonewald LF. J Bone Miner Res. 2011.
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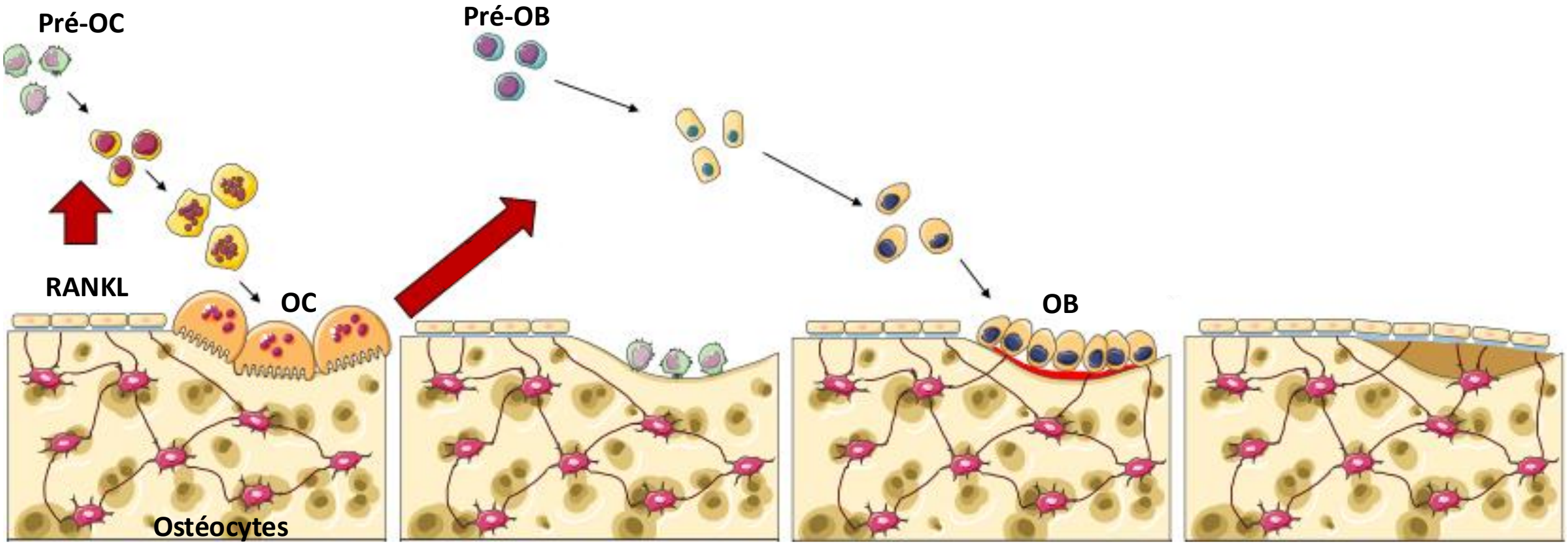
Notion de Basic Multicellular Unit



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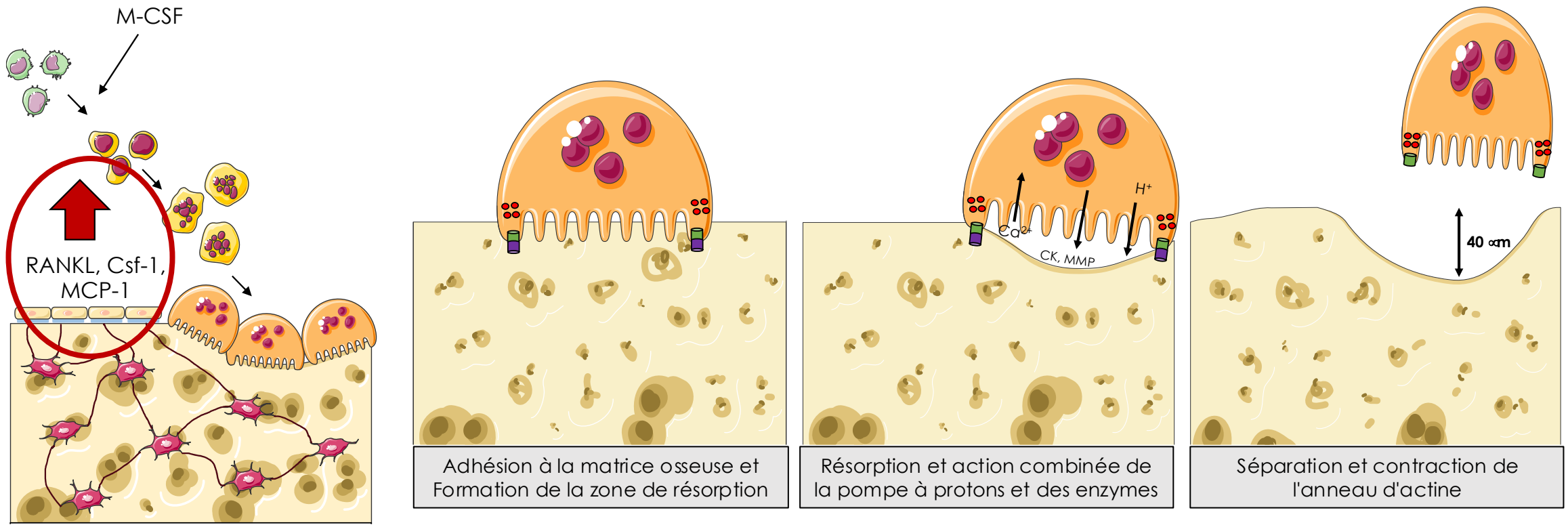

Arnett TR, Bone. 2018.
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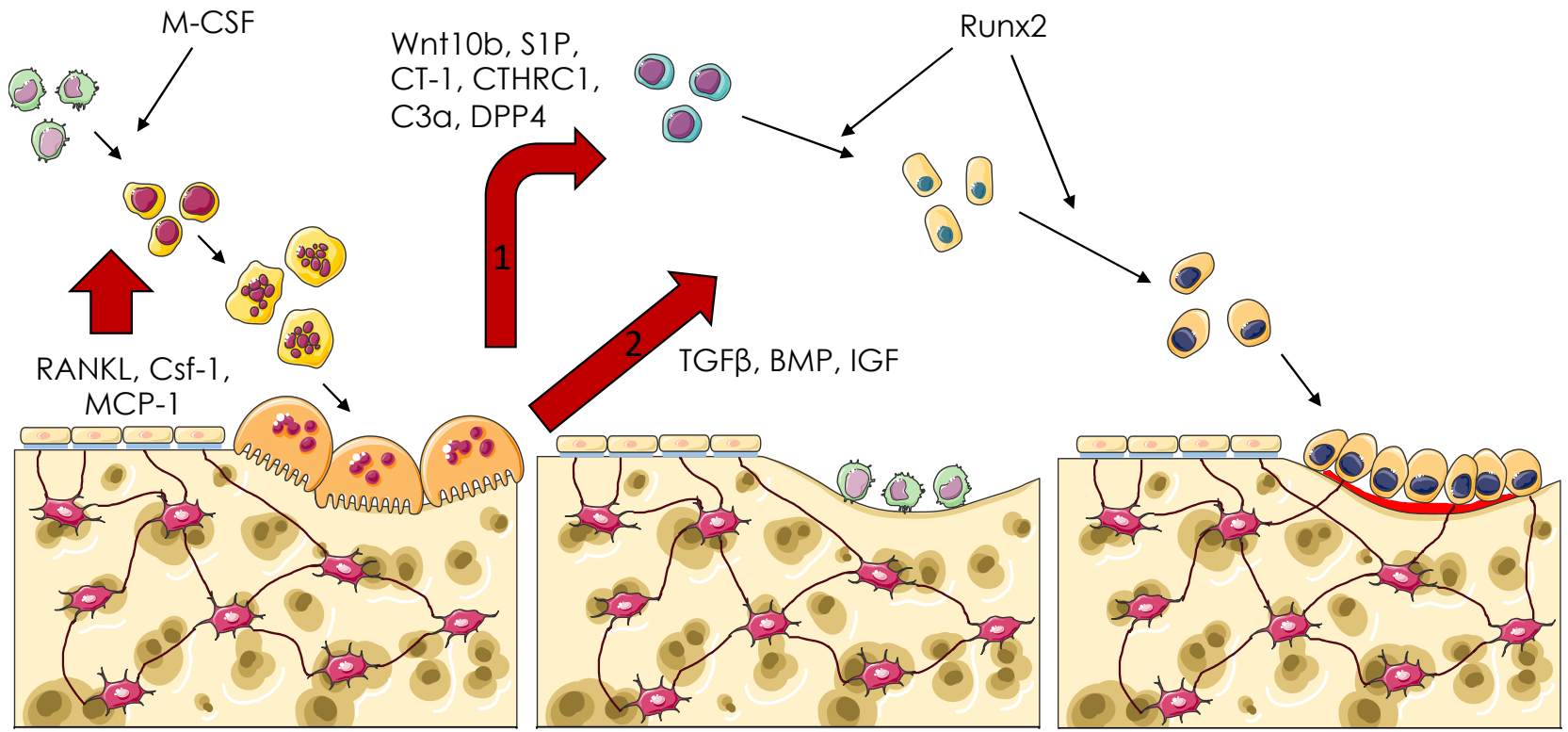
Formation osseuse



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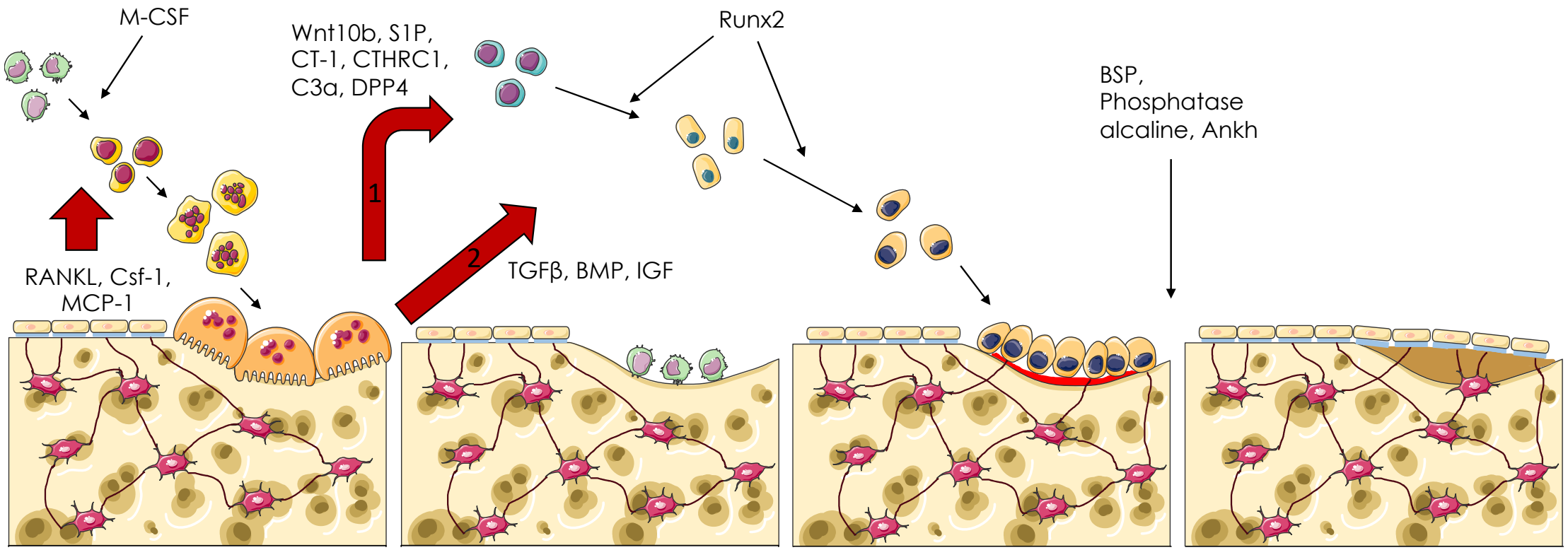
Finalisation



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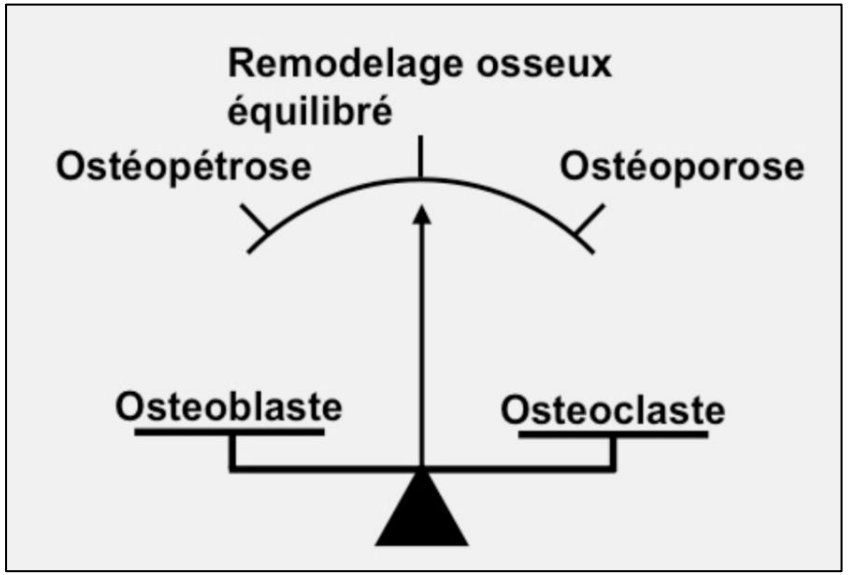
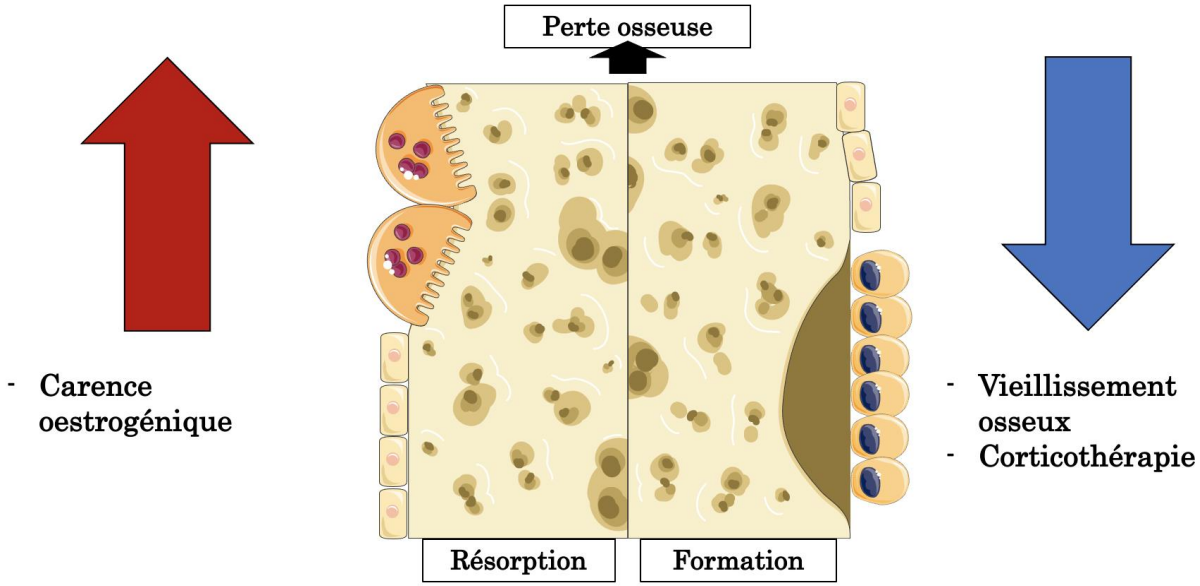
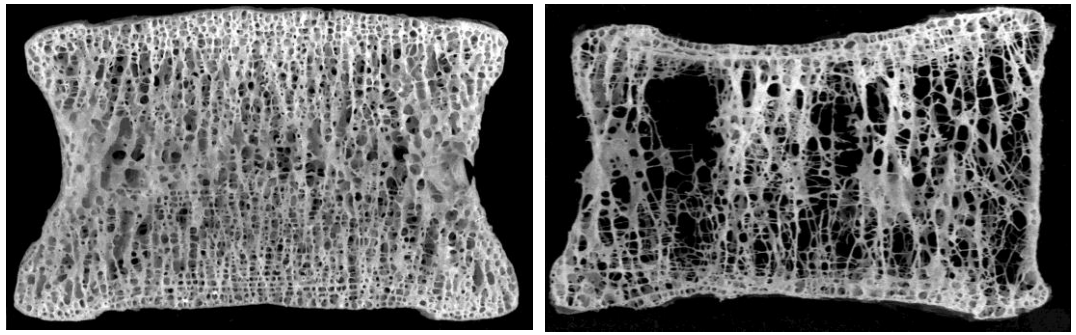
Le risque ? Le déséquilibre

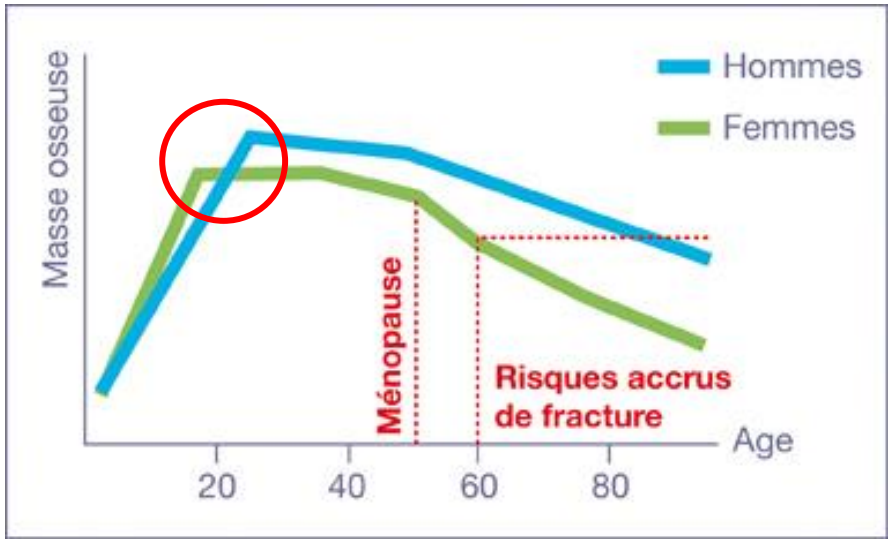


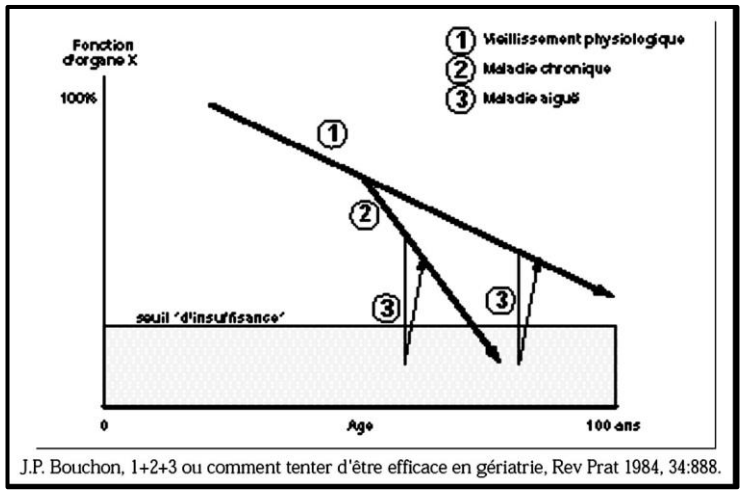




Willers C, Arch Osteoporos. 2022.
Reginster JY, Bone. 2006. .

Autre notion oubliée, le pic de masse osseuse





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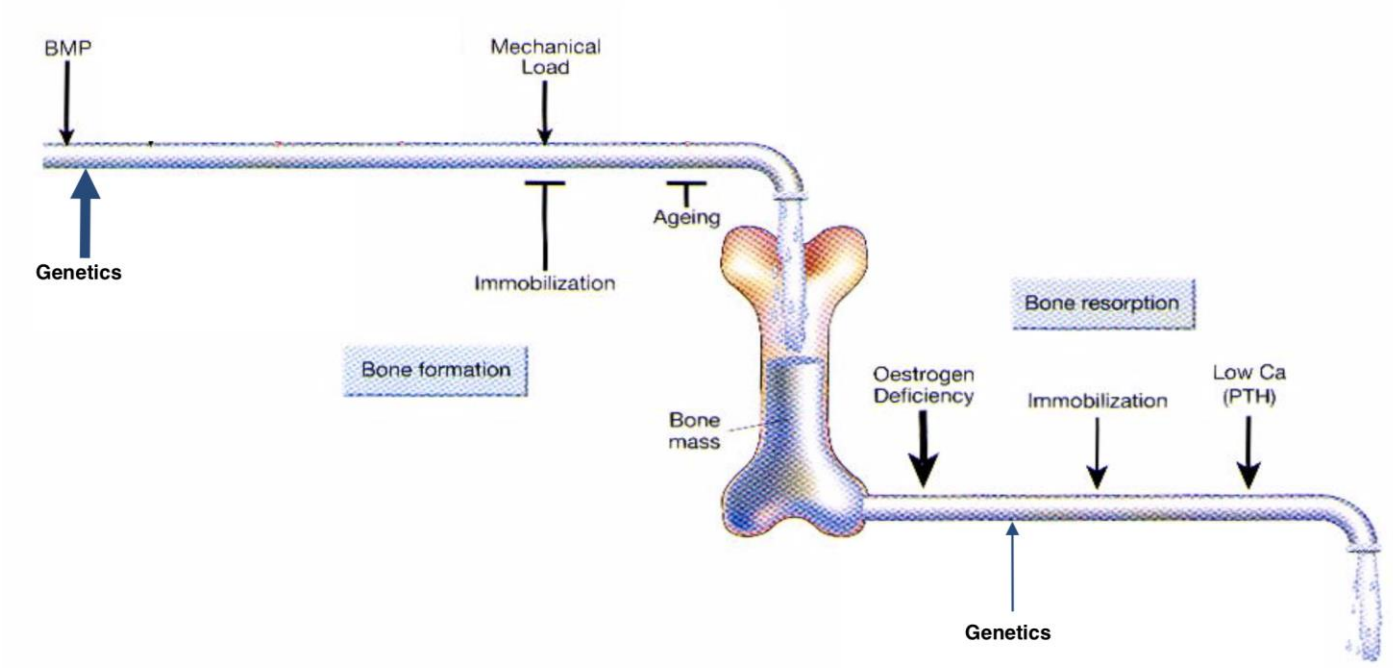
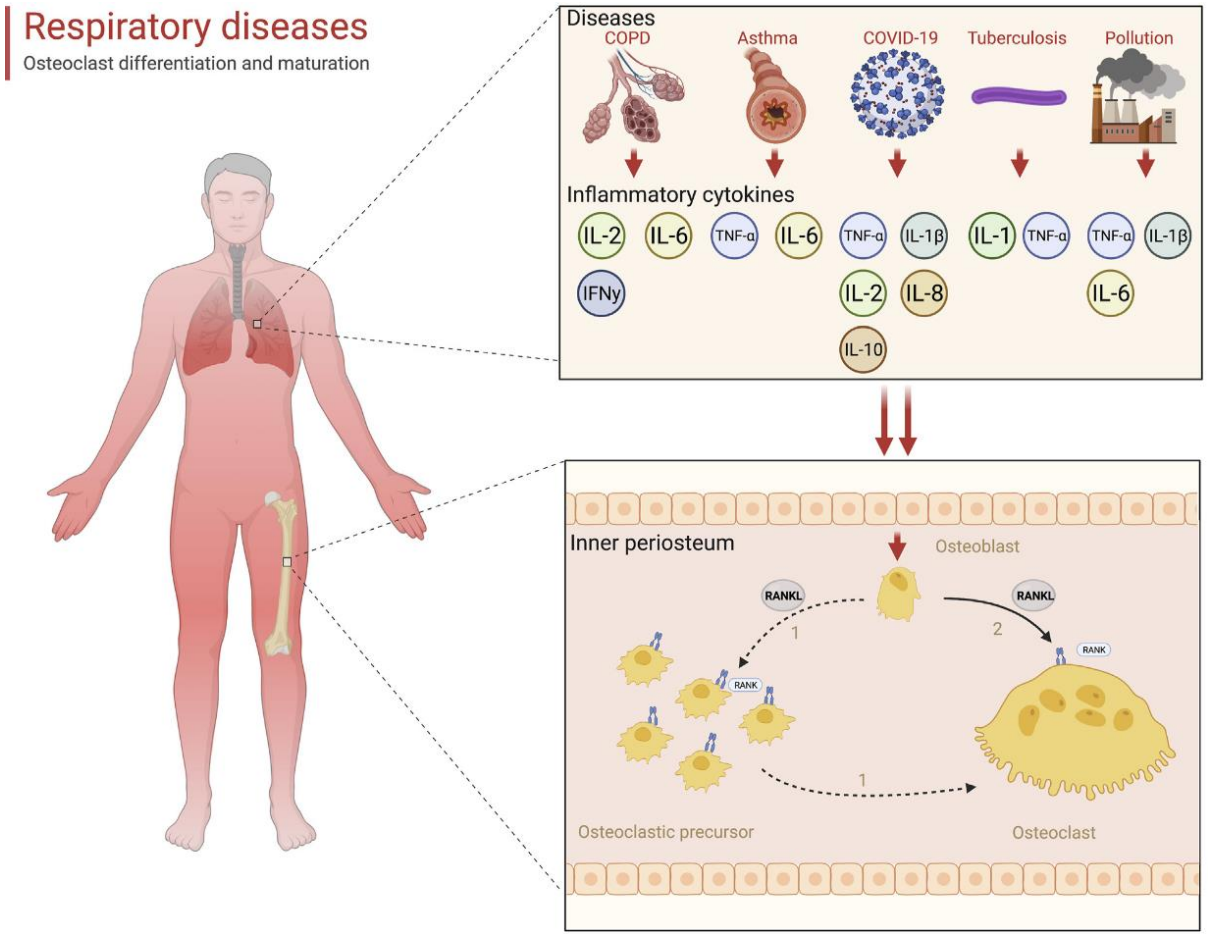
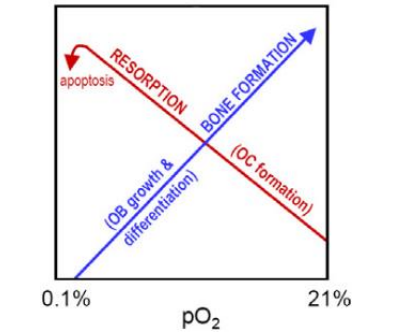


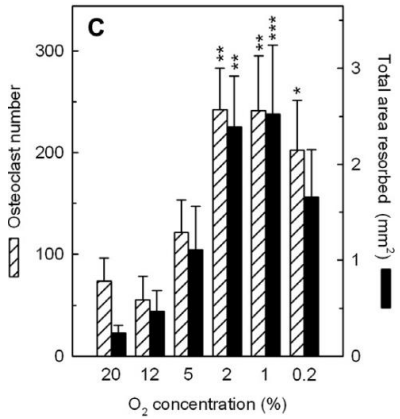
Harada S, et al. Nature. 2003

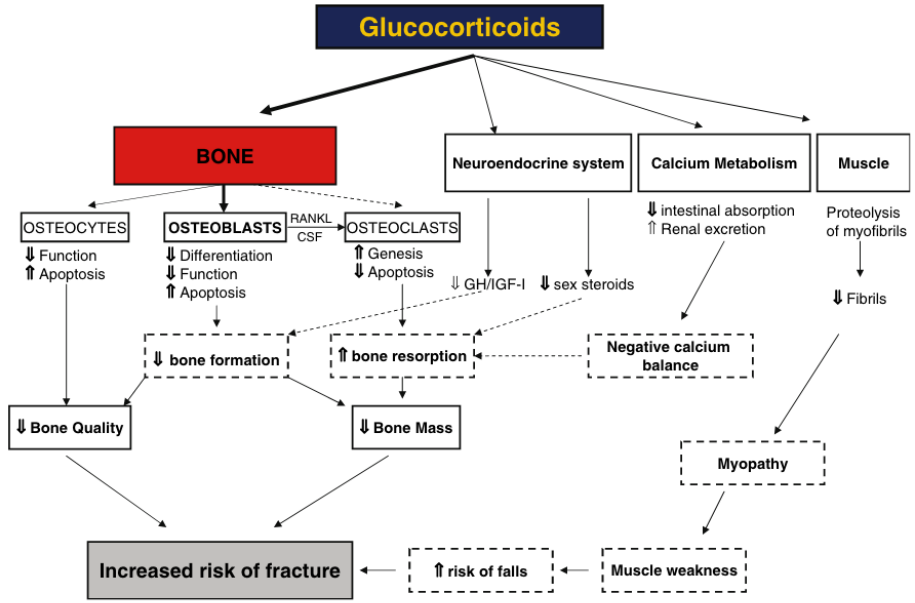
Poumons et Os en général

Poumons -> Os, quelles sont les causes ?



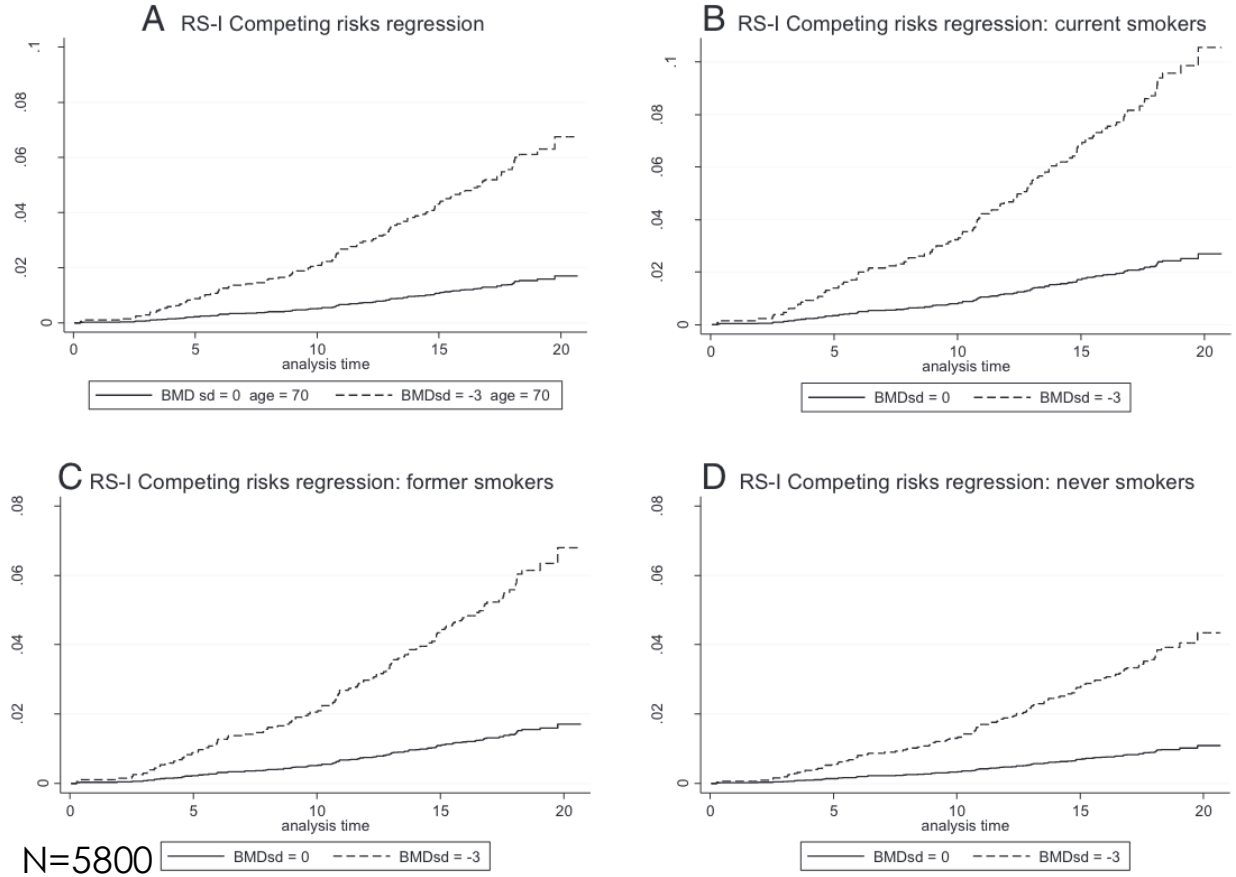






Ma Y, et al. Front Physiol 2022
Canalis E, et al. Osteoporos Int 2007
Arnett TR. Archives of Biochemistry and Biophysics 2010

Os -> Poumons, quels sont les risques ?



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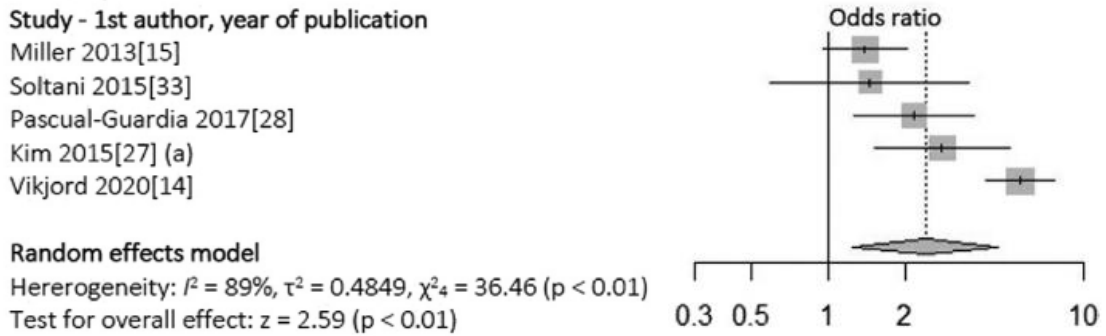
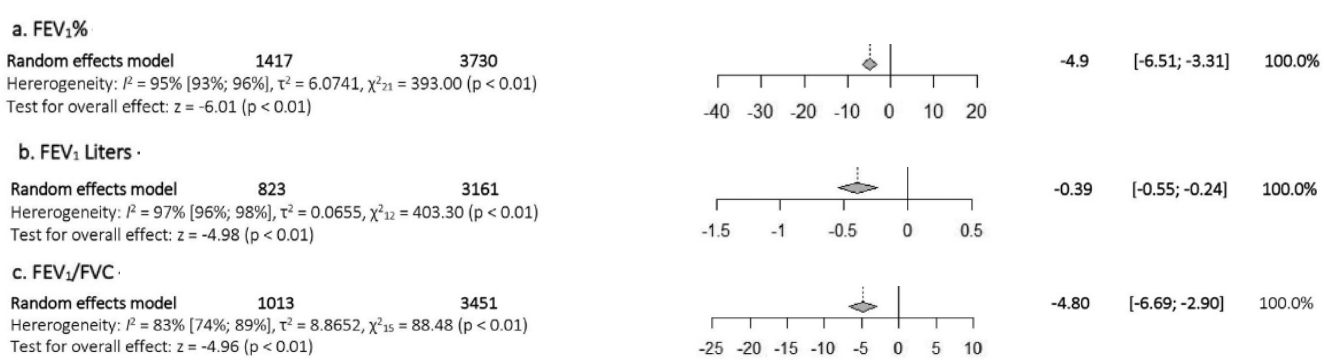
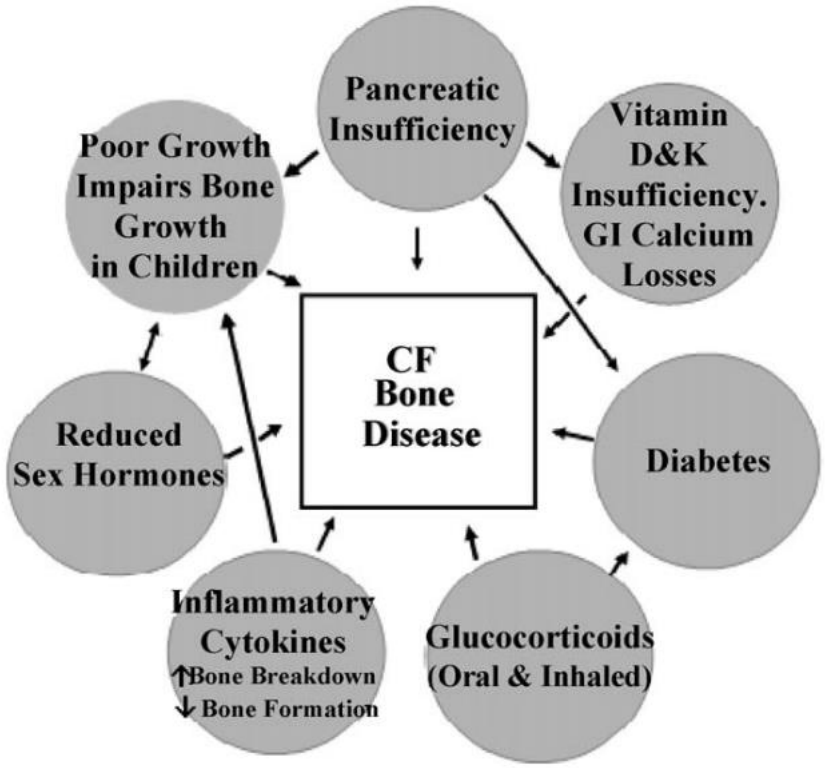


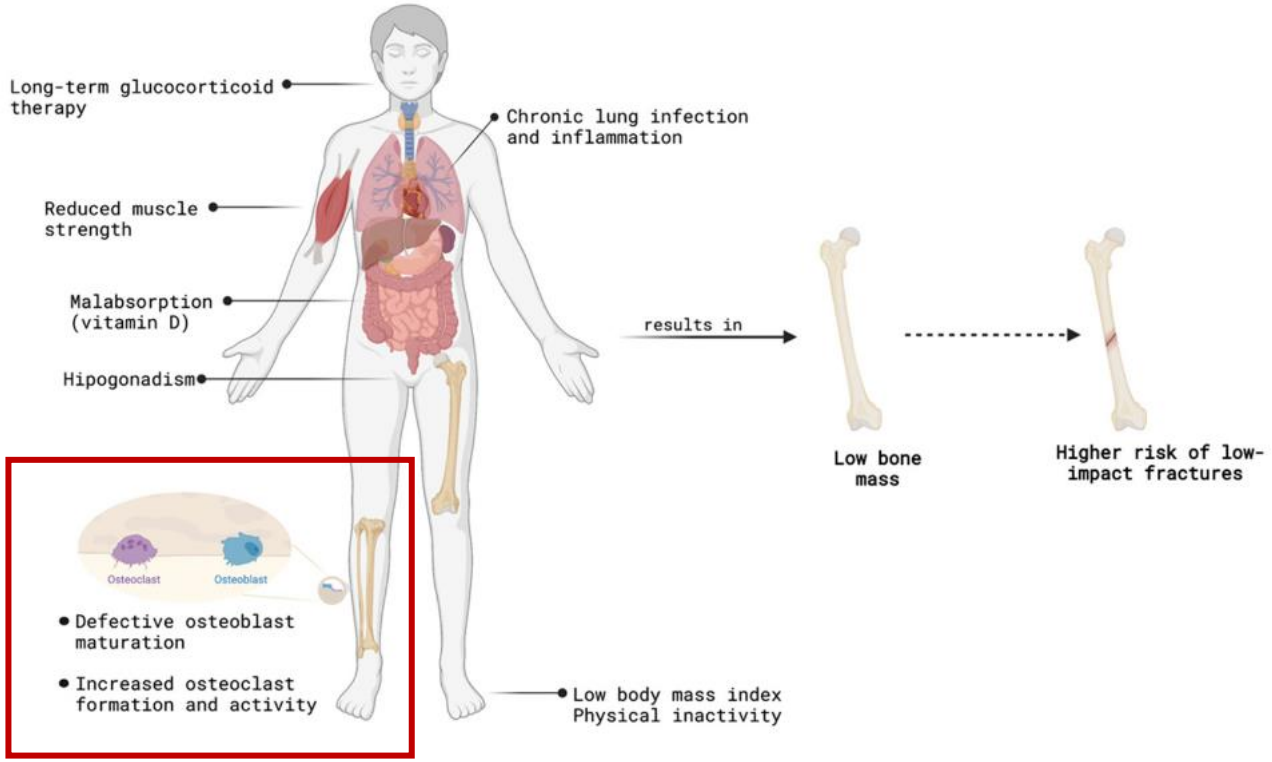


Campos-Obando N, et al. JCEM 2014.
Kakoullis L, et al. Joint Bone Spine 2022.

Mucoviscidose et Os, pourquoi et comment ?

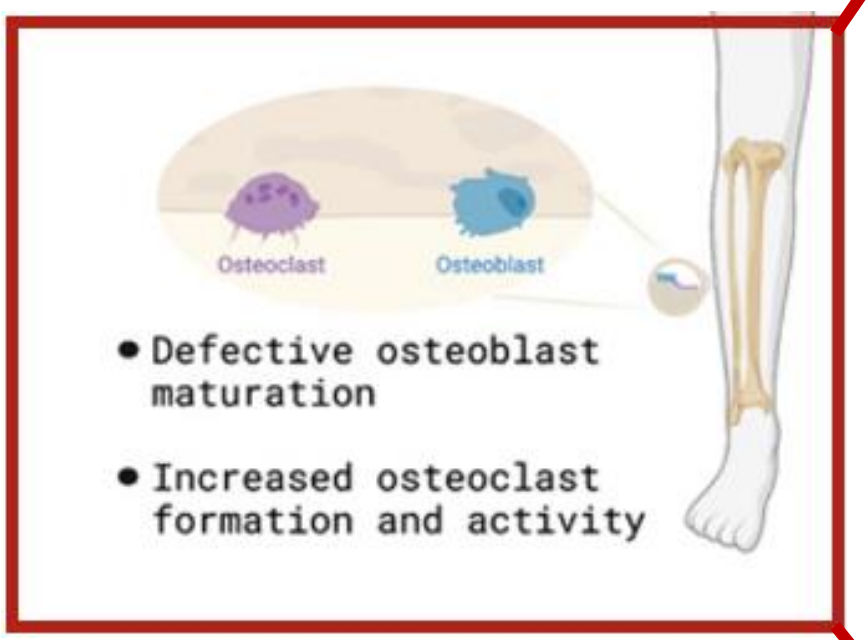
Mécanismes généraux de la perte osseuse dans le contexte de mucoviscidose

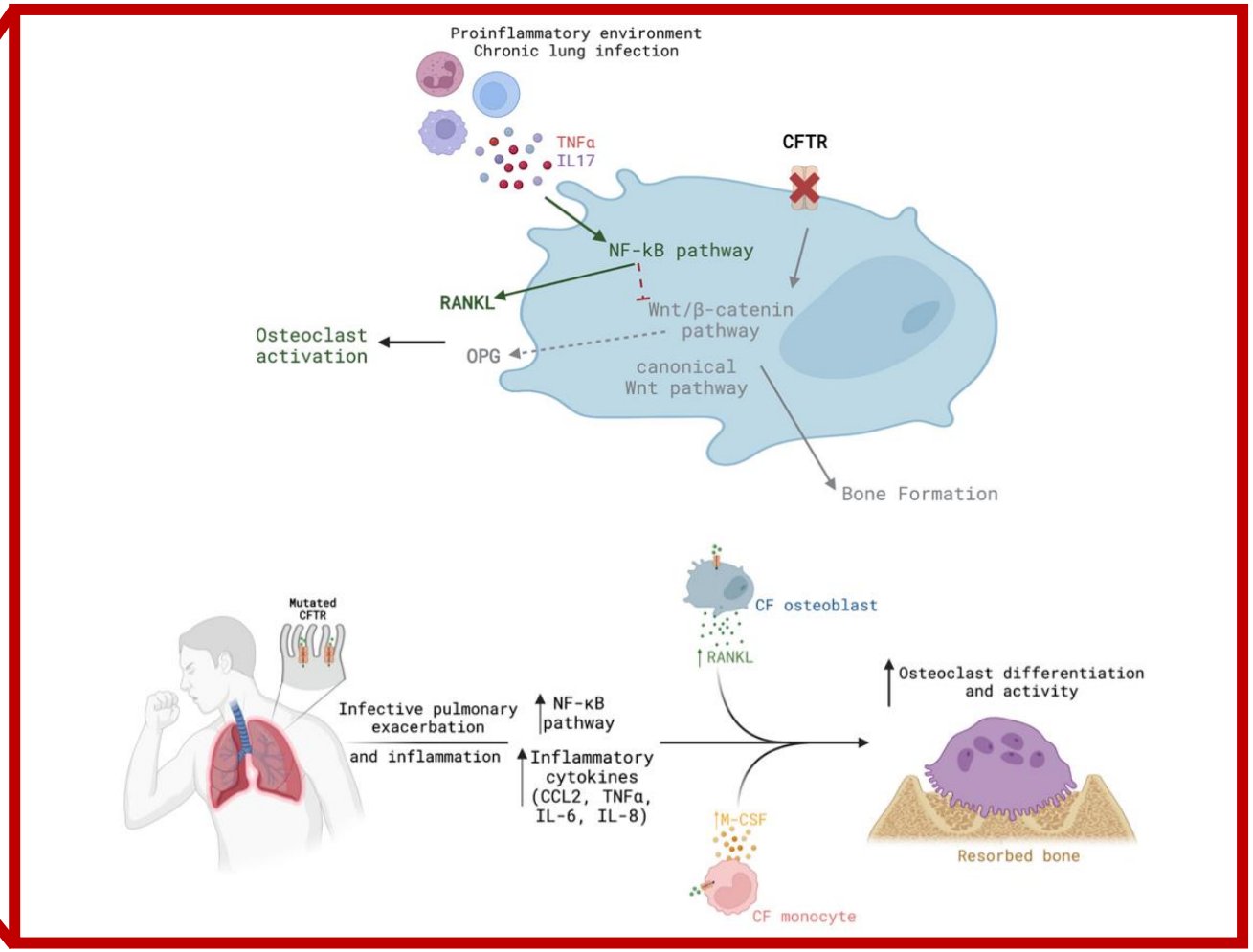




Sermet-Gaudelus I, et al. Paediatric Respiratory Reviews 2009.
Fonseca Ó, et al. Biomolecules 2023.

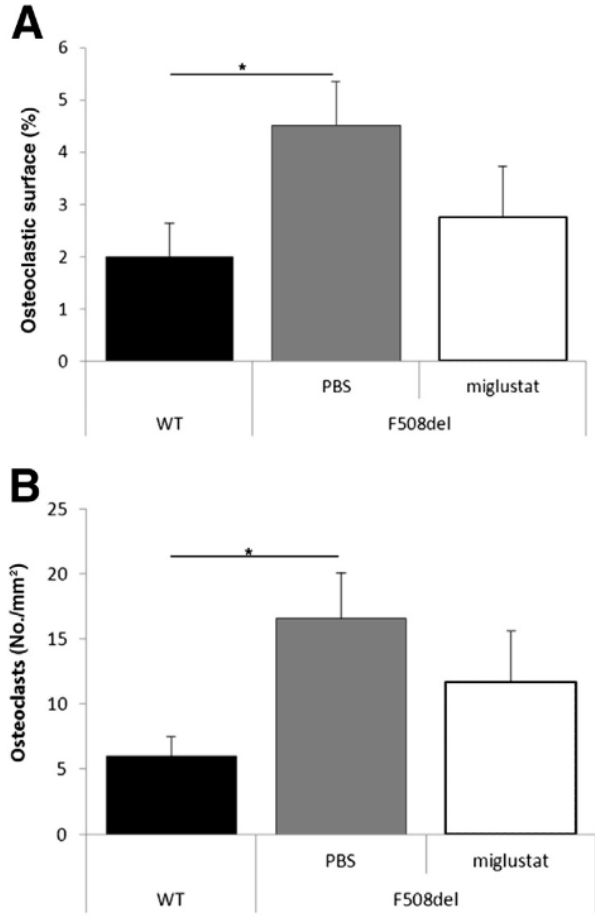
Mécanismes cellulaires de la perte osseuse dans le contexte de mucoviscidose



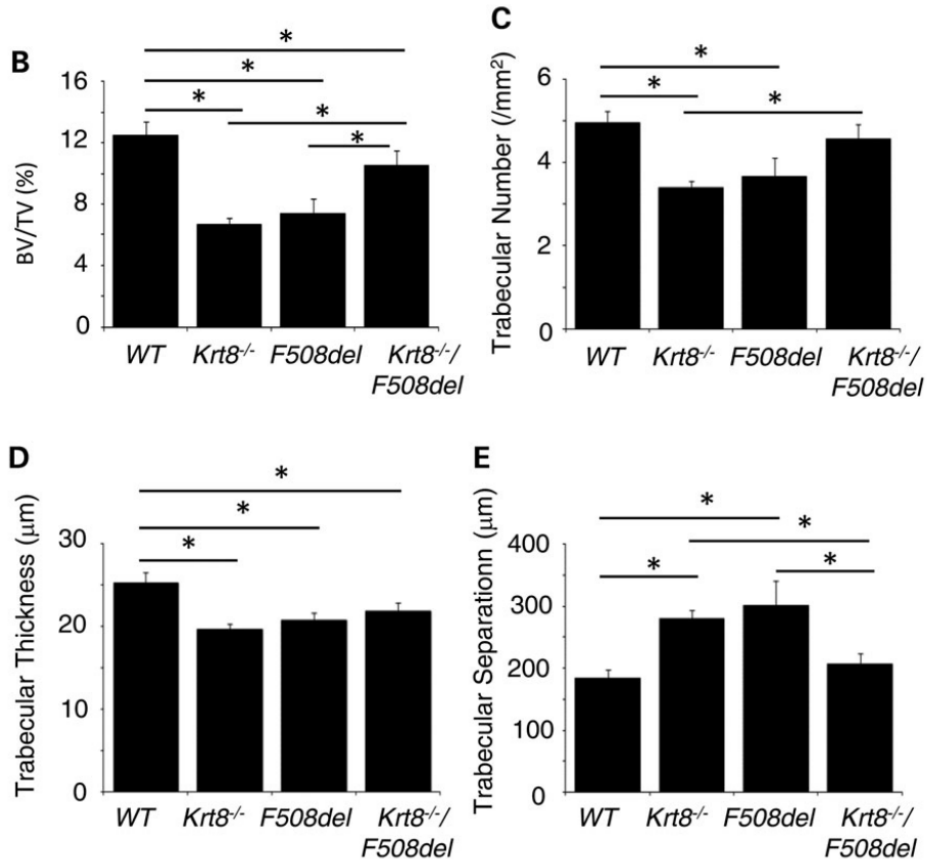


Fonseca Ó, et al. Biomolecules 2023.

Effet rescue ? Piste thérapeutique ? Efficacité cellulaire de l'action sur CFTR



Effet rescue partiel de l'action sur CFTR

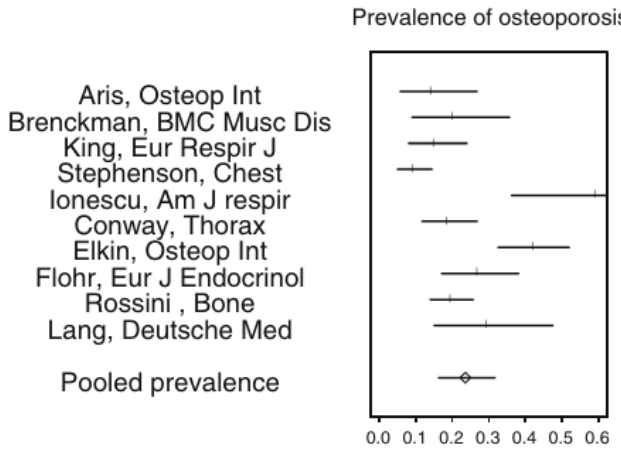


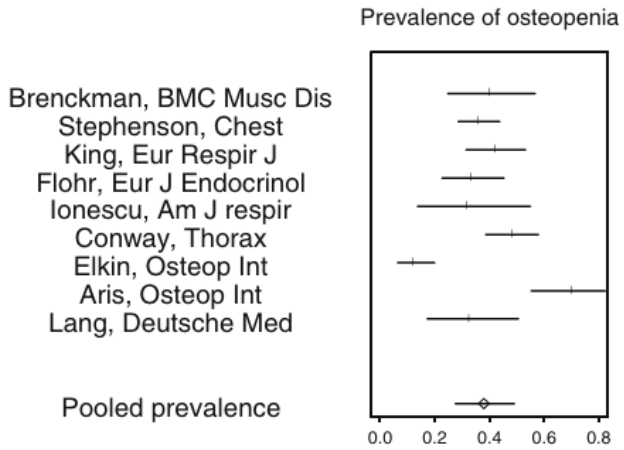
Effet attendu d'une action sur la keratine 8 ?

Le Henaff C, et al. Hum Mol Genet 2016.
Le Henaff C, et al. The American Journal of Pathology 2014.

Proportion de population à risque et données de méta-analyse dans la mucoviscidose

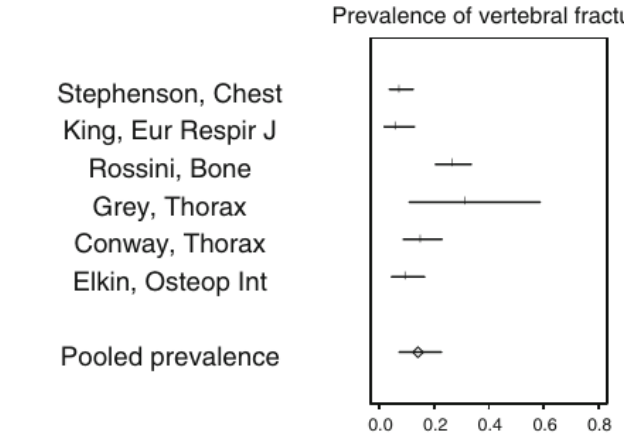
23,5%

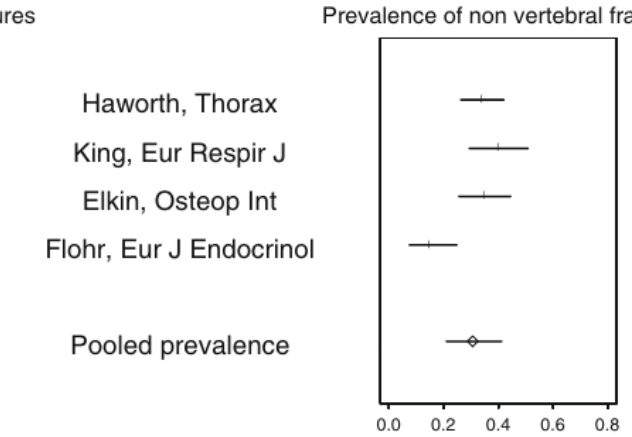




38%

14%





19,7%

Paccou J. Calcif Tissue Int 2010.

Evolution attendue de la DMO, diminution avec l'âge

Table 1. Baseline demographic and clinical characteristics of the study population measured at first DXA scan ($n = 500$).

Variable	Frequency
Age, years median (IQR)	28.4 (26.1-33.6)
Males	296 (59.2%)
Race	
White	478 (95.6%)
Non-white	21 (4.4%)
Genotype	
Heterozygous F508del	233 (46.6%)
Homozygous F508del	195 (39%)
Other	68 (13.6%)
Unknown	4 (0.8%)
Pancreatic insufficiency	405 (81%)
CF-related diabetes	233 (46.6%)
FEV_1 % predicted median (IQR)	60.2 (42.1-78)
Body mass index (kg/m^2) median (IQR)	22.4 (20.4-24.7)
25-hydroxyvitamin D level (nmol/l) median (IQR)	58 (41.5-77)
Missing	41 (8.2%)
LS BMD median (IQR)	1.1 (1-1.2)
Normal BMD (z-score > -2.0)	412 (82.4%)
Low BMD (z-score ≤ -2.0)	73 (14.6%)
Missing	15 (3%)
FN BMD median (IQR)	1 (09-1.1)
Normal BMD (z-score > -2.0)	444 (88.8%)
Low BMD (z-score ≤ -2.0)	37 (7.4%)
Missing	19 (3.8%)

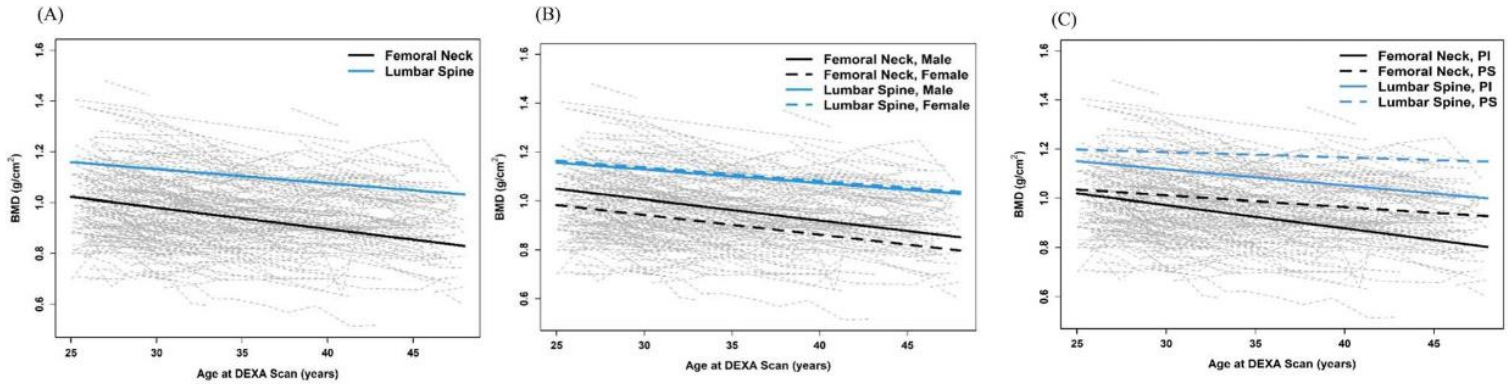


Figure 2. Individual trends in LS and FN BMD by (A) all, (B) sex, and (C) pancreatic status.

Table 2. Percent change in BMD using predicted values.

	Predicted BMD at age 25 y, g/cm^2 (95% CI)	Predicted BMD at age 48 y, g/cm^2 (95% CI)	% change between age 25 and 48 y	% change over 1 y
Overall				
FN	1.02 (1.01, 1.04)	0.83 (0.81, 0.85)	−18.8	−0.82
LS	1.16 (1.14, 1.17)	1.03 (1.01, 1.05)	−11.0	−0.48
Pancreatic insufficient				
FN	1.02 (1.0, 1.04)	0.80 (0.78, 0.82)	−21.3	−0.92
LS	1.15 (1.13, 1.17)	1.0 (0.98, 1.02)	−13.1	−0.57
Pancreatic sufficient				
FN	1.03 (1.0, 1.07)	0.93 (0.89, 0.97)	−10.4	−0.45
LS	1.20 (1.16, 1.24)	1.15 (1.11, 1.19)	−4.1	−0.18

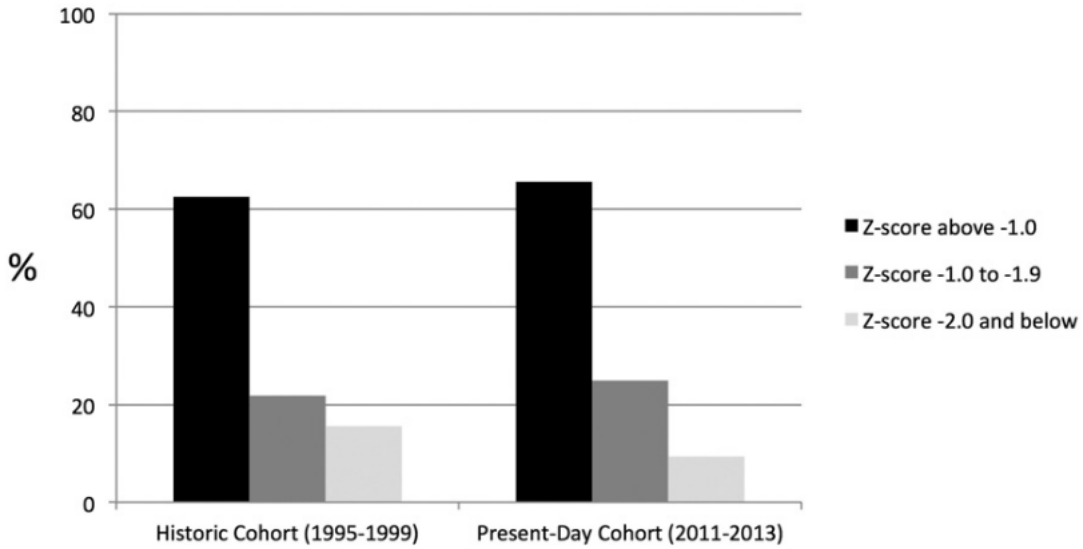
Abbreviation: CI, confidence interval.

Jad R, et al. Journal of Bone and Mineral Research 2024.

Est-ce mieux au cours du temps ? Amélioration des prises en charge ?

Table 1
Clinical and Demographic features of subjects with CF in the historic and present-day cohorts. BMI, body mass index; FEV1, % predicted forced expiration in 1 s.

	Mean (SD), median (range), or n (%)		
	Historic cohort (n = 32)	Present-day cohort (n = 32)	p-Value
Age (yr)	27.6 (7.0)	27.5 (7.7)	0.94
Female	19 (59%)	19 (59%)	–
Caucasian race	32 (100%)	32 (100%)	–
Height (cm)	167.0 (6.2)	166.3 (8.3)	0.71
Weight (kg)	57.7 (10.1)	58.5 (11.3)	0.76
BMI (kg/m^2)	20.6 (2.7)	21.1 (3.7)	0.52
Percent predicted FEV1 (%)	53.9 (21.8)	67.5 (28.2)	**0.039**
Calcium intake (mg/day)	1927 (426–4762)	1836 (539–9795)	0.81
Vitamin D intake (IU/day)	910 (77–1501)	1397 (36–8279)	0.09
Pancreatic insufficiency	26 (81%)	27 (84%)	0.74
CFTR genotype			
F508del/F508del	15 (47%)	11 (34%)	0.51
F508del/Other	12 (37.5%)	13 (41%)	
Other/Other	5 (15.5%)	8 (25%)	
Previous fracture	14 (44%)	13 (41%)	0.80
Age menarche (y)	13.6 (2.6)	12.7 (1.4)	0.16
Amenorrhea >6months	5 (26%)	1 (3%)	0.18
Pregnancy	7 (22%)	5 (16%)	0.56
Age pubarche (males)	12.5 (11–19)	13 (11–15)	0.75
Use of oral glucorticoids			
Current use	2 (6%)	1 (3%)	1.0
Previous use	14 (44%)	22 (69%)	**0.029**
Lifetime exposure (mo)	4.0 (8.7)	8.4 (10.4)	**0.012**
Current use of inhaled glucocorticoids	8 (25%)	22 (69%)	<**0.001**



	Unadjusted			Multivariable-adjusted		
DXA areal BMD	Historic cohort	Present-day cohort	p Value	Historic cohort	Present-day cohort	p Value
PA spine (g/cm^2)	0.983 ± 0.034	0.981 ± 0.034	0.94	0.987 ± 0.022	0.968 ± 0.023	0.59
Lateral spine (g/cm^2)	0.780 ± 0.017	0.803 ± 0.019	0.37	0.771 ± 0.019	0.809 ± 0.024	0.26
1/3 distal radius (g/cm^2)	0.723 ± 0.016	0.730 ± 0.012	0.68	0.731 ± 0.019	0.731 ± 0.014	0.99

Putman MS, et al. Journal of Cystic Fibrosis 2015.

Quels sont les facteurs de risque de perte osseuse ?

Table 1. Baseline Study Population Characteristics

	Overall ($n = 234$)	Normal BMD ($n = 111$)	Lower than expected BMD ($n = 123$)	p Value
Age, mean (SD)	32.9 (11.88)	31.5 (10.17)	34.2 (13.10)	0.089
Male, *n* (%)	107 (45.9)	40 (36.4)	67 (54.5)	0.006
Race, non-White, *n* (%)	16 (7.0)	5 (4.6)	11 (9.1)	0.180
Genotype, *n* (%)				0.945
Homozygous F508del	99 (42.3)	48 (43.2)	51 (41.5)	
Heterozygous F508del	104 (44.4)	49 (44.1)	55 (44.7)	
Other	31 (13.3)	14 (12.6)	17 (13.8)	
Pancreatic insufficiency, *n* (%)	192 (82.8)	86 (78.9)	106 (86.2)	0.143
CF-related diabetes mellitus, *n* (%)	71 (30.3)	34 (30.6)	37 (30.1)	0.92
CF-related liver disease, *n* (%)	29 (12.4)	12 (10.8)	17 (13.8)	0.81
FEV_1% predicted, mean (SD)	69.3 (24.09)	76.6 (22.43)	62.8 (23.74)	<0.001
FEV_1% predicted, *n* (%)				<0.001
>50	167 (76.3)	90 (87.4)	77 (66.4)	
30–50	42 (19.2)	12 (11.7)	30 (25.9)	
<30	10 (4.6)	1 (1.0)	9 (7.8)	
BMI, mean (SD)	24.2 (4.95)	24.9 (5.67)	23.5 (4.11)	0.027
Fragility fracture, *n* (%)	7 (3.0)	3 (2.7)	4 (3.3)	
CFTR modulator use, *n* (%)	35 (15.00	18 (16.2)	17 (13.8)	0.608
Bisphosphonate use, *n* (%)	23 (9.8)	2 (8.1)	21 (17.1)	<0.001
25OHD, mean (SD)	31.3 (13.57)	29.4 (12.29)	32.8 (14.39)	0.157
Calcium, mean (SD)	9.05 (0.82)	9.2 (0.4)	9 (1.0)	0.1
Creatinine, mean (SD)	0.9 (0.65)	0.8 (0.2)	1 (0.8)	0.09

Table 2. Risk Factor Identification for lower than expected BMD

	Unadjusted RR (95% CI)	P value	Adjusted RR (95% CI)	P value
Age (years)	**1.01 (1.003, 1.018)**	**0.004**	**1.01 (1.004, 1.023)**	**0.005**
Male sex	**1.33 (1.047, 1.682)**	**0.019**	**1.32 (1.043, 1.664)**	**0.021**
Race, non-white	1.29 (0.897, 1.851)	0.171	1.42 (0.960, 2.112)	0.079
Genotype				
Homozygous F508del	Ref		Ref	
Heterozygous F508del	1.02 (0.791, 1.309)	0.892	1.03 (0.788, 1.358)	0.809
Other	1.08 (0.742, 1.569)	0.689	1.21 (0.801, 1.817)	0.370
Pancreatic insufficiency	1.16 (0.818, 1.647)	0.403	1.06 (0.741, 1.525)	0.739
FEV_1 % predicted	**0.99 (0.984, 0.993)**	**<0.001**	**0.99 (0.987, 0.996)**	**<0.001**
BMI (kg/m^2)	**0.97 (0.947, 0.9999)**	**0.049**	**0.97 (0.939, 0.995)**	**0.022**
CFTR modulator use	1.16 (0.911, 1.470)	0.233	1.25 (0.971, 1.599)	0.084

Boyle RL, et al. JBMR Plus 2022.

Quels sont les facteurs de risque de fracture ?

Patient characteristic	All $N=202$	Fractures $N=36$	No fractures $N=166$	P-value
Age (years)	31.1 (11.2)	35.7 (13.8)	30.1 (10.3)	**0.013**
BMI (kg/m^2)	22.3 (3.6)	22.1 (3.7)	22.4 (3.6)	0.51
Gender, N (%)				0.14
Female	101 (50)	22 (21.8)	79 (78.2)	
Male	101 (50)	14 (13.9)	87 (86.1)	
Race, N (%)				0.62
White	191 (94.6)	35 (18.3)	156 (94)	
Black	7 (2)	1 (14.3)	6 (85.7)	
Other	4 (3.5)	0 (0)	4 (100)	
Genotype, N (%)				0.085
F508del	175 (86.63)	28 (16)	147(84)	
Homozygous	100 (57.1)	21 (21)	79 (79)	
Heterozygous	75 (42.9)	7 (9.3)	68 (90.6)	
Other	27 (13.4)	8 (29.6)	19 (70.3)	
CFRD, N (%) ($N=197$)				0.60
Yes	90 (45.7)	18 (20)	72 (80)	
No	107 (54.3)	17 (15.9)	90 (84.1)	
Hemoglobin A1c ($N=157$)	6.9 (2)	7.8 (2.7)	6.7 (1.7)	**0.024**
25-hydroxy vitamin D ($N=188$)	31.9 (13.2)	25.4 (10.1)	32.9 (13.6)	0.080
FEV1 (% predicted)	66.7 (25.8)	61.6 (25.4)	67.9 (25.8)	0.24*
Prednisone > 3 months, N (%)				0.10
Yes	38 (19.4)	10 (26.3)	28 (73.7)	
No	158 (80.6)	24 (15.2)	134 (84.8)	
History of lung Tx, N (%)				**< 0.001**
Yes	18 (8.9)	9 (50)	9 (50)	
No	184 (91.1)	26 (14.1)	148 (80.4)	
On bisphosphonate at the time of DXA, N (%)				**0.002***
Yes	19 (9.5)	9 (47.4)	10 (52.6)	
No	179 (90.4)	26 (14.5)	153 (85.5)	

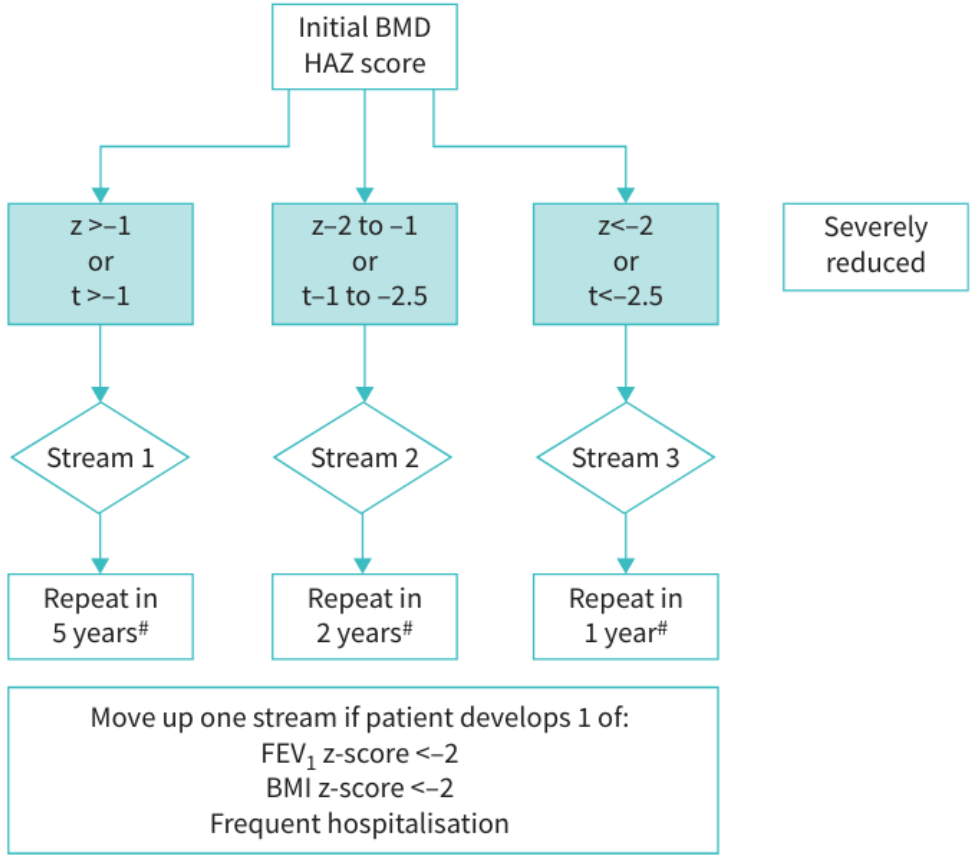
Bone parameter	All $N=202$	Fractures $N/F=36/59$*	No fractures $N=166$	P-value$^+$
Lumbar spine BMD (g/cm^2)	1.09 (0.16)	1.04 (.15)	1.10 (.16)	**0.032**
Lumbar spine (L-spine) Z/T-score$^\#$	−0.69 (1.29)	−1.09 (1.24)	−.61 (1.29)	0.11
L-spine Z/T-score categories, N (%)				**0.019**
> −1.0	113 (55.9)	13 (11.5)/19	100 (88.5)	
≤ −1.0, > −2.0	53 (26.2)	12 (22.6)/17	41 (77.4)	
≤ −2.0	36 (17.8)	11 (30.6)/23	25 (69.4)	
Femoral neck BMD (g/cm^2)	0.95 (0.16)	.86 (.15)	.97 (.15)	**0.0003**
Femoral neck (FN) Z/T-score	−0.55 (1.10)	−1.05 (1.08)	−.44 (1.08)	**0.012**
FN Z/T-score categories, N (%)/F*				**< 0.001**
> −1.0	123 (60.9)	11 (8.9)/22	112 (89.2)	
≤ −1.0, > −2.0	59 (29.2)	19 (32.2)/27	40 (68.5)	
≤ −2.0	20 (9.49)	6 (30.0)/10	14 (70.0)	
Total hip BMD (g/cm^2)	0.97 (0.16)	.88 (.16)	.99 (.16)	**0.0002**
Total hip (TH) Z/T-score	−0.40 (1.10)	−.96 (1.41)	−.28 (1.09)	**0.003**
TH Z/T-score categories, N (%)				**0.001**
> −1.0	139	16 (11.5)/22	123 (88.5)	
≤ −1.0, > −2.0	44	12 (27.3)/21	32 (72.7)	
≤ −2.0	19	8 (42.1)/15		
TBS	1.39 (0.11)	1.36 (.13)	1.40 (.11)	0.050
TBS categories, N (%)/F*				0.123
Normal: ≥ 1.31	158 (78.2)	25 (15.8)/33	133 (84.2)	
Partially degraded: < 1.31, > 1.23	24 (11.9)	4 (16.7)/9	20 (83.3)	
Degraded: ≤ 1.23	20 (9.9)	7 (35.0)/17	13 (65.0)	

Anabtawi A, et al. Osteoporos Int 2022.

Quand et comment suivre la DMO ? à quelle fréquence ?

Tabel 2: Guidelines for Bone Density Screening

	Bone Density score*	Ongoing DEXA monitoring
Starting @ 18 years	Z-score > -1.0	Repeat in 5 years
	Z- or T-score between -1.0 and -2.0	Repeat in 2 to 4 years
Children with: ■ FEV1 % predicted < 50% ■ frequent or prolonged systemic glucocorticoids ■ < 90 % ideal body weight ■ delayed puberty ■ a history of fracture	Z- or T-score < -2.0 or a significant decline from prior scores	Repeat annually
Adults > 50 years[9]	T-score > -1.0	Repeat in 5 years
	T-score between -1.0 and -2.5	Repeat every 2 years
	T-score <-2.5 or patient is felt to be at significant risk	Repeat annually
Patients on continuous systemic steroids		Repeat annually



Yaacoby-Bianu K, et al. ERJ Open Res 2025.
Wilcox, P. et al. 2018.

Quid des traitements classiques et des prises en charge ?

Calcium et vitamine D ?

	Supplementation	Serum Reference Values Monitoring Frequency
Vitamin D	Dependent on serum values, which vary with dietary intake and sun exposure. **Vitamin D3 (cholecalciferol) routine dosing*** 0 to 12 months = 400 to 500 IU 1 to 10 years = 800 to 1000 IU 10 to 18 years = 800 to 2000 IU > 18 years = 800 to 2000 IU *Increase dosage when bone density levels remain low following stepwise dosing (see 'Cystic Fibrosis Care Guidelines for Nutritional Management')	Serum 25-hydroxyvitamin D minimum 30 ng/mL (75 nmol/L)[7] When bone density decreases, aim for Serum 25-hydroxyvitamin D of 30 to 60 ng/mL (75 to 150 nmol/L) Monitor annually, preferably at the end of winter Repeat bloodwork 3 to 6 months after initiation or change in therapy
Vitamin K	Supplement based on INR or PT **Vitamin K1** Infants: 0.3 to 1.0mg/day Older children and adults: 1 to 10mg/day	Target normal INR (< 1.2) Repeat bloodwork 3 to 6 months after initiation or change in therapy
Calcium	**Calcium Carbonate** > 10 years 1300 to1500 mg daily in divided doses (up to 500mg/dose)	Repeat bloodwork 3 to 6 months after initiation or change in therapy

– Dans un 1er temps, prescrire une **dose de « recharge » :**

50 000 UI de vitamine **D3** par **semaine** pendant **8 semaines** chez les patient(e)s qui ont une **25OHD < 20 ng/mL**

50 000 UI de vitamine **D3** par **semaine** pendant **4 semaines** chez les patient(e)s qui ont une **25OHD** entre **20 et 30 ng/mL**

– Après cette phase de **recharge**, prescrire un « **traitement d'entretien** » :

50 000 UI par **mois** de vitamine **D3**

– Après **3 à 6 mois** sous ce « **traitement d'entretien** », redoser la **25OHD** :

Si la **25OHD** est toujours < **30 ng/mL**, on peut :

- ou réduire l'intervalle entre les prises (par ex : **50 000 UI** toutes les **2 semaines**)
- ou augmenter la posologie (par ex : **80 000** ou **100 000 UI** par **mois**)

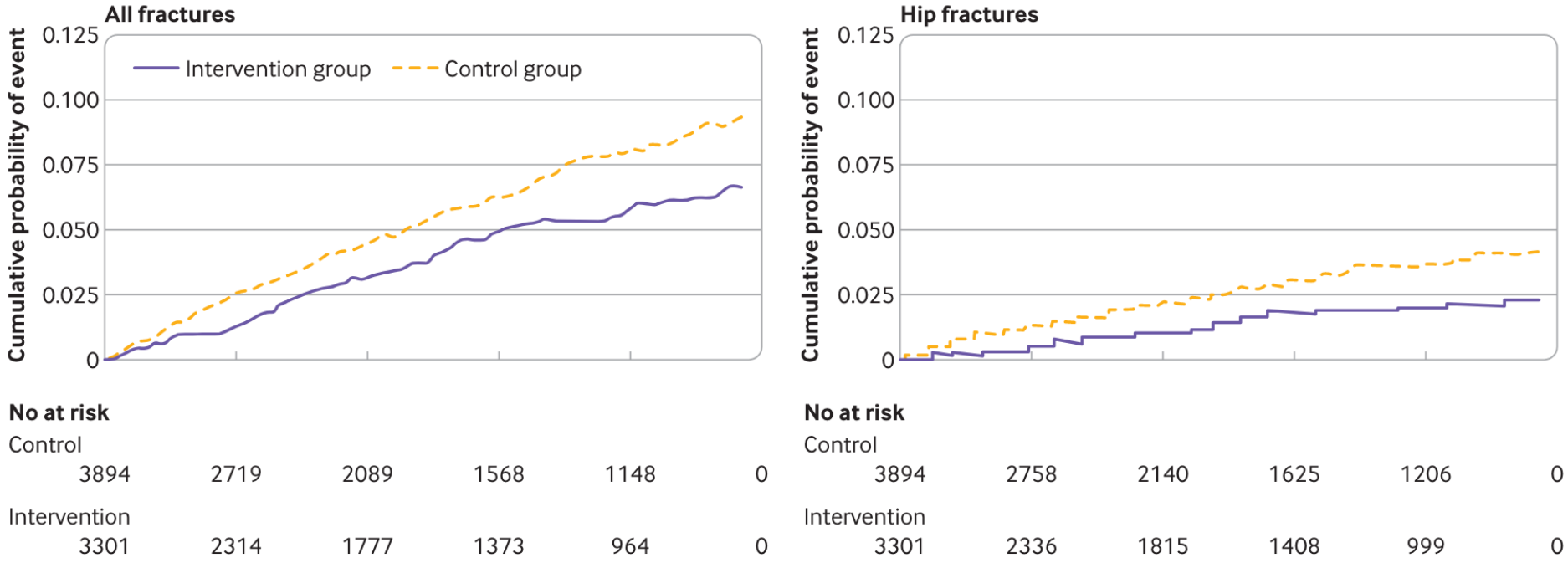
Si la **25OHD** est > **60 ng/mL** (situation exceptionnelle) :

- la seule solution est contradictoire avec les recommandations précédentes
- Il faut espacer davantage les prises (par ex : **50 000 UI** tous les **2 mois**) en attendant une éventuelle disponibilité de formes moins dosées.

Wilcox, P. et al. 2018.

Souberbielle, J.-C. et al. Joint Bone Spine, 2020.
Wilcox, P. et al. 2018.

Calcium quelle forme ? Si possible alimentation !



60 résidences en Australie, 7185 résidents (Age moyen 86 ans)

30 résidences avec ajout : lait, fromage et yahourt, pour atteindre 1142 mg/jour de calcium et 69 g/jour de protéines

Réduction du risque à 2 ans : 33% du risque de fracture, 46% du risque de fracture de hanche et 11% du risque de chute

Iuliano S, et al. BMJ. 2021.

Bisphosphonates ? Oui, globalement population générale

Recommendations for bisphosphonate treatment in adults

62. Bisphosphonate treatment should be considered in adults with CF when: a) the patient has had a low trauma fracture; and/or b) the lumbar spine or total hip or femoral neck Z/T-score is −2 or less and there is evidence of significant bone loss (>4% per year) on serial DXA measurements despite optimisation of their clinical care; and/or c) the patient is awaiting or has undergone solid organ transplantation and has a BMD Z/T-score of −1.5 or less; and/or d) the patient is starting a prolonged course of oral glucocorticoids (> three months) and has a BMD Z/T score of −1.5 or less.
63. Before prescribing bisphosphonates to adults with CF, vitamin D deficiency should be corrected and calcium intake must be optimised.
64. Calcium supplements should be prescribed if the patient's dietary intake is below the recommended intake or if the plasma calcium level is low. If the bisphosphonate preparation recommends calcium supplementation, this recommendation should be followed.
65. Patients should be counselled about the risk of osteonecrosis of the jaw and should consider seeing their dentist before starting bisphosphonate treatment if they have significant dental disease.
66. Oral bisphosphonates should be avoided in patients with oesophageal disease (including severe reflux and varices) in view of the risk of oesophageal ulceration.
67. Oral and intravenous bisphosphonates should be used cautiously in patients with chronic renal insufficiency.
68. Female patients should be advised to take appropriate contraception and counselled about the risk of bisphosphonates to the unborn child before starting bisphosphonate therapy.
69. The prescription of paracetamol, or non steroidal anti-inflammatory drugs, or prednisone may be considered prior to first bisphosphonate infusion to reduce the incidence of bone pain and flu-like symptoms. Non steroidal anti-inflammatory drugs or paracetamol may also be prescribed prior to starting oral bisphosphonates to reduce the incidence of flu-like symptoms. These symptoms are mainly observed one to three days after the first dose of bisphosphonate therapy and are more common with intravenous than oral formulations.
70. Bone densitometry should be repeated after 12 months of bisphosphonate treatment to assess response and then repeated according to the algorithm in statements 25 and 26.

Sermet-Gaudelus I, et al. Journal of Cystic Fibrosis, 2011.

Autres ? Peu d'études…

	Patient 1	Patient 2	Patient 3	Patient 4
Age (year)	59	35	31	48
BMI (kg/m^2)	19.6	21.8	20	18.5
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian
Gender	Female	Female	Male	Female
Gene mutation	—	ΔF508 Homozygous	2184delA/R553	R117H/R560T
Baseline 25(OH)D (ng/mL)	48	56	33	47
BMD (T-score)				
L1–L4	−1.6	−1.6*	−2.1	−0.7
Left femoral neck	−2.2	−1.9*	−1.9	−1.5
Left total hip	−1.6	−2.5*	−2.6	—

1 fracture sacrée
3 côtes

3 efficaces, 1 arrêt

2 ans de traitement

Siwamogsatham O, et al. Case Reports in Endocrinology 2014.

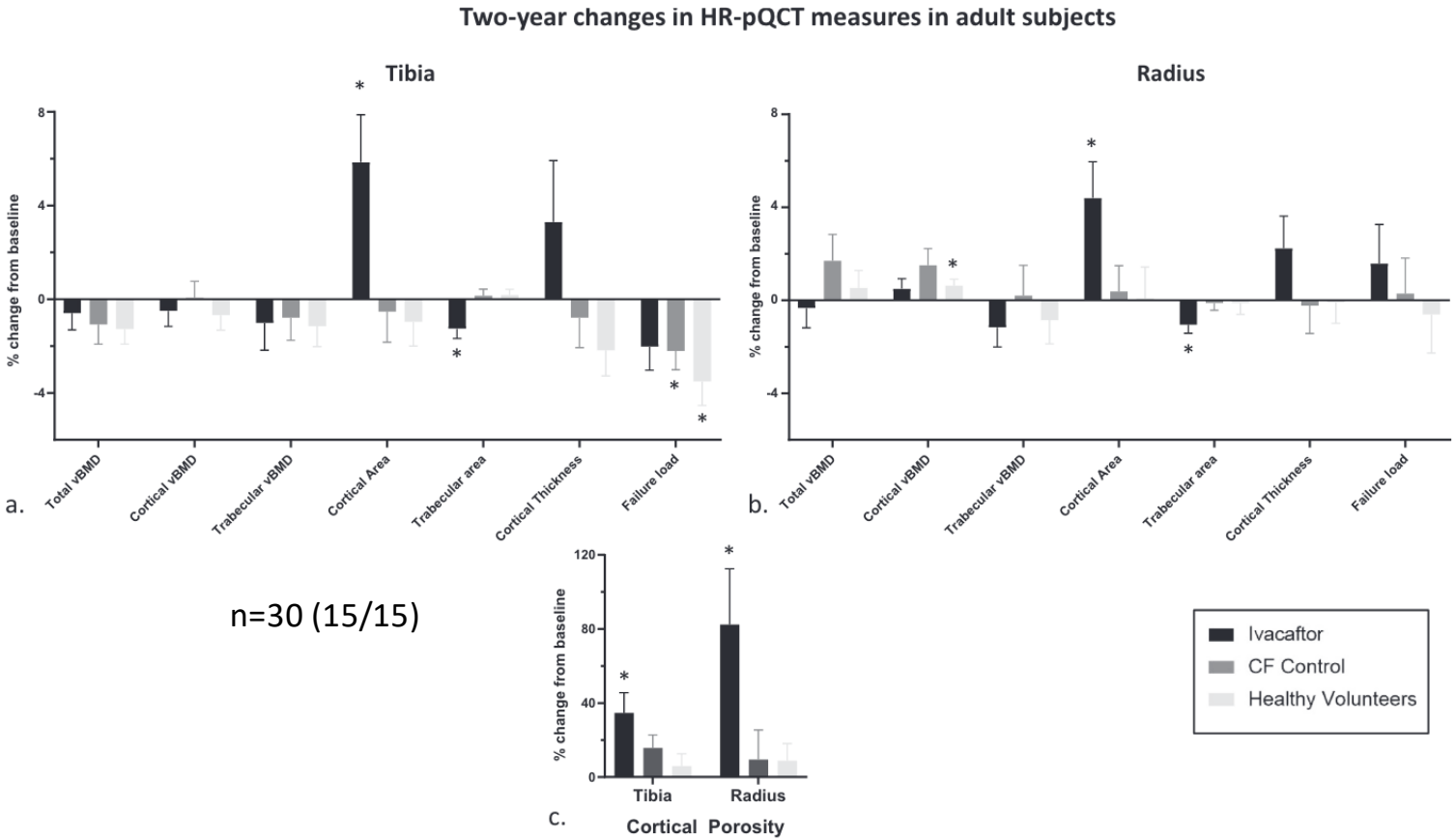
Et les traitements spécifiques de la mucoviscidose ?

Kalydeco (Ivacaftor) 2 ans

Table 1 n=7

Modification of lumbar spine z-score and other clinical parameters after ivacaftor treatment.

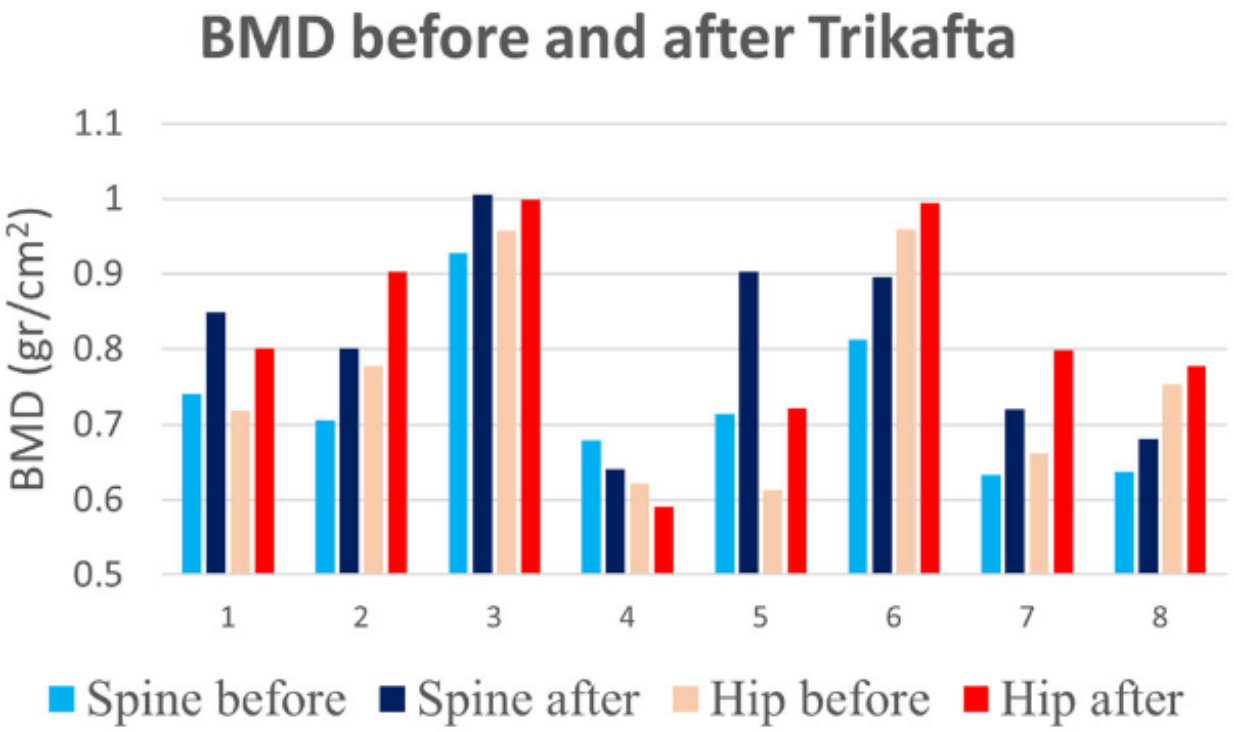
	Pre-ivacaftor	Post-ivacaftor *	*p* **
LS *z*-score	−1.1 (0.7)	−0.4 (0.3)	0.04
FEV1% predicted	48 (9)	59 (9)	0.02
Weight (kg)	60 (2)	64 (4)	0.04
Number of antibiotic courses	1.3 (0.4)	1 (0.6)	0.4
25(OH)vit D level (mmol/l)	62 (10)	71 (8)	0.6



n=30 (15/15)

Sermet-Gaudelus I. Journal of Cystic Fibrosis, 2016.

Trikafta (Kaftrio) 2 ans



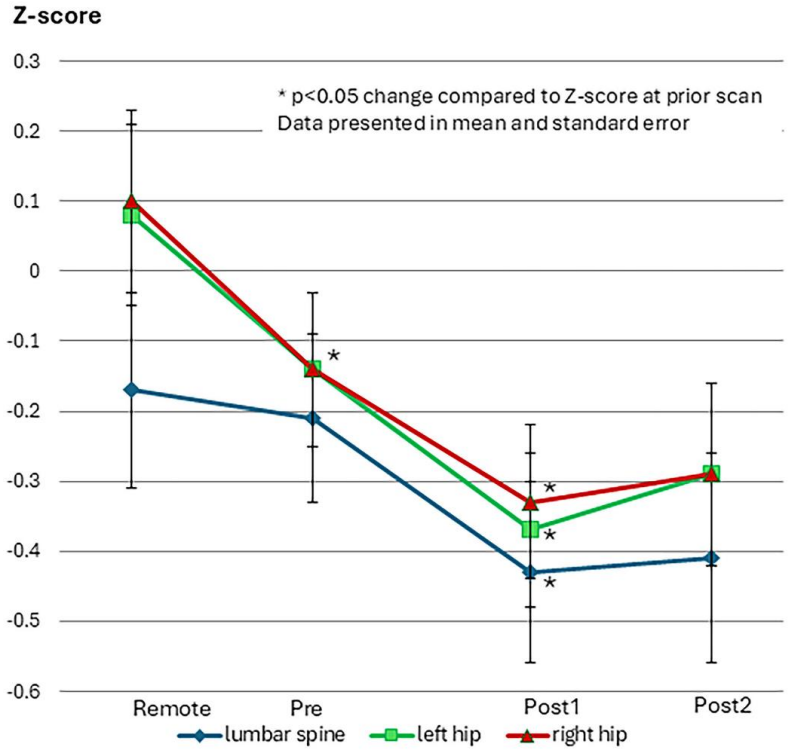
	Before	After	*p* Value
Weight (kg)	51.63 ± 10.47	54 ± 10.82	0.05
Height	162.6 ± 13.23	162.5 ± 13.21	0.46
BMI (kg/m^2)	19.4 ± 2.6	20.3 ± 2.19	0.05
Hip BMD (gr/cm^2)	0.73 ± 0.098	0.81 ± 0.12	0.017
Spine BMD (gr/cm^2)	0.76 ± 0.14	0.82 ± 0.14	0.025
Total BMC (gr)	1795.7 ± 457.6	1820.6 ± 411.1	0.58
LBM (gr)	34770.23 ± 10521.21	37430.16 ± 10330.09	0.017
% Fat	23.13 ± 6.08	27.55 ± 6.54	0.069
% Fat z-score	−0.8 ± 0.75	0.46 ± 0.58	0.012
Fat mass/height^2 z-score	−0.98 ± 0.66	−0.04 ± 0.51	0.025

Gur M, et al. Pediatric Pulmonology 2023.

Trikafta (Kaftrio) 2 ans

TABLE 2 | Bone mineral density based on DXA scan in pwCF before and after ETI initiation.

	Bone mineral density					Pairwise comparison *p* value		
	Remote ($n = 57$)	Pre ($n = 74$)	Post1 ($n = 74$)	Post2 ($n = 51$)	Overall *p* value	Remote versus pre	Pre versus post1	Post1 versus post2
Z-score lumbar spine	−0.17 (1.03)	−0.21 (1.01)	−0.43 (1.12)	−0.41 (1.09)	< 0.01	0.69	< 0.01	0.98
Z-score left hip	0.08 (0.97)	−0.14 (0.96)	−0.37 (0.96)	−0.29 (0.95)	< 0.01	0.07	< 0.01	1.00
Z-score right hip	0.10 (1.00)	−0.14 (0.92)	−0.33 (0.97)	−0.29 (0.95)	< 0.01	< 0.01	< 0.01	0.99



Trost SU, et al. Pediatric Pulmonology 2025.

Pour conclure

Santé osseuse et maladies pulmonaires : une prévention nécessaire pour limiter un cercle vicieux délétère pour tous

Mucoviscidose : Effet direct et indirect sur l'os

Prise en charge classique peu différente de la population générale, discussion **multidisciplinaire** nécessaire

Effet des traitements spécifiques : attendons de voir, étude à faire ?

Mucoviscidose et conséquences articulaires

Dr Emilie Chotard

PH Service Rhumatologie

CHU Rennes

Cystic fibrosis arthropathy : un problème de définition

ou arthrites épisodiques de la mucoviscidose

Arthrite≠Arthropathie≠Arthralgie

Problème déjà soulevé depuis 1999

Des cas rapportés au fil des ans dans la littérature
5 en 1979
72 en 1999

Des atteintes cutanées souvent associées avec l'atteinte articulaire : érythème noueux, purpura

Rheumatic disease and cystic fibrosis. P.A. Merkel, arthritis and rheumatism 1999

Cystic fibrosis arthropathy : un problème de définition

Observational Study > J Cyst Fibros. 2016 Jul;15(4):e35-40. doi: 10.1016/j.jcf.2015.12.022.
Epub 2016 Jan 20.

Ultrasound and magnetic resonance imaging assessment of joint disease in symptomatic patients with cystic fibrosis arthropathy

G Fitch [1], K Williams [1], J E Freeston [2], S Dass [3], A Grainger [4], R Hodgson [5], L Horton [5], P Whitaker [1], D Peckham [1]

Observational Study > Respir Med. 2019 Feb:147:66-71. doi: 10.1016/j.rmed.2019.01.003.
Epub 2019 Jan 17.

Clinical manifestations and risk factors of arthropathy in cystic fibrosis

Jobst F Roehmel [1], Tilmann Kallinich [2], Doris Staab [1], Carsten Schwarz [3]

ELSEVIER

Journal of Cystic Fibrosis

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

.003

Original Article

Risk factors for cystic fibrosis arthropathy: Data from the German cystic fibrosis registry

Claudia Grehn [a,*], A.-M. Dittrich [b], J. Wosniok [c], F. Holz [a], S. Hafkemeyer [d], L. Naehrlich [e], C. Schwarz [a], Registry working group of the German CF Registry [f]

[a] Department of Pediatric Pneumology, Immunology and Intensive Care Medicine, Charité – Universitätsmedizin, Berlin, Germany
[b] Pediatric Pneumology, Allergology and Neonatology, Hannover Medical School, Hannover, Germany
[c] Interdisziplinäres Zentrum für Klinische Studien (IZKS), Universitätsmedizin der Johannes-Gutenberg-Universität, Mainz, Germany
[d] Mukoviszidose Institut gGmbH (MI), Bonn, Germany
[e] Department of Pediatrics, Justus-Liebig-University, Giessen, Germany

Cystic fibrosis arthropathy : un problème de définition

- pas de critères diagnostiques
- arthralgies vs arthrite
- pas toujours d'évaluation rhumatologique
- pas de screening auto-immun systématique
- pas d'évaluation rx/echo systématique

- Prévalence difficile à estimer (2-8,5%) : à interpréter selon l'âge moyen des cohortes

E. Botton et al. / Revue du Rhumatisme 70 (2003) 703–712

Les atteintes articulaires de la mucoviscidose

Etude Danoise 2020-2022

- N= 11 patients + 53 issus d'une revue de la littérature
- H=F
- Age moyen 26 /11 ans
- Greffés pulmonaires 0?
- Ivacaftor 90%/ 0
- Atteinte oligo/mono articulaire 58% > polyarticulaire 42%
- 10 polyarthrites rhumatoïdes (dont 4 anti CCP+)
- 1 patient rhumatisme psoriasique
- 1 sarcoïdose
- Soit 52 non étiquetés = « cystic fibrosis arthropathy »
- Traitement immunomodulateur/suppresseurs n=31

Etude Cochin 2008-2022

- N= 15
- H 40%/F 60%
- Age moyen 39 ans
- Greffés pulmonaires 20%
- Ivacaftor 66%
- 5 polyarthrites rhumatoïdes (tous anti CCP+)
- 5 autres rhumatismes : 1 rhumatisme psoriasique, 3 inclassés, 1 syndrome auto-inflammatoire
- 5 avec arthralgies aspécifiques
- Traitement : méthotrexate n= 6 , biothérapie (rituximab, anti-TNF, anti-IL12/23) n=3 , corticothérapie (5 à 10 mg/j) n=5,

Arthritis in Cystic Fibrosis-Comparison of a Single-Center Cohort and Published Case Reports/Series and a Review of the Literature Rosenborg Peretz et Al, APMIS, 2025 Aug
Atteinte articulaire au cours de la mucoviscidose : description des phénotypes cliniques O. Al Tabaa et al; Revue du Rhumatisme 2023

Les atteintes articulaires de la mucoviscidose

Hypothèses physiopathologiques

- inflammation articulaire médiée par des complexes immuns
- induction d'auto anticorps
- expression phénotypique propre de la mutation CFTR
- en lien avec exposition bactérienne pulmonaire/gastro intestinale (hypothèse réactionnelle)

Mucoviscidose : un surrisque probable de polyarthrite rhumatoïde (PR)

Mucoviscidose : un surrisque probable de polyarthrite rhumatoïde

Prévalence 0,5-1% pop générale **F**>H

Evolution par **poussée**

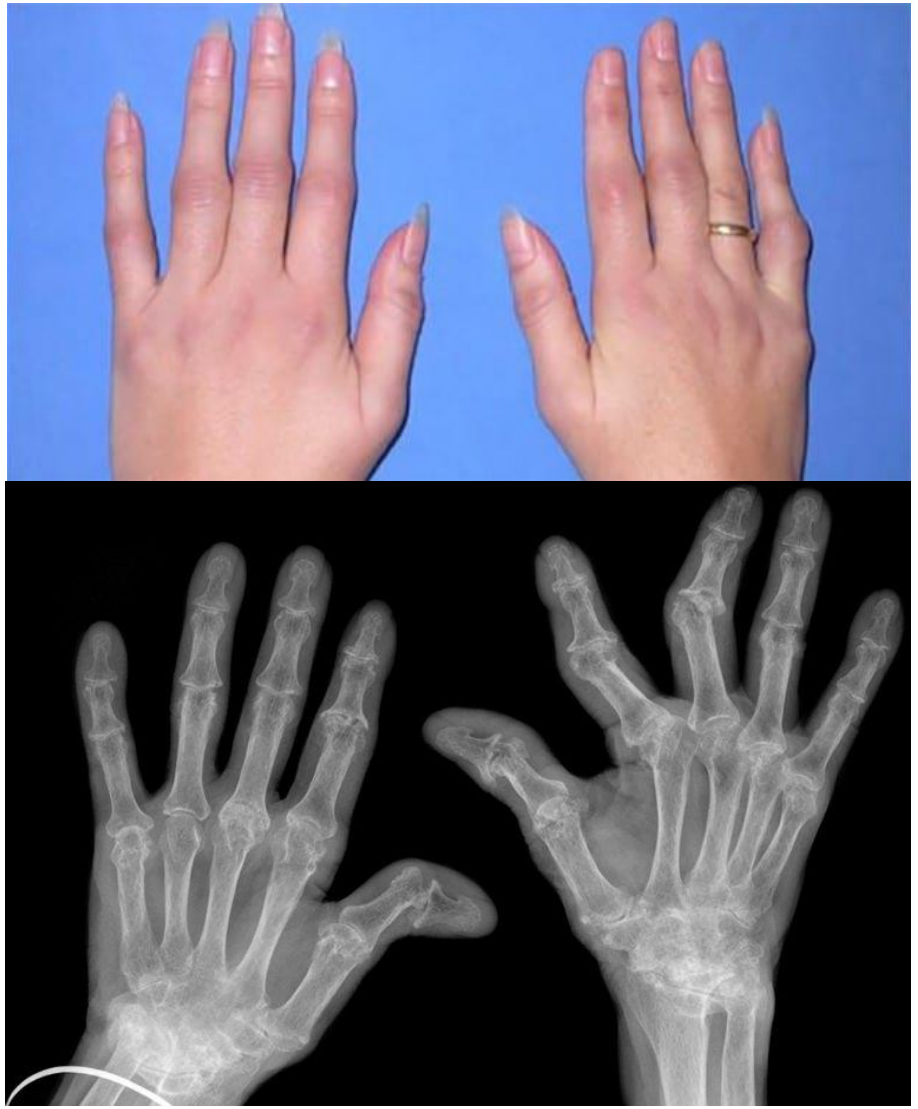
Gonflement articulaire douloureux inflammatoire

Atteinte **bilatérale et symétrique** petites articulations (**mains/pieds**)

Parfois atteintes extra-articulaires (pulmonaire/vasculaire/oculaire)

Biologie : syndrome inflammatoire, **Ac anti CCP et facteur rhumatoïde**

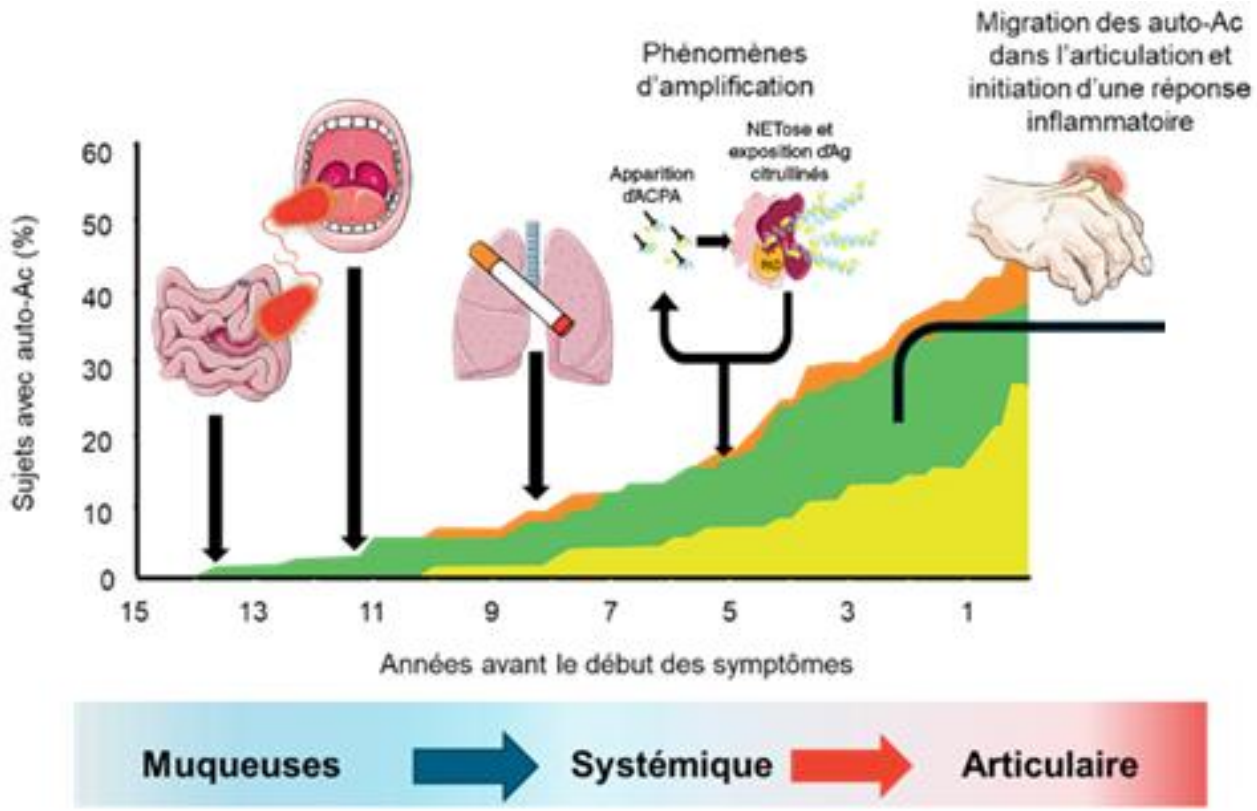
Radios : **érosions**, pincements articulaires, déformations



Mucoviscidose : un surrisque probable de polyarthrite rhumatoïde

Pourquoi ?

- Rôle du microbiote intestinal et pulmonaire dans la génèse des Ac anti CCP



Pneumopathie interstitielle dans la polyarthrite rhumatoïde Sylvie Froidevaux-Janin et al ; Revue medicale Suisse 2011
Increased frequency of cystic fibrosis deltaF508 mutation in bronchiectasis associated with rheumatoid arthritis X Puéchal et al, ; Eur Respir J ; 1990
Mutations of the cystic fibrosis gene in patients with bronchiectasis associated with rheumatoid arthritis Xavier Puéchal et al, ARD 2011

Mucoviscidose : un surrisque probable de polyarthrite rhumatoïde

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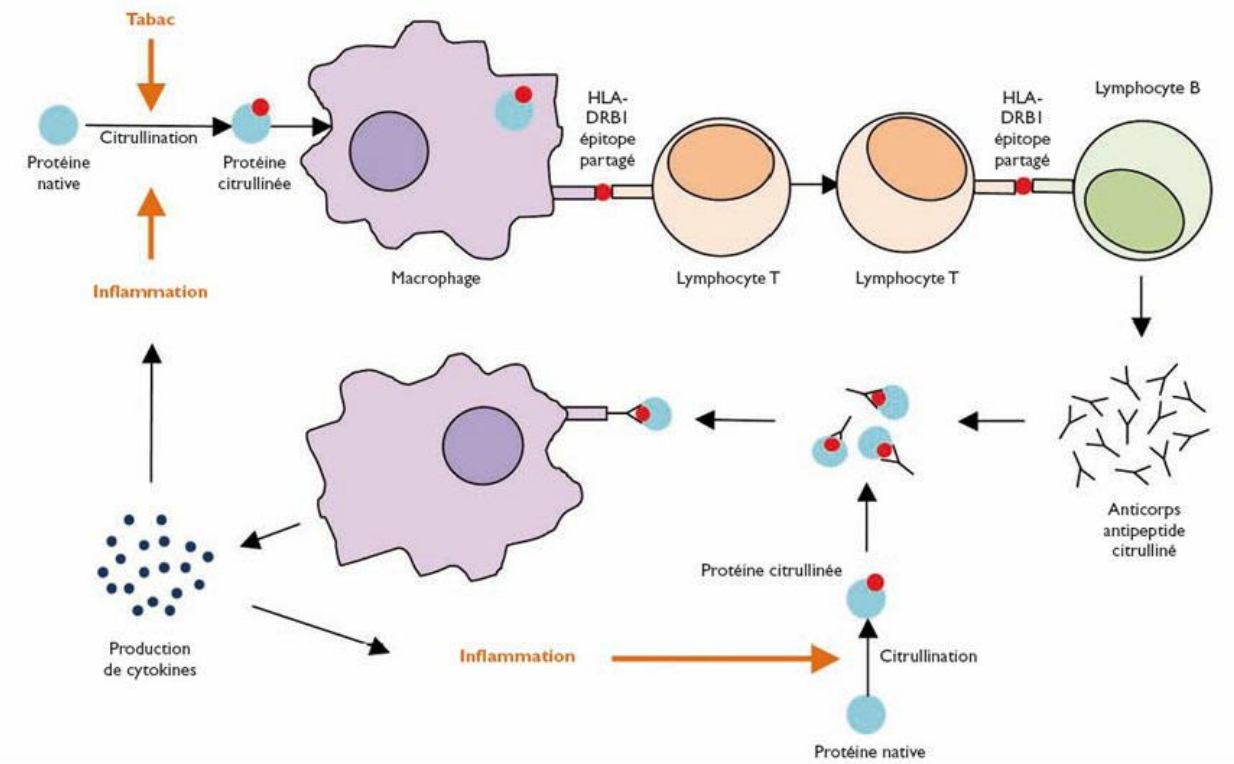

Pneumopathie interstitielle dans la polyarthrite rhumatoïde Sylvie Froidevaux-Janin et al ; Revue medicale Suisse 2011
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Mucoviscidose : un surrisque probable de polyarthrite rhumatoïde

Pourquoi ?

- Rôle du microbiote intestinal et pulmonaire dans la génèse des Ac anti CCP
- ↑ taux sérique TNFα, IL-17
- Role mutation gene CFTR deltaF508

Pneumopathie interstitielle dans la polyarthrite rhumatoïde Sylvie Froidevaux-Janin et al ; Revue medicale Suisse 2011
Increased frequency of cystic fibrosis deltaF508 mutation in bronchiectasis associated with rheumatoid arthritis X Puéchal et al, ; Eur Respir J ; 1990
Mutations of the cystic fibrosis gene in patients with bronchiectasis associated with rheumatoid arthritis Xavier Puéchal et al, ARD 2011

Mucoviscidose et PR : quel traitement ?

- Traitement de fond : DMARDs ou thérapie ciblées semblent bien tolérées
- Intérêt = épargne cortisonique+++, éviter lésions structurales
- Co administration avec tri-thérapie ETI semble possible
- Aphérèse leucocytaire : 1 cas rapporté

→

- Ne repose que sur des cas rapportés
- Doit être discuté au cas par cas avec le pneumologue référent et selon sévérité de la PR

Immuno-aphérèse leucocytaire pour une polyarthrite multicomorbide en impasse thérapeutique : une première utilisation très prometteuse en France, M. Thomas et al

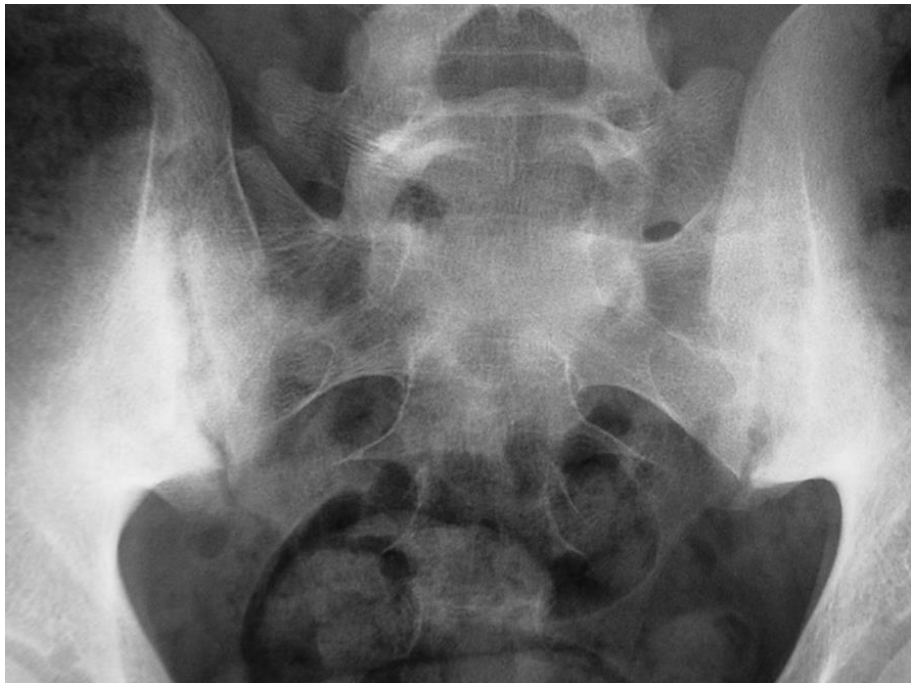
Arthritis in Cystic Fibrosis-Comparison of a Single-Center Cohort and Published Case Reports/Series and a Review of the Literature Rosenborg Peretz et Al, APMIS, 2025 Aug

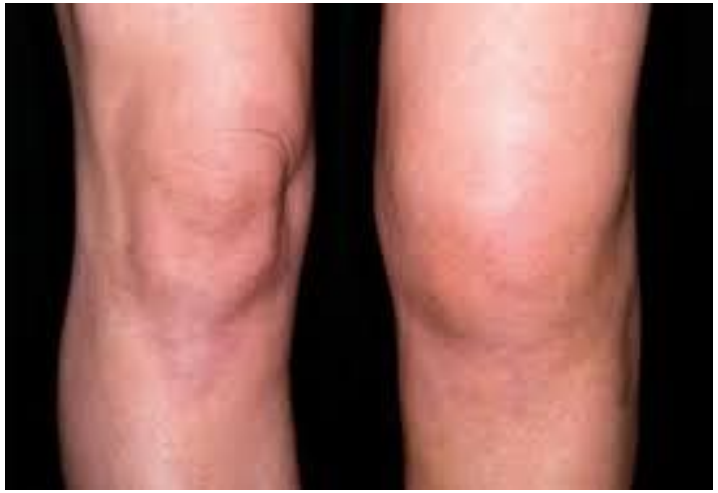
Mucoviscidose : d’autres rhumatismes associés ?

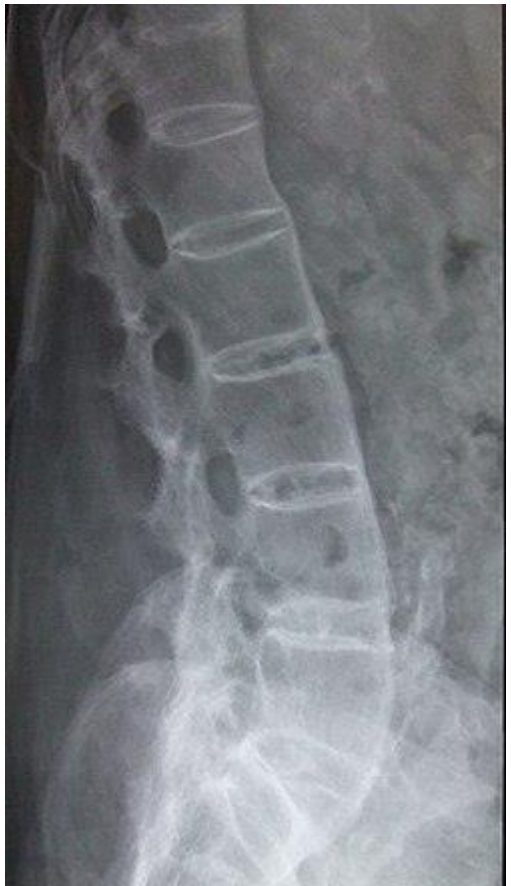
Mucoviscidose : d'autres rhumatismes associés ?

- La spondylarthrite/le rhumatisme psoriasique

Benjamin CM, Clague RB. Psoriatic or cystic fibrosis arthropathy?Difficulty with diagnosis and management. Br J Rheum 1990







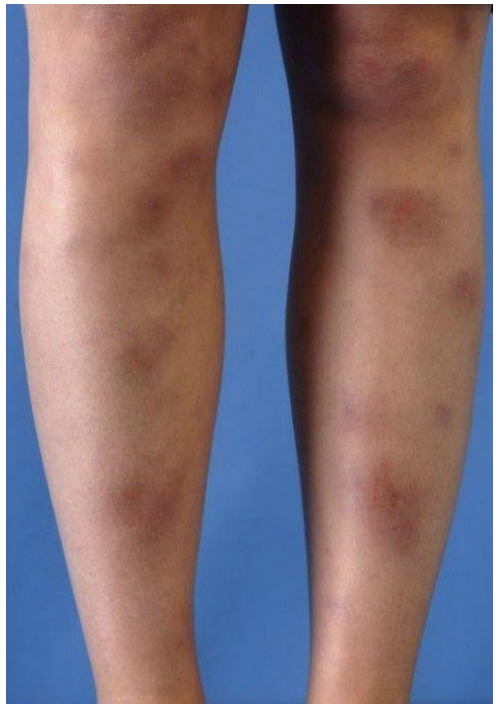
Mucoviscidose : d'autres rhumatismes associés ?

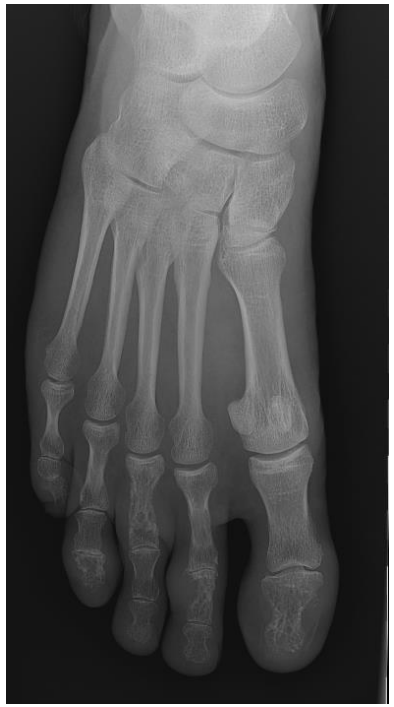
- La spondylarthrite/le rhumatisme psoriasique

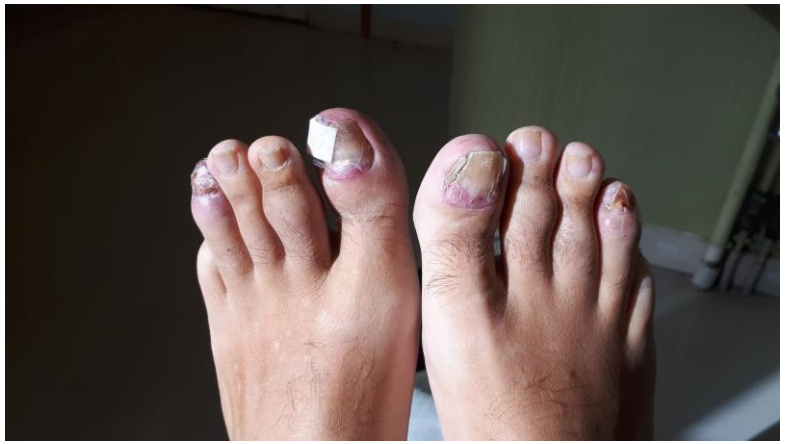
Benjamin CM, Clague RB. Psoriatic or cystic fibrosis arthropathy?Difficulty with diagnosis and management. Br J Rheum 1990

- La sarcoidose : 8 cases reports dont 3 avec atteinte articulaire

Cooper TJ,. Sarcoidosis in two patients with cystic fibrosis: A fortuitous association? Thorax. 1987
Kamarova H, Cystic fibrosis with sarcoidosis: Genetics vs immunology - A paradigm shift? Arch Dis Child. 2010
Dobbin CJ, Granulomatous diseases in a patient with cystic fibrosis. J Cyst Fibros. 2003
Burton CM, Pulmonary sarcoidosis in a child with cystic fibrosis. Pediatr Pulmonol. 2005
Soden M, Sarcoid arthropathy in cystic fibrosis. Br J Rheumatol. 1989
Rettinger SD, Sarcoidosis in an adult with cystic fibrosis. Thorax. 1989
B Jayakrishnan Hypercalcaemia A portent of sarcoidosis in cystic fibrosis Sultan Qaboos Univ Med J 2019







Mucoviscidose : d'autres rhumatismes associés ?

- **Amylose AA**
- Aucun cas de mucoviscidose décrit avec une atteinte rhumatismale
- Atteinte rénale ++
- Ancienne complication connue des RIC mais a disparu avec l'avènement des thérapies ciblées

Gaffney K, Amyloidosis complicating cystic fibrosis. Thorax 1993

Bontempini L, et al. Secondary amyloidosis and cystic fibrosis. A morphological and histochemical study of 5 cases. Histol Histopath 1987

McGlennen R, Systemic amyloidosis complicating cystic fibrosis. Arch Pathol Lab Med 1986

Ristow SC, Systemic amyloidosis in cystic fibrosis. Am J Dis Child 1977

Skinner M, Isolation and sequence analysis of amyloid proteinAA from a patient with cystic fibrosis. J Lab Clin Med 1988

Mucoviscidose et goutte ? A surveiller

En population générale : prévalence 0,9% en France

H>F

Atteinte initiale = pieds ++

Evolution par crises

Hyperuricémie (constante en dehors des crises)

Comorbidités CV et rénales

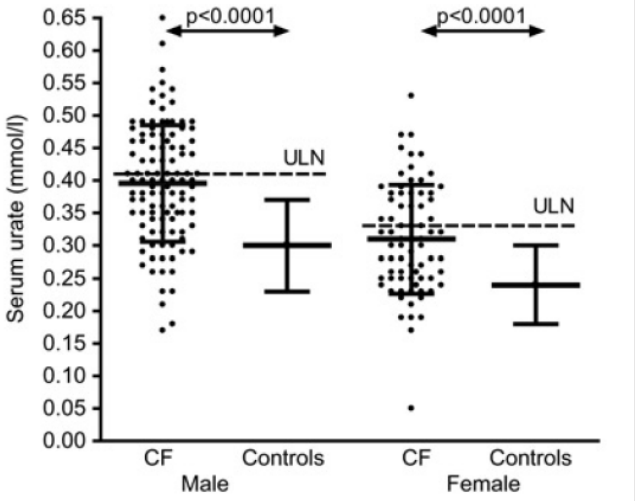
Cohorte de Manchester : prévalence de la goutte estimée à 2,5% (n=9/360) -2008-2010

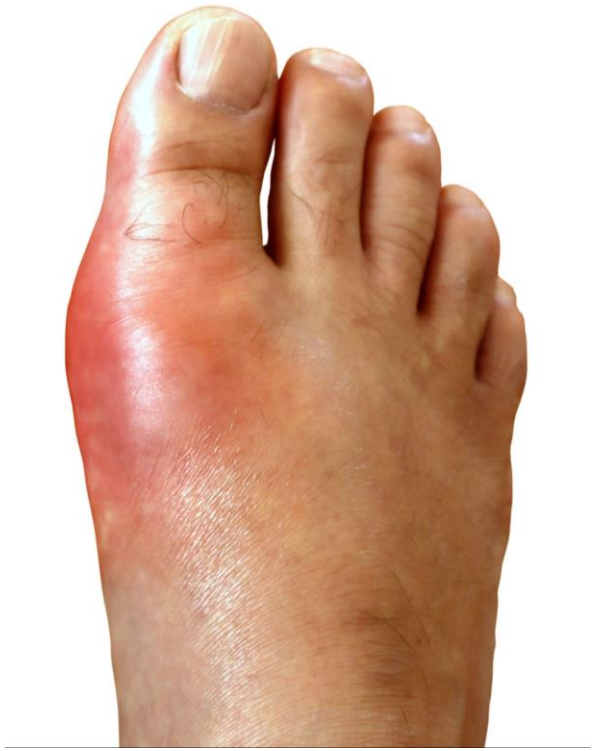
Prévalence hyperuricémie 32% - âge moyen 30 ans (vs environ 10% NZ)

Rôle de la supplémentation d'enzymes pancréatiques riche en purines précurseurs de l'urate.

Gout and hyperuricaemia in adults with cystic fibrosis, Horsley et al, J R Soc Med 2011

Figure 1
Serum urate levels in CF patients compared to those from historic controls.[6] Individual patient data are shown for CF patients, together with mean and SD. Control data are presented as mean and SD. ULN = gender-specific upper limit of normal range, as derived from control data





Petit focus : ostéopathie hypertrophiante ?

Mucoviscidose et OAH

Triade

- Douleurs des os longs avec appositions périostées
- Hippocratisme digital
- Polyarthralgies/polyarthrite (genoux poignets et chevilles)

Prévalence 2 à 7% – 4 à 15% ? (5 % si critères radiographique de périostose)

Paraclinique

Echo recherche de synovite

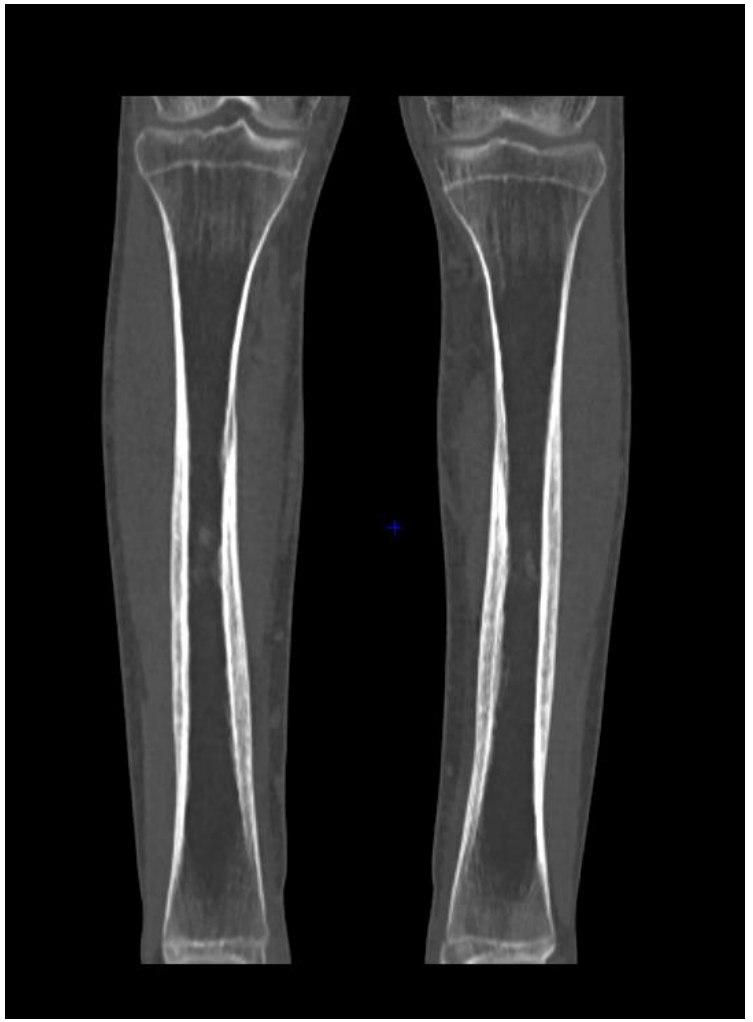
Cytologie sur liquide articulaire si épanchement

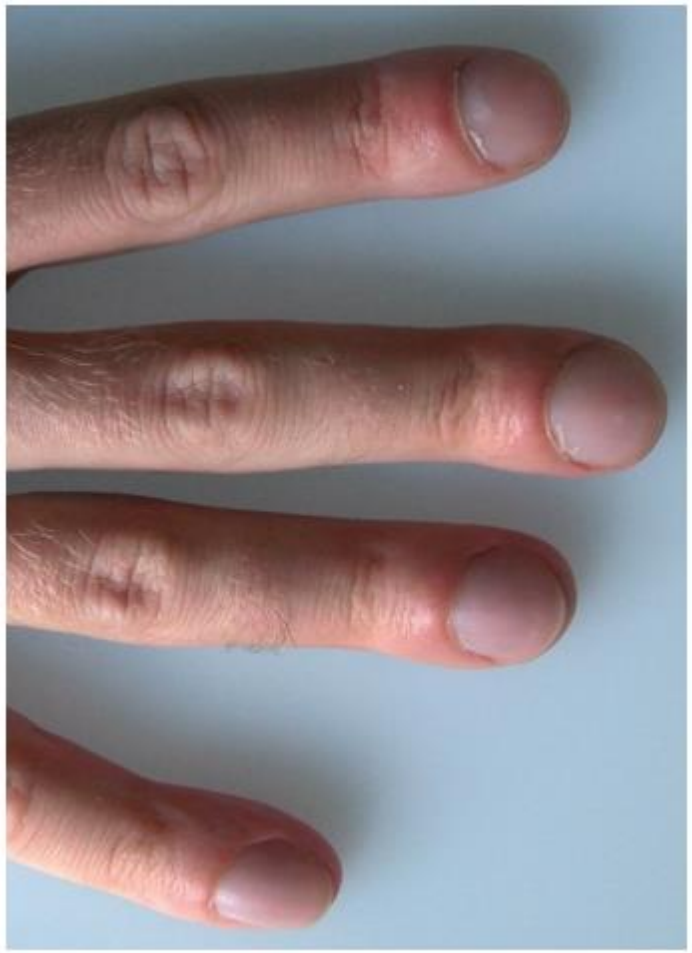
↑ Marqueurs résorption osseuse (PALo, CTX)

Scintigraphie-TDM++++

Traitement mal codifié

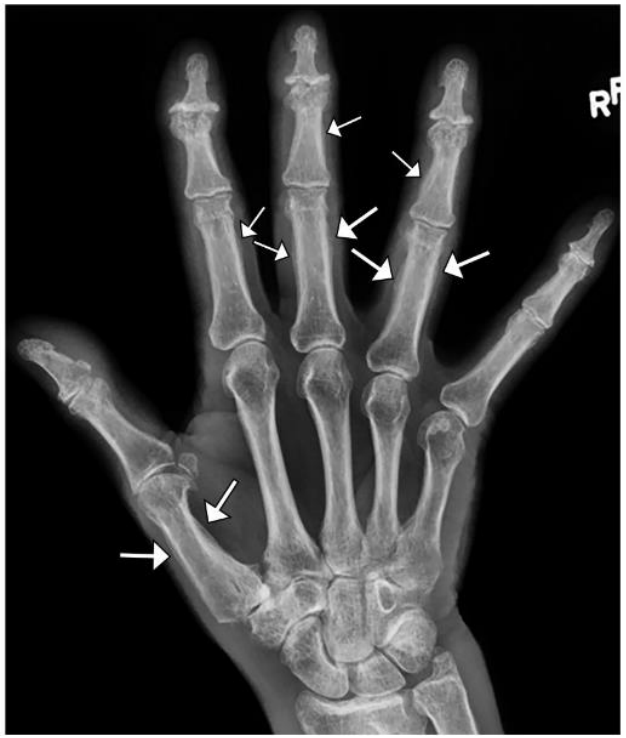
- Amélioration de la fonction pulmonaire +++
- AINS à visée antalgique
- Bisphosphonate ?

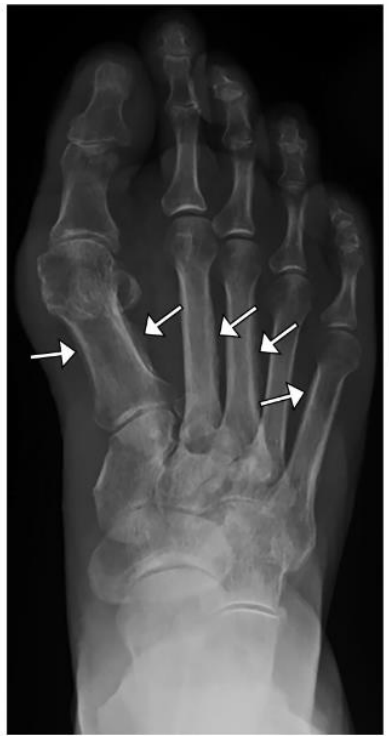


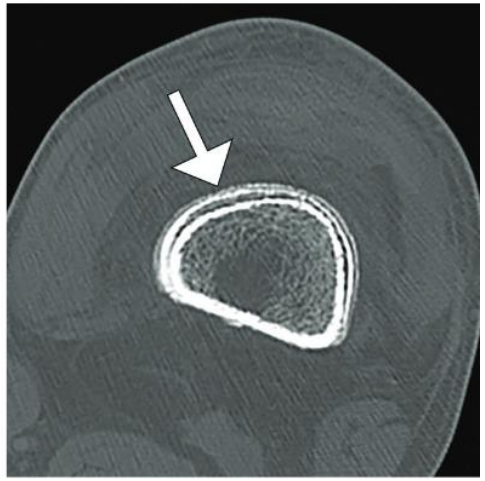


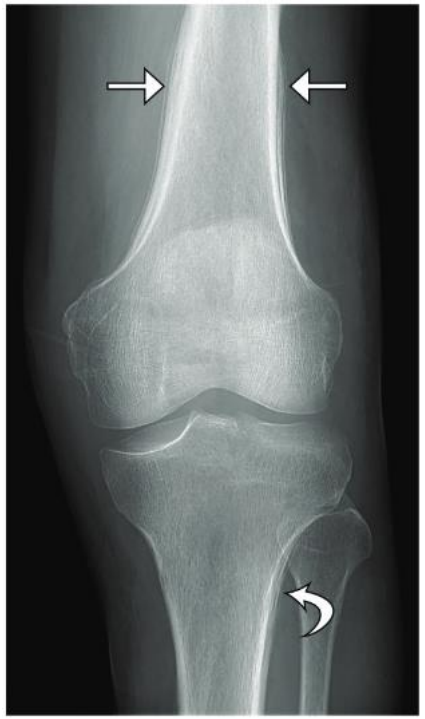
E. Botton et al. / Revue du Rhumatisme 70 (2003) 703–712
Ostéoarthropathie hypertrophiante G. Chalès, et al, EMC 2022

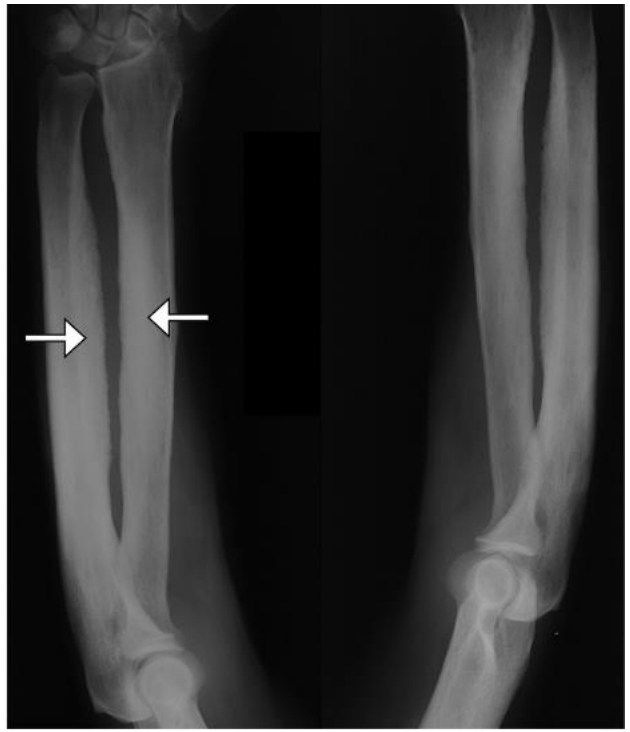
Que retrouve-t-on en imagerie ?





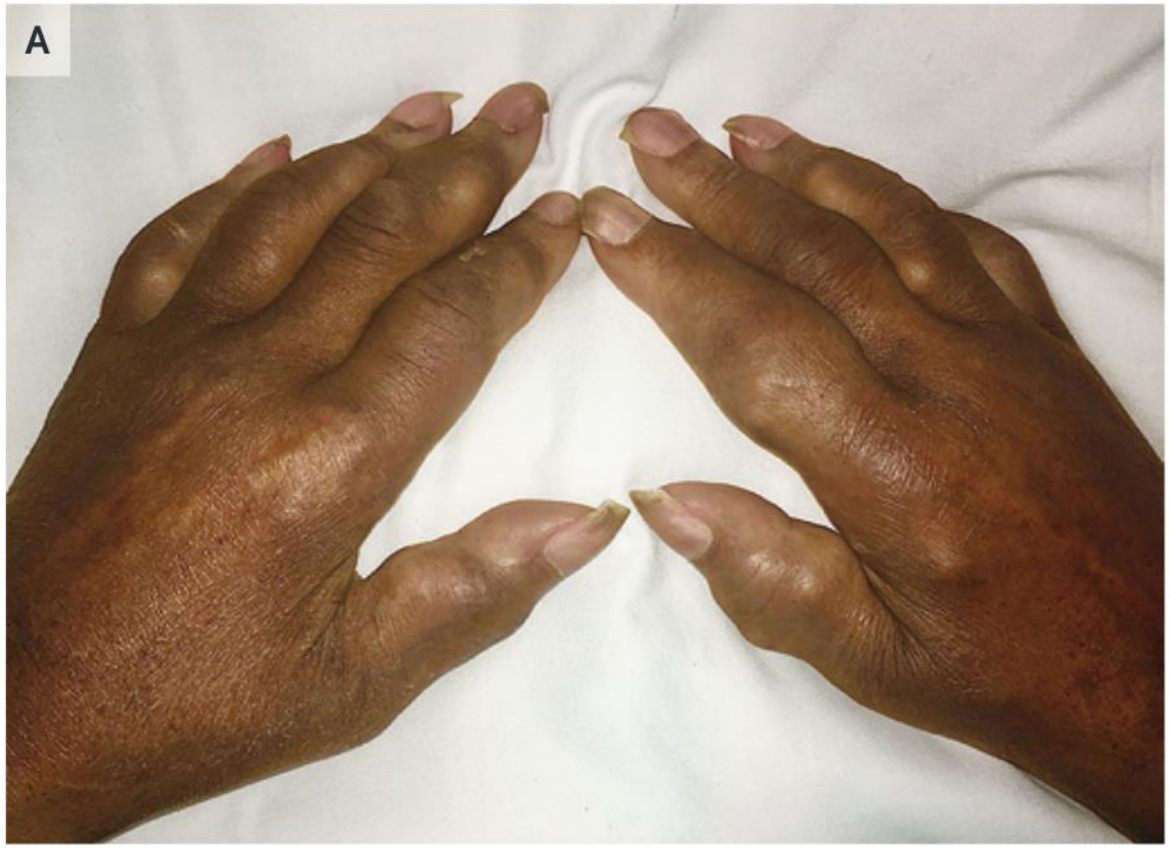


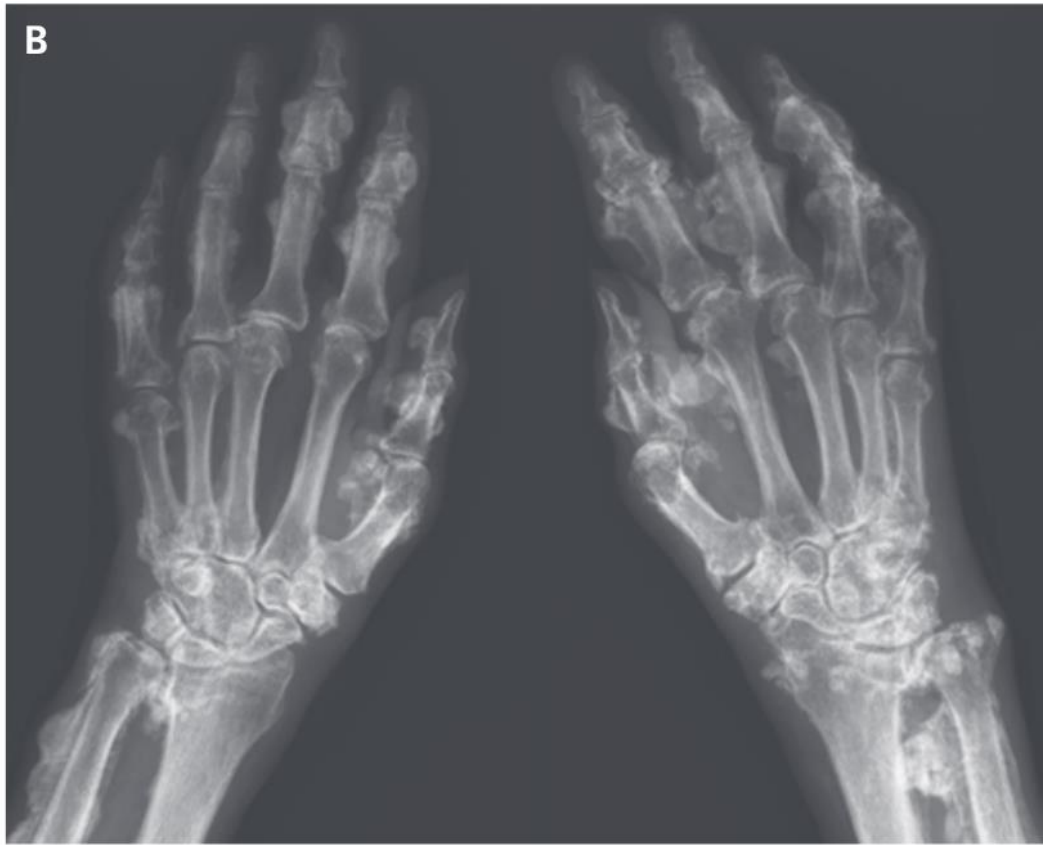




Yap FY, et al. Radiographics 2017.

Attention au diagnostic différentiel !





Hedrick J, et al. N Engl J Med. 2019

Attention au diagnostic différentiel !

Table 2. Comparison of Patients Without and Those With Periostitis

Characteristics	Negative[a]	Positive[a]	*P* Value	Reference Range
Average age, y	59 ± 3.7	68 ± 2.6	.098	
Daily voriconazole dose, mg	450 ± 82	780 ± 43	<.001	
Cumulative voriconazole dose through bone scan date, g	94.7 ± 9.5	130.5 ± 7.3	.024	
Plasma fluoride, μmol/L	3.61 ± 1.29	12.78 ± 0.96	<.001	<5.26
Serum voriconazole trough, μg/mL	1.63 ± 0.43	2.37 ± 0.28	.188	1–5.5
Serum creatinine, mg/dL	0.71 ± 0.08	0.84 ± 0.06	.309	Females: 0.44–1.03 Males: 0.64–1.27
Serum alanine transaminase, mg/dL	32.1 ± 11.9	29.8 ± 4.8	.830	Females: 10–54 Males: 10–63
Serum total bilirubin, IU/L	0.52 ± 0.1	0.54 ± 0.04	.876	Females: 0–2 Males: 0–1.6
Serum alkaline phosphatase, IU/L	117 ± 15.7	273 ± 35.6	.020	27–120
Periostitis involving rib		15 of 21 (71%)		
Periostitis involving ulna		16 of 21 (76%)		
Periostitis involving rib and ulna		10 of 21 (48%)		
Improved pain after voriconazole reduction or discontinuation		17 of 19 (89%)		

Moon WJ, et al. Clinical Infectious Diseases. 2014.

Attention au diagnostic différentiel !

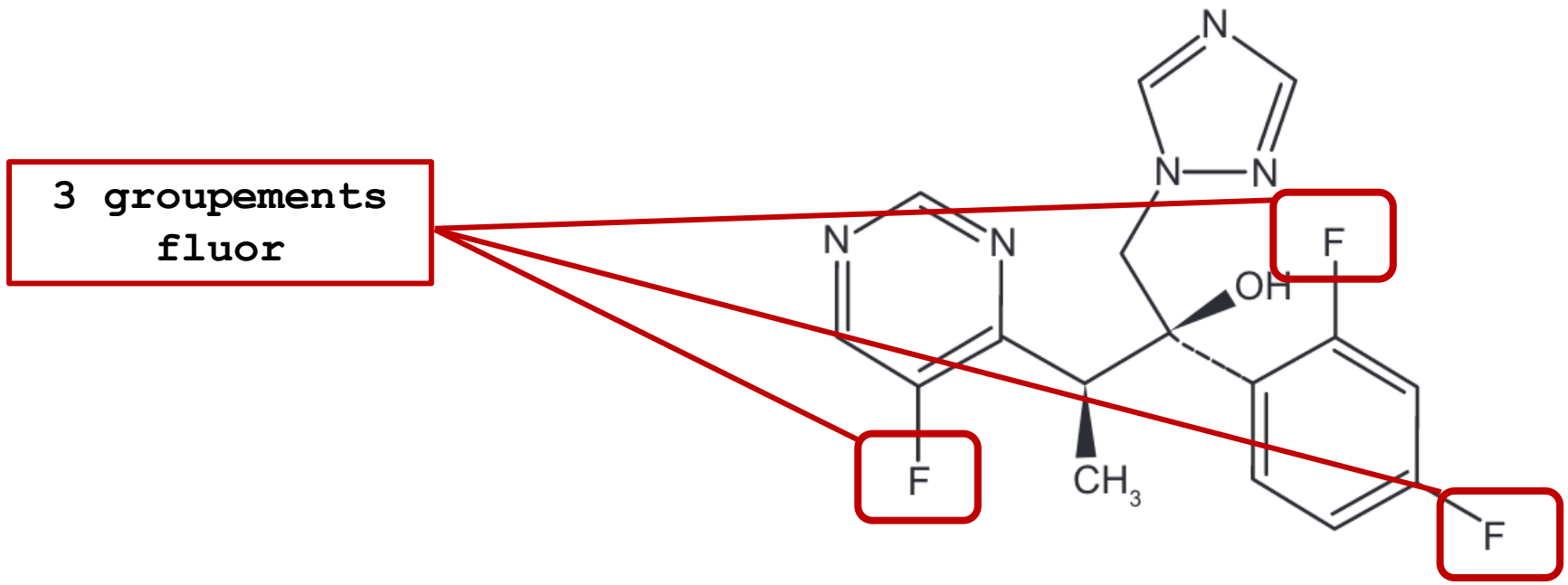


Figure 1 Chemical structure of voriconazole.[83]

Attention au diagnostic différentiel !

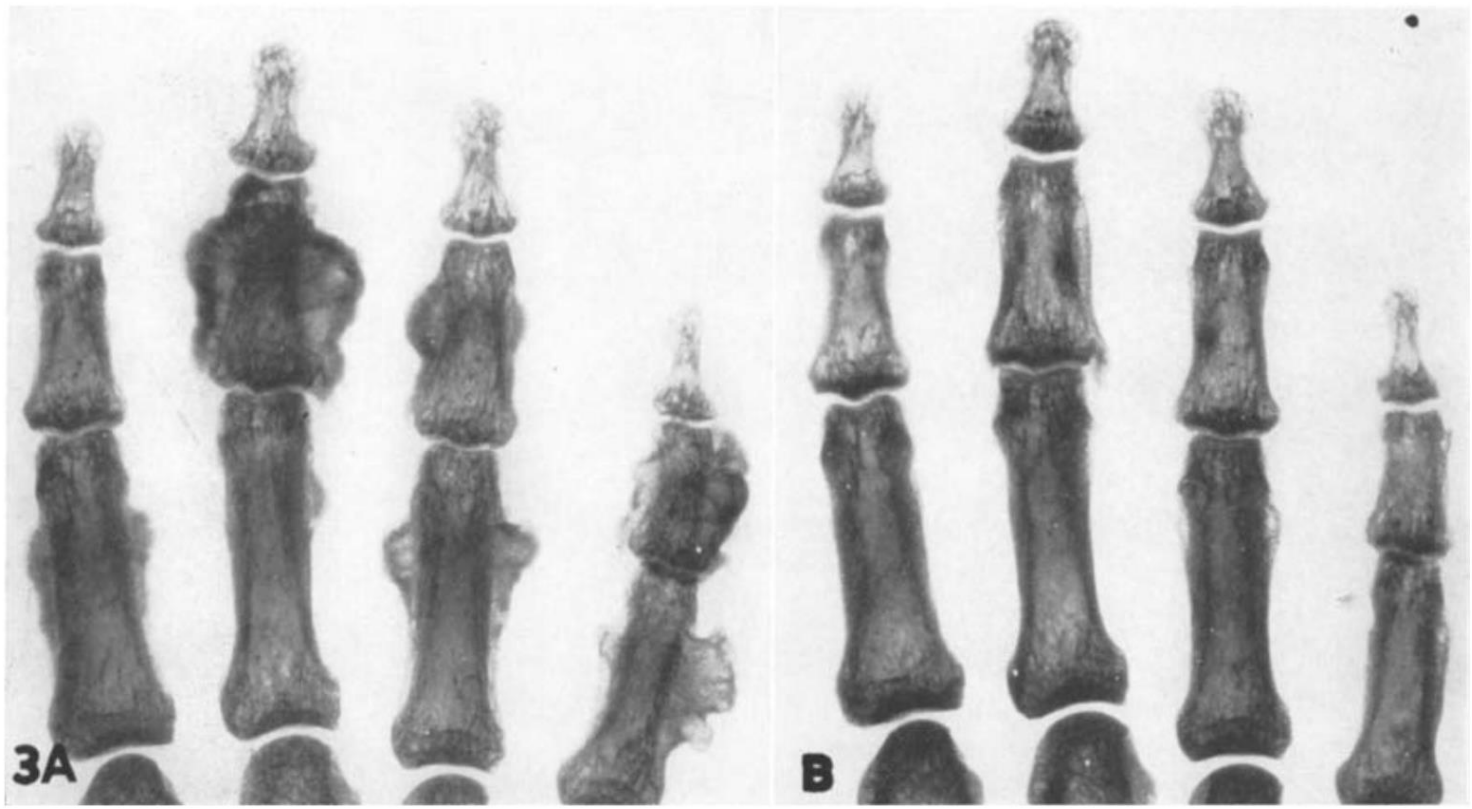
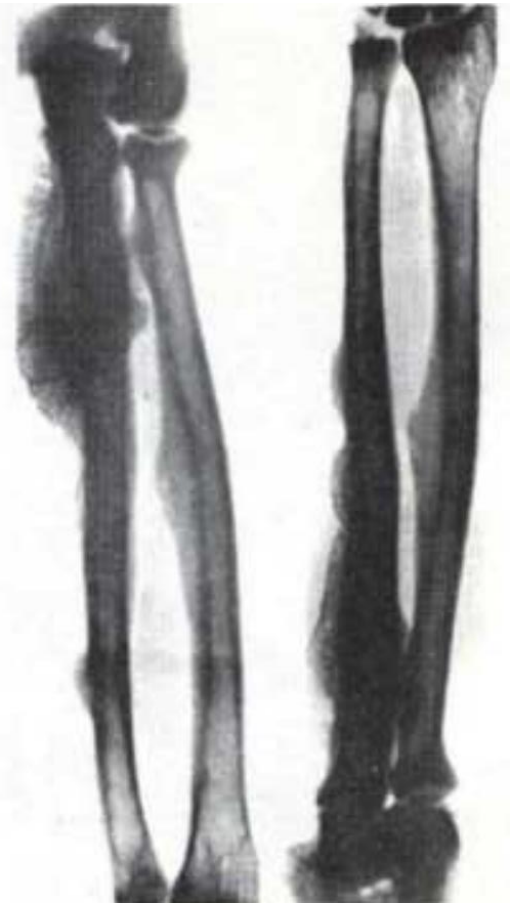


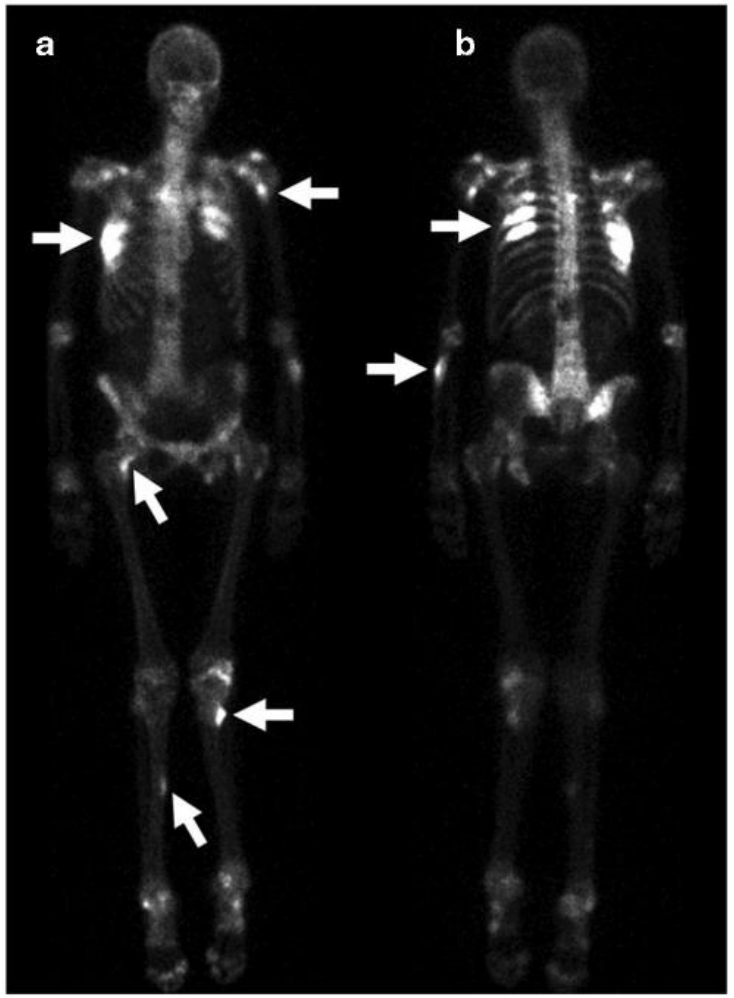
Fig. 3. A. Appearance of periostitis deformans in the phalanges of the hand.
B. The same fingers as in Fig. 3, A, a year later. The newly formed bone tissue previously shown has been almost entirely reabsorbed.

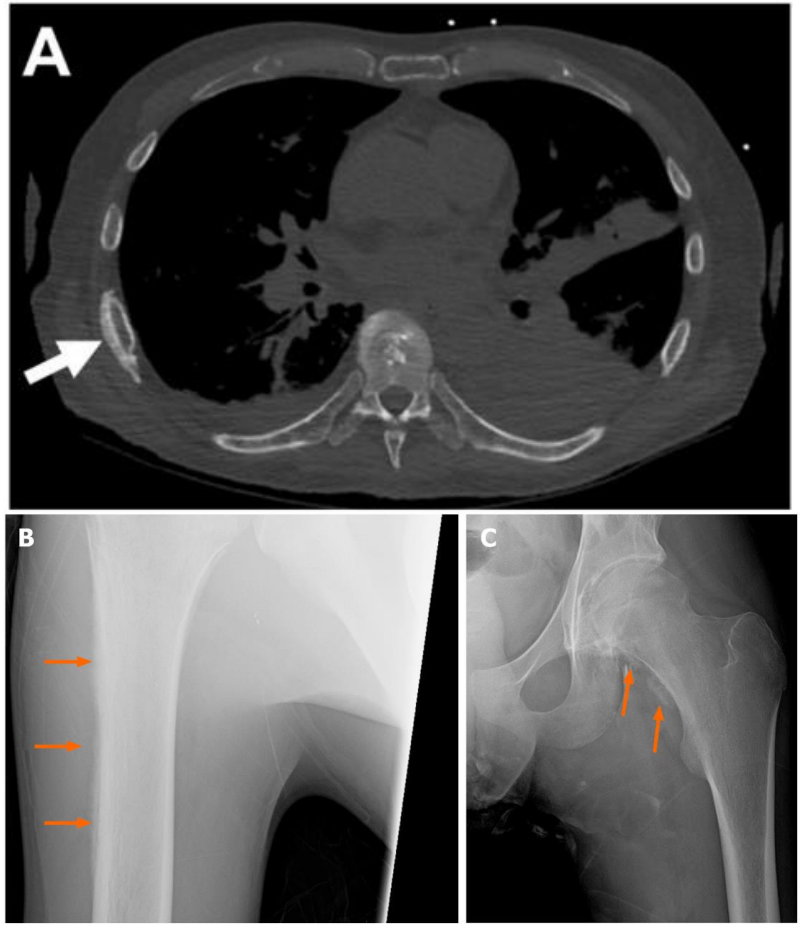


Soriano M. Radiology. 1966.

Attention au diagnostic différentiel !

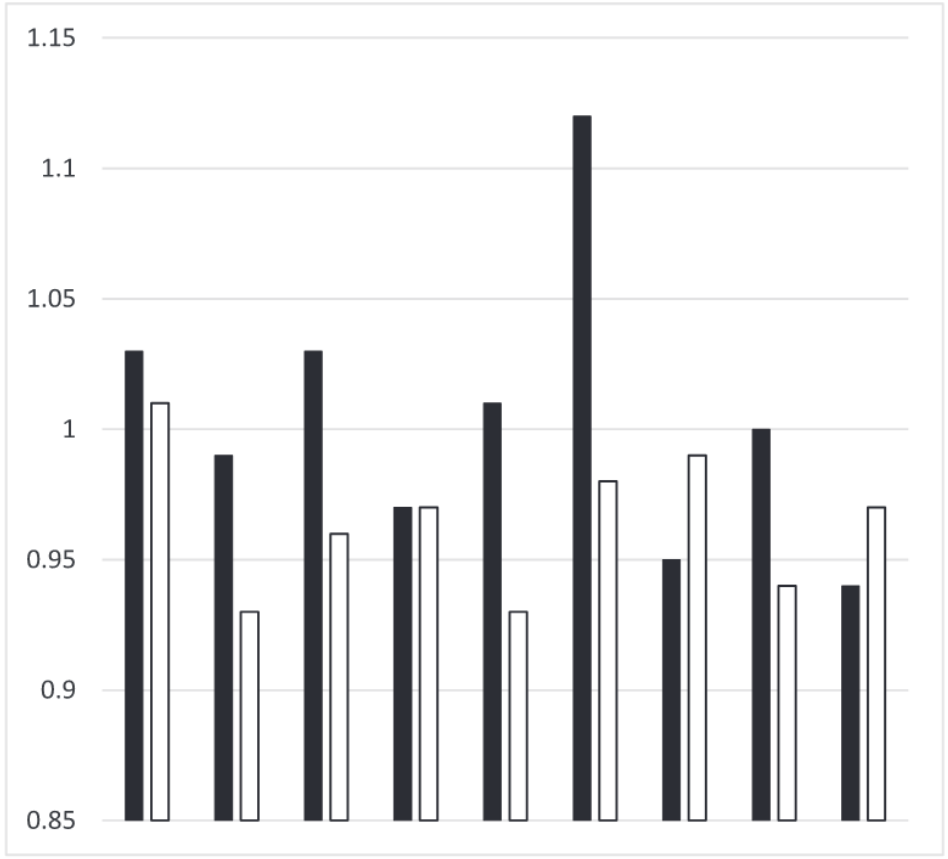
	Patients with VIP ($n=9$)
Total number of lesions, *N*	116
Number of lesions per patient, median (IQR)	10 (6–16)
Number of lesions per patient, min–max	3–36
Length of lesions, mean (SD) mm	26.5 (11.5)
Length of lesions, min–max mm	2.8–112.0
Lesion location in the body, *n* (%)	
Ribs	43 (37%)
Hands	27 (23%)
Legs	19 (16%)
Arms	15 (13%)
Scapulae	8 (7%)
Clavicles	2 (2%)
Costovertebral joints	1 (1%)
Feet	1 (1%)
Lesion location in the bone, *n* (%)	
Diaphysis	49 (42%)
Body	43 (37%)
Metaphysis	9 (8%)
Epiphysis	7 (6%)
Fossa	7 (6%)
Glenoid	1 (1%)

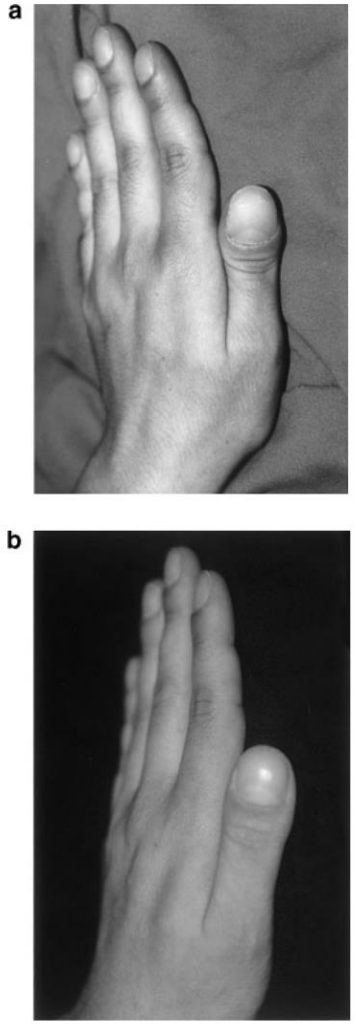




Ashmeik W, et al. Skeletal Radiol. 2025.
Guarascio AJ, et al. WJT. 2021.

Niveau thérapeutique ? Effet transplantation





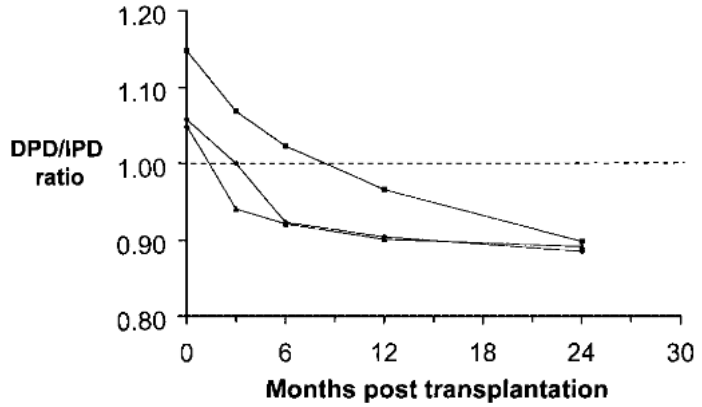


Fig. 3. DPD/IPD ratio in 3 patients prior to and following transplantation. Horizontal dashed line represents upper limit of normal DPD/IPD ratio.

Mahlen T, et al. Journal of Cystic Fibrosis 2022.
Augarten A, et al. Pediatric Pulmonology 2002.

Niveau thérapeutique ? Traitements spécifiques

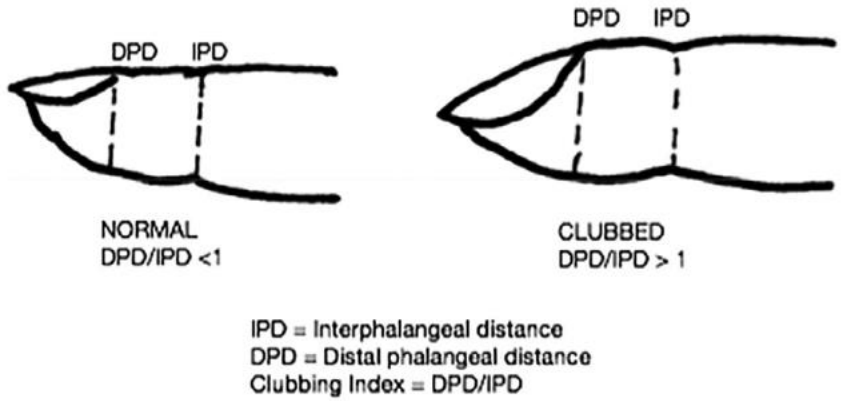
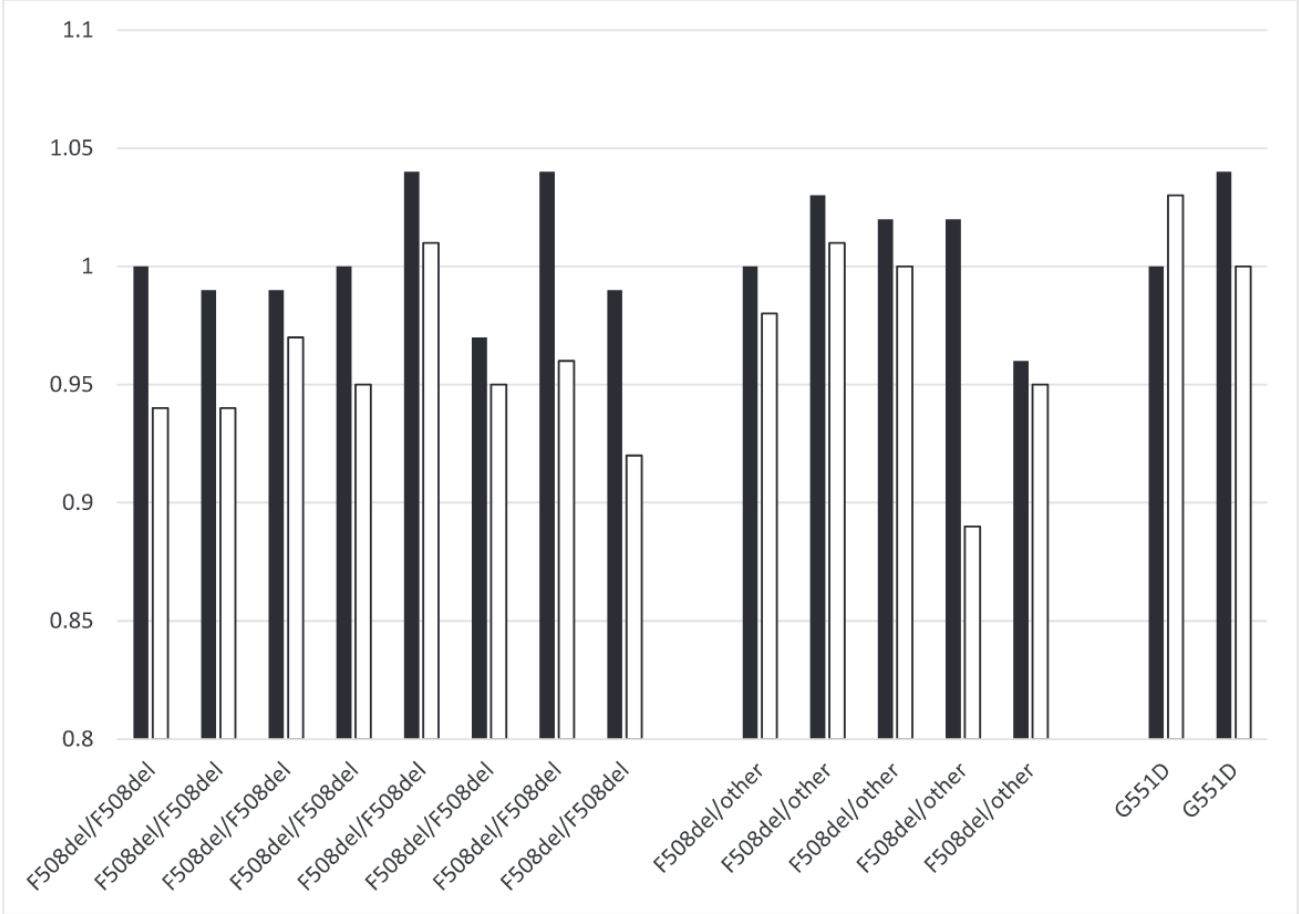


Fig. 1. Representation of measurements used to determine clubbing index.



15 patients
Kalydeco : 2 patients
ETI : 13 patients

Mahlen T, et al. Journal of Cystic Fibrosis 2022.

Niveau thérapeutique ? Autre ?

Table 1 Laboratory Test Results

Laboratory Test	Normal Range	At Presentation	2 Months After Pamidronate Infusion	11 Days After ZA Infusion	9 Months After ZA Infusion
Hemoglobin (g/L)		9.7			
Alkaline Phosphatase (U/L)	40-150	270		117	
Creatinine (mg/dL)	0.7-1.4	1.41	1.08		
BUN (mg/dL)	8-25	38			
Calcium (mg/dL)	8.5-10.5			8.9	
eGFR		46	>60		
Creatinine kinase (U/L)	30-220	23			
Uric acid (mg/dL)	2.0-7.0	4.7			
Phosphorus (mg/dL)	2.5-4.5	2.4		2.4	
Calcium (mg/dL)	8.5-10.5	9.6			
Intact PTH (pg/mL)	10-60	43			
25-hydroxy vitamin D level (ng/mL)	31-80	42.2			
1,25-hydroxy vitamin D (pg/mL)	18-78	38			
TSH (uU/mL)	0.4-5.5	0.945			
ESR (mm/h)	0-15	56			
CRP (mg/dL)	0-1.0	1.9			
RF (IU/mL)	<20	7			
ANA by EIA (OD ratio)	<1.5	1.1			
NTX (nM/mmol/L creatinine)	14.4-75.0	159.3	95.1		51.4

ANA, anti-nuclear antibody; BUN, blood urea nitrogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NTX, cross-linked N-telopeptide; PTH, parathyroid hormone; RF, rheumatoid factor; TSH, thyroid stimulating hormone; ZA, zoledronic acid.

Table 2 Use of Bisphosphonates in Patients with HOA

Reference[a]	Bisphosphonate	Underlying Disease	Dose (mg)	Route	Noticeable Effects (days)	Effect Duration	Repeat Infusions
Amital et al (2)	Pamidronate	Congenital cyanotic heart disease	60	IV	7	4 mo	No
Garske et al (4)	Pamidronate	Cystic fibrosis	30	IV	3	10-16 wk	4
Suzuma et al (7)	Pamidronate	Breast cancer with pulmonary metastasis	30	IV	7	21 d	Every 2 wk × 5 mo
Yao et al (8)	Pamidronate	Lung transplant rejection	60	IV	7	NA	No
Jojima et al (17)	Risedronate	Pachydermoperiostosis	5	Oral	90	NA	Daily
Mauricio et al (5)	Pamidronate	Non-small-cell lung cancer	90	IV	4	4 mo	No
Bhansali et al (3)	Pamidronate	Pachydermoperiostitis	60	IV	NA	NA	NA
Speden et al (6) case 1	Pamidronate	Non-small-cell bronchogenic carcinoma	45	IV	8	3 mo	2
Speden et al (6) case 2	Pamidronate	Lung adenocarcinoma	15	IV	60	NA	No
Speden et al (6) case 3	Pamidronate	Lung squamous cell carcinoma	30	IV	12 h	7 d	2
King et al (9)	ZA	Bronchogenic carcinoma	4	IV	3	3 wk	No
Thompson et al (10)	ZA	Metastatic melanoma	4	IV	60	NA	Every 3-4 wk × 4

IV, intravenously; NA, not applicable; ZA, zoledronic acid.
[a]No adverse reactions reported.

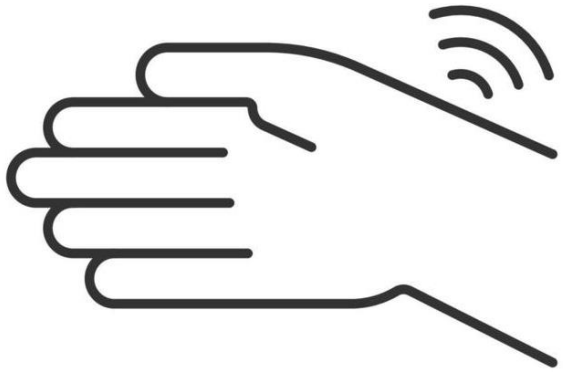
Jayakar BA, et al. Seminars in Arthritis and Rheumatism 2011.

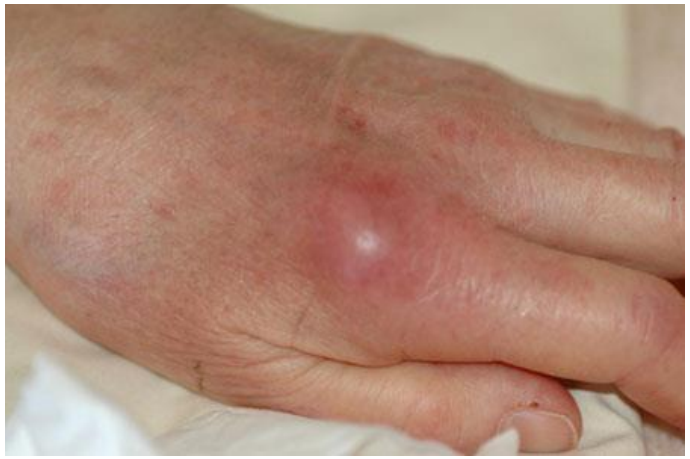
Que faire si douleurs ostéo-articulaires ?

Quel bilan devant des douleurs articulaires ?

Clinique

- Douleur osseuse ou articulaire
- Articulation touchées / nombre
- Horaire inflammatoire ou mécanique
- Gonflement articulaire ?
- Evolution par crise
- Signes extra rhumatologiques





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Biologie

- Marqueurs inflammatoires : CRP, NFS
- Bilan auto immun : facteur rhumatoïde et anti CCP (si inflammatoire > 6 sem)

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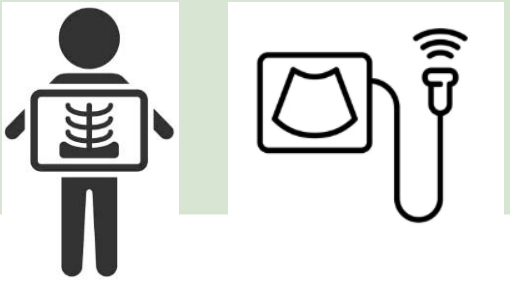
Biologie

- Marqueurs inflammatoires : CRP, NFS
- Bilan auto immun : facteur rhumatoïde et anti CCP (si inflammatoire > 6 sem)

Imagerie

- Radios standard bilatérale et comparatives : mains/pieds, et toute articulation douloureuse
- Echographie à la recherche de synovite/tenosynovite



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- Echographie à la recherche de synovite/tenosynovite

Consultation rhumato

Comment traiter ?

Quel traitement envisager ?

Discussion au cas par cas

Dépend de la sévérité de l'atteinte articulaire et pulmonaire

Traitements symptomatiques à la demande dans les formes mineures

- AINS
- Corticoides avec vigilance sur la dose au long cours/cumulée
- Infiltrations cortisonées
- Traitement non médicamenteux : APA/kiné/ergo

Traitements « de fond » dans les atteintes rhumatismales chroniques/destructrices/à risque évolutif

- DMARDs
- Thérapie ciblées

Points essentiels

Atteintes articulaires de la mucoviscidose : hétérogènes et méconnues

Entité « atteinte articulaires épisodique de la mucoviscidose » : la définition n'est pas établie

Probable surrisque de développer une polyarthrite rhumatoïde avec la mucoviscidose avec des mécanismes physiopathologiques explicatifs

Surrisque d'autres rhumatismes inflammatoires chroniques est débattu et non prouvé à ce jour

Le traitement peut se calquer sur les recommandations rhumatologiques pour la PR-mucoviscidose après discussion avec le pneumologue (risque d'immunodépression)

Lorsque le diagnostic rhumatologique n'est pas clair : traitement au cas par cas, sur avis d'expert et selon la gravité et le retentissement de l'atteinte articulaire

OAH : restauration de la fonction pulmonaire++, AINS et bisphosphonate avec faible niveau de preuve