

Densité minérale et remodelage osseux dans la maladie de Gaucher

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Atteinte Osseuse

- 80% des cas dans types 1 et 3
- Fréquemment révélatrice
- **Principale cause de morbidité et d'invalidité**
 - Douleurs osseuses
 - fractures
 - Ostéonécrose
 - Infarctus osseux
 - Douleurs articulaires
- Pas de corrélation avec l'atteinte viscérale

Ostéopénie et Gaucher

- **11-58% de fractures vertébrales**
- **Fractures os longs plus rares**
- **Relation DMO/fracture dans ce contexte ?**
- **L'enzymothérapie est-elle efficace ?**
- **Est-elle suffisante ?**

Quelle est la cause de la perte osseuse ?

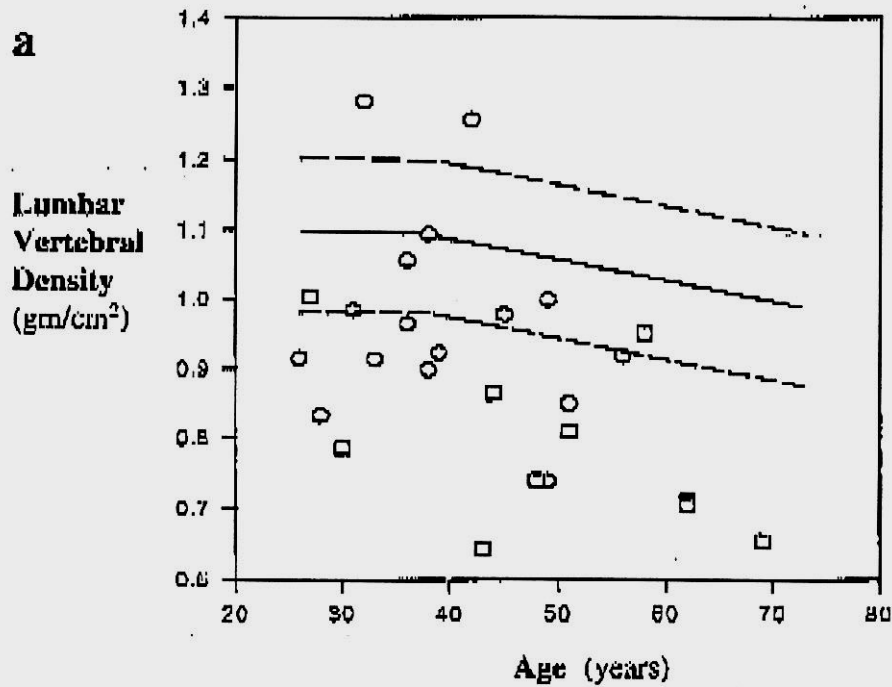
- **Élévation de l'IL-6, IL-1, TNF α ...**
- **Activation de la cathepsin K**
- **Diminution des précurseurs ostéoblastiques ?**
- **Augmentation de la résorption dans certains cas ?**

DXA et Gaucher

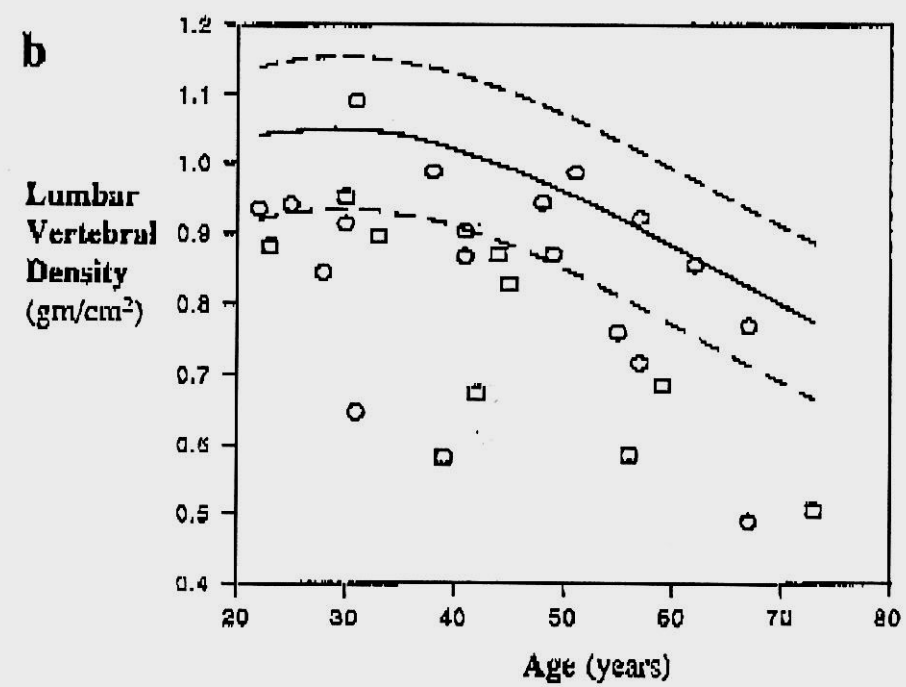
- **61 adultes de 22-77 ans**
- **Z-score diminué au rachis lombaire, à l'ESF et radius**
- **Corrélation* avec**
 - la sévérité de la maladie
 - la sévérité de l'atteinte RX osseuse
- **DMO N370S/N370S > N370S/84GG**

* Après ajustement

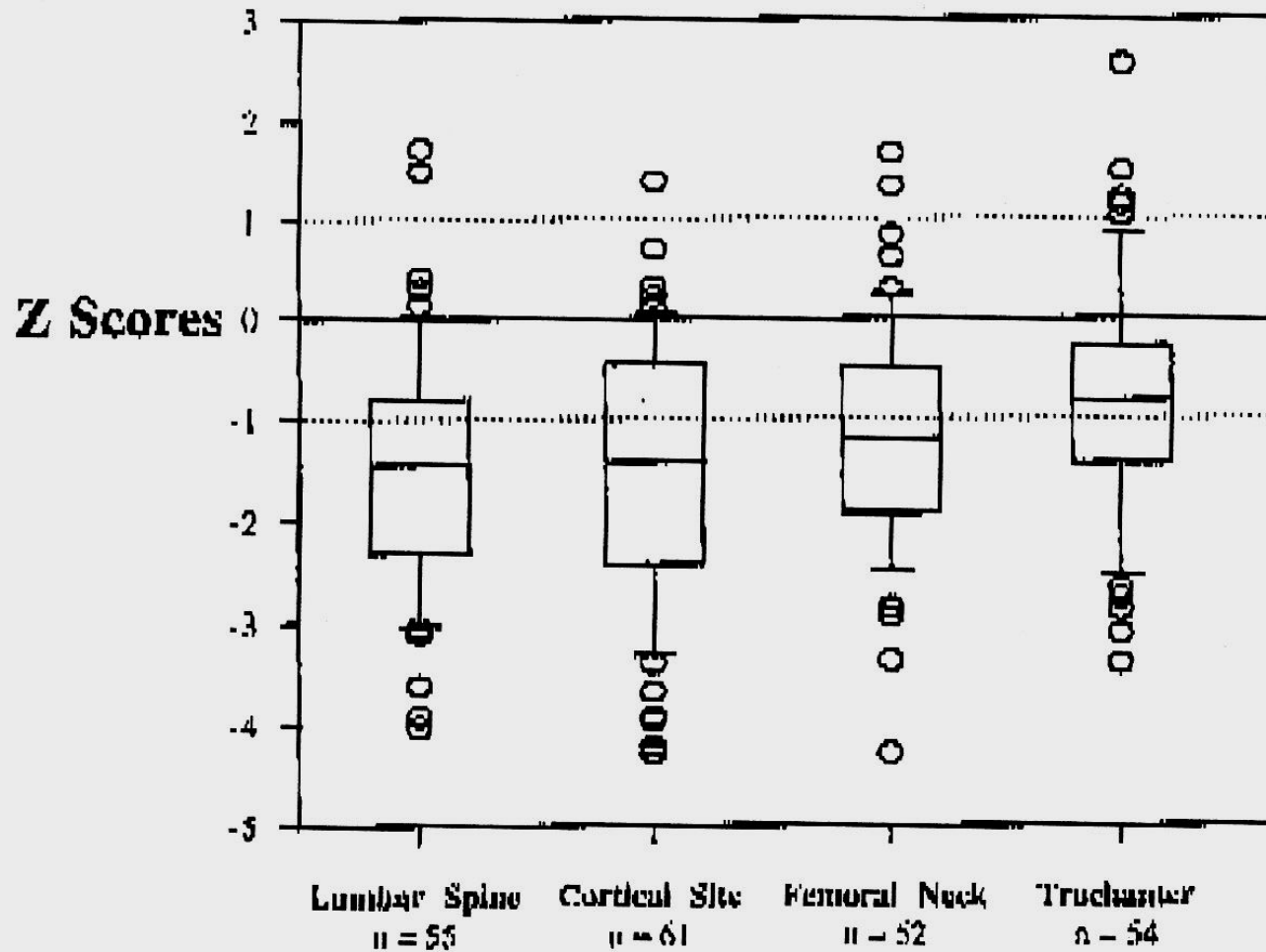
Hommes



Femmes

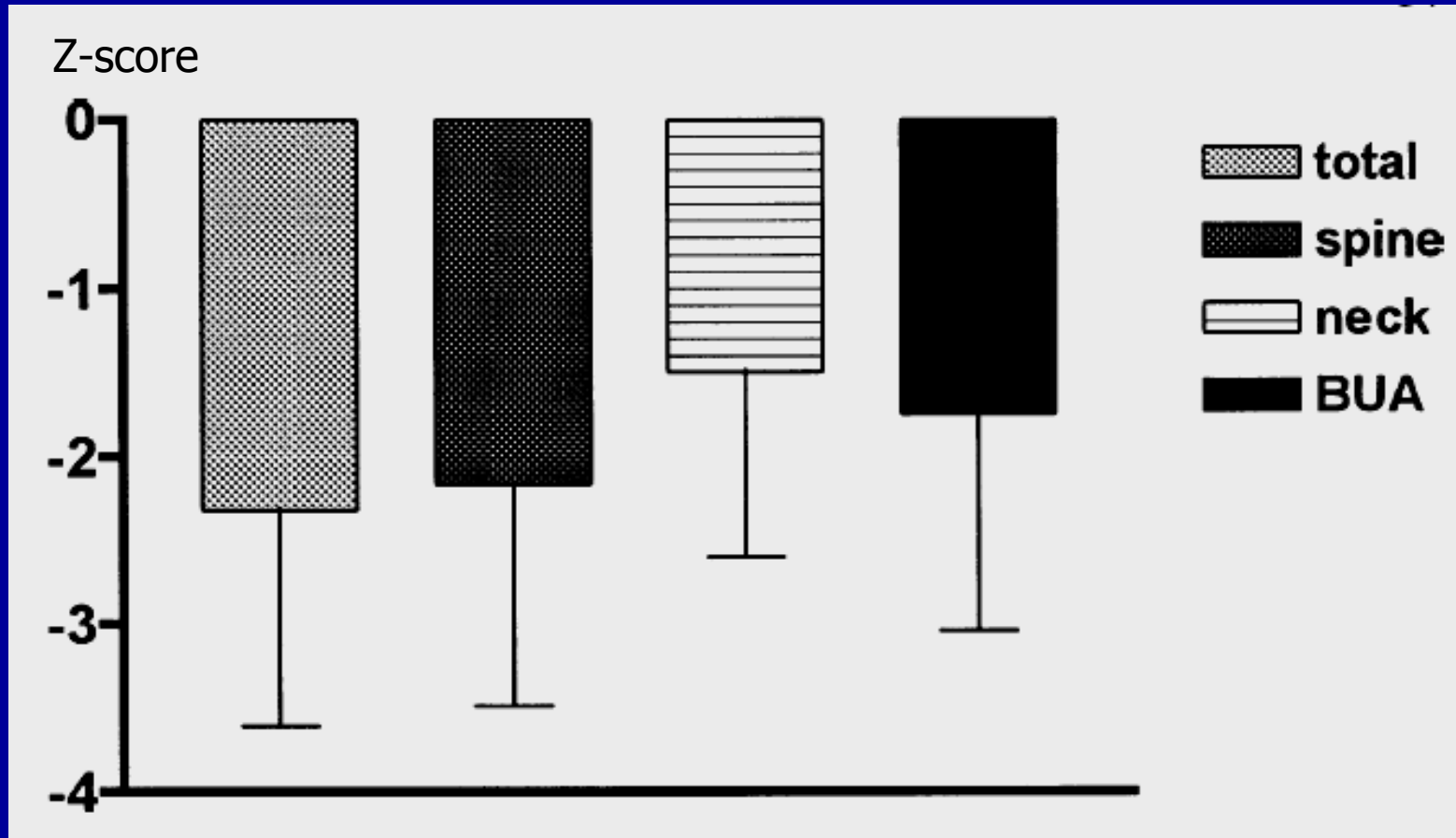


- avec rate
- Splénectomie (n=25)



DMO corrélée à la sévérité clinique et RX même après ajustement (âge, sexe, poids, génotype, splénectomie, hépatomégalie)

Perte osseuse en DXA et US dans la maladie de Gaucher



12 patients GD type I, 33±13 ans

Corrélation entre DXA, US et sévérité de la maladie de gaucher

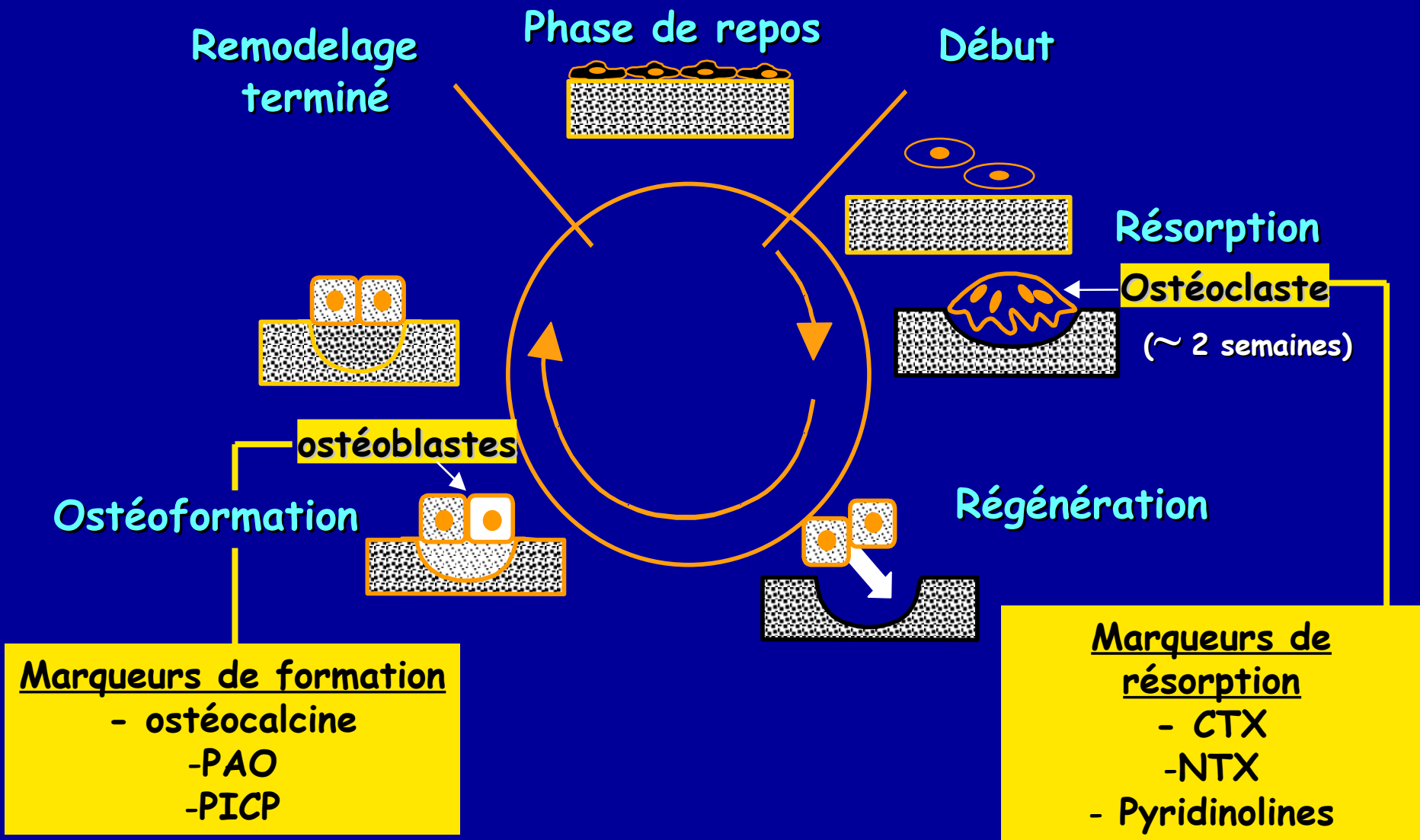
Table 3. Correlations (Spearman r) between Severity Score Index (SSI), Bone Involvement Index (BSSI), bone densitometric parameters, and markers of bone turnover in 12 patients with type 1 GD

	SSI	BSSI	BUA	BMD ^{TB}	BMD ^{LS}	BMD ^{FN}
BUA	-0.52	-0.77**	1	0.37	0.59*	-0.88**
BMD ^{TB}	-0.41	-0.67*	0.37	1	0.50	0.52
BMD ^{LS}	-0.42	-0.68*	0.59*	0.50	1	0.58*
BMD ^{FN}	0.54	-0.70*	0.88**	0.52	0.58*	1
BAP	0.07	0.33	-0.18	-0.52	-0.24*	-0.15
OC	0.04	0.39	-0.18	-0.45	-0.40	-0.26
Upyr/Cr	0.26	0.59*	-0.55**	-0.51	-0.34	-0.34
Ud-pyr/Cr	0.16	0.49	-0.39	-0.61*	-0.10	-0.25
SSI	1	0.81**	-0.52	-0.41	-0.42	0.54

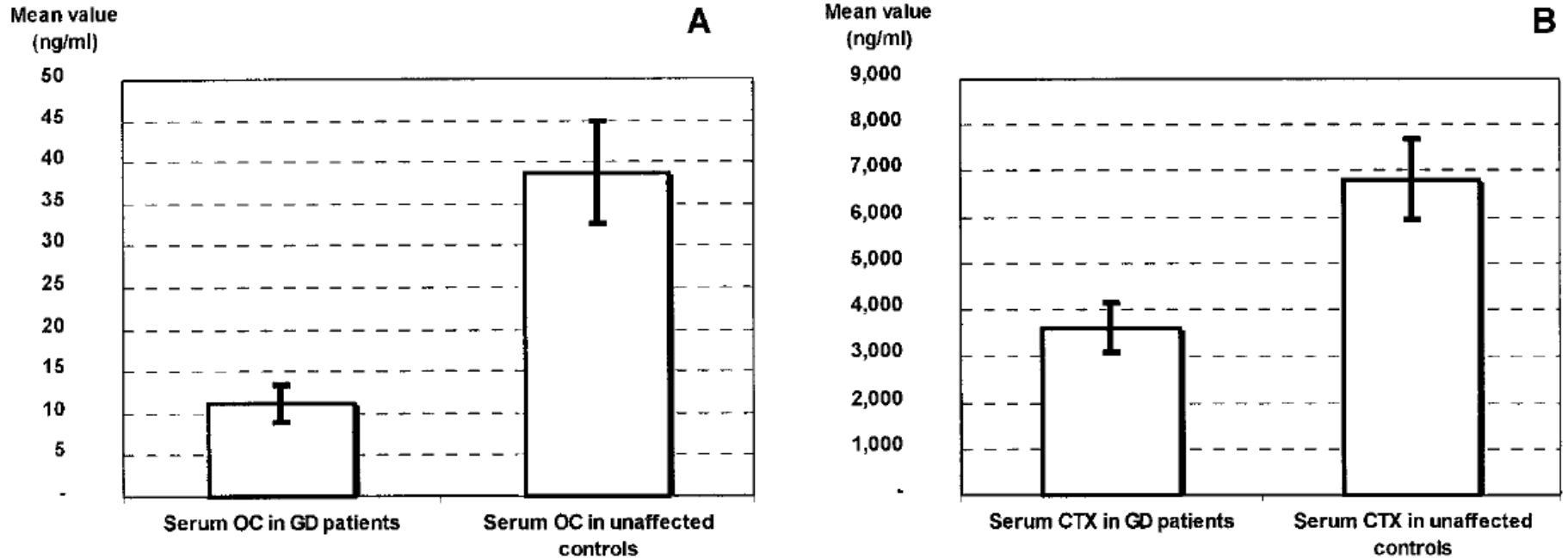
BUA, broadband ultrasound attenuation at calcaneus; BMD^{TB}, total body bone mineral density; BMD^{LS}, lumbar spine bone mineral density; BMD^{FN}, femoral neck bone mineral density; BAP, serum bone-specific alkaline phosphatase; OC, serum osteocalcin; Upyr/Cr, urinary pyridinoline/creatinine; Ud-pyr, urinary deoxypyridinoline/creatinine

$P < 0.05$; $P < 0.001$

Remodelage osseux

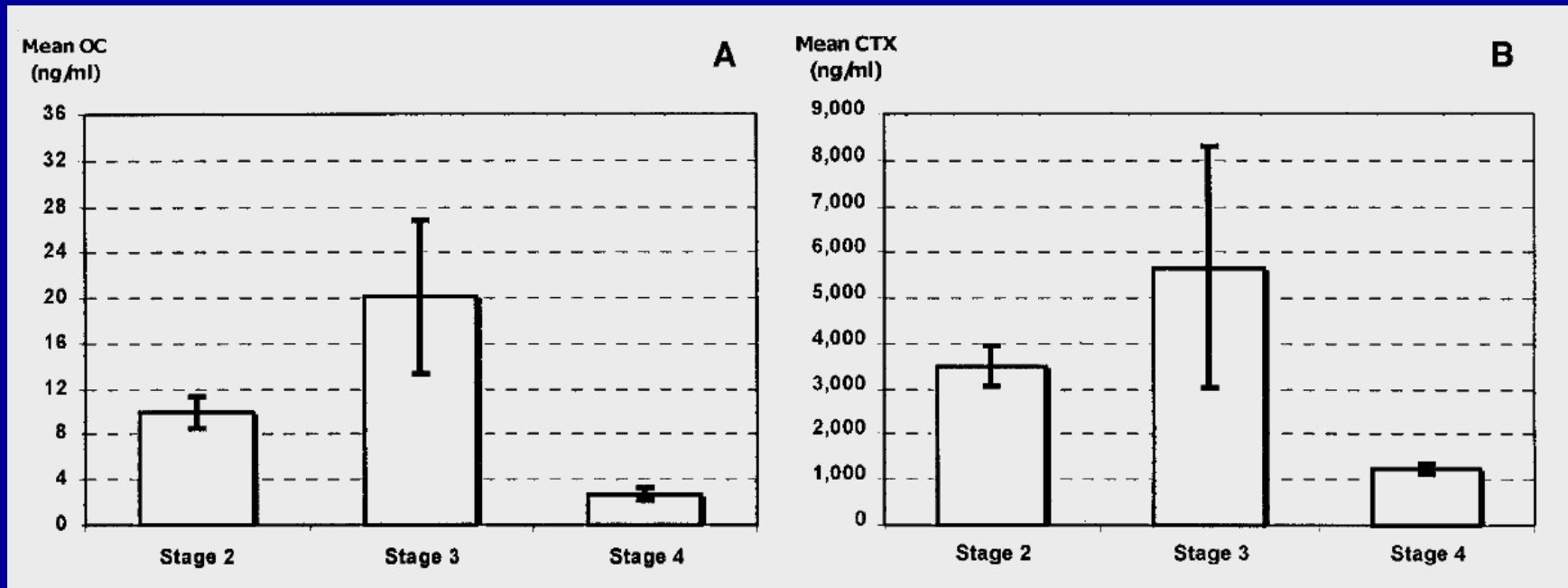


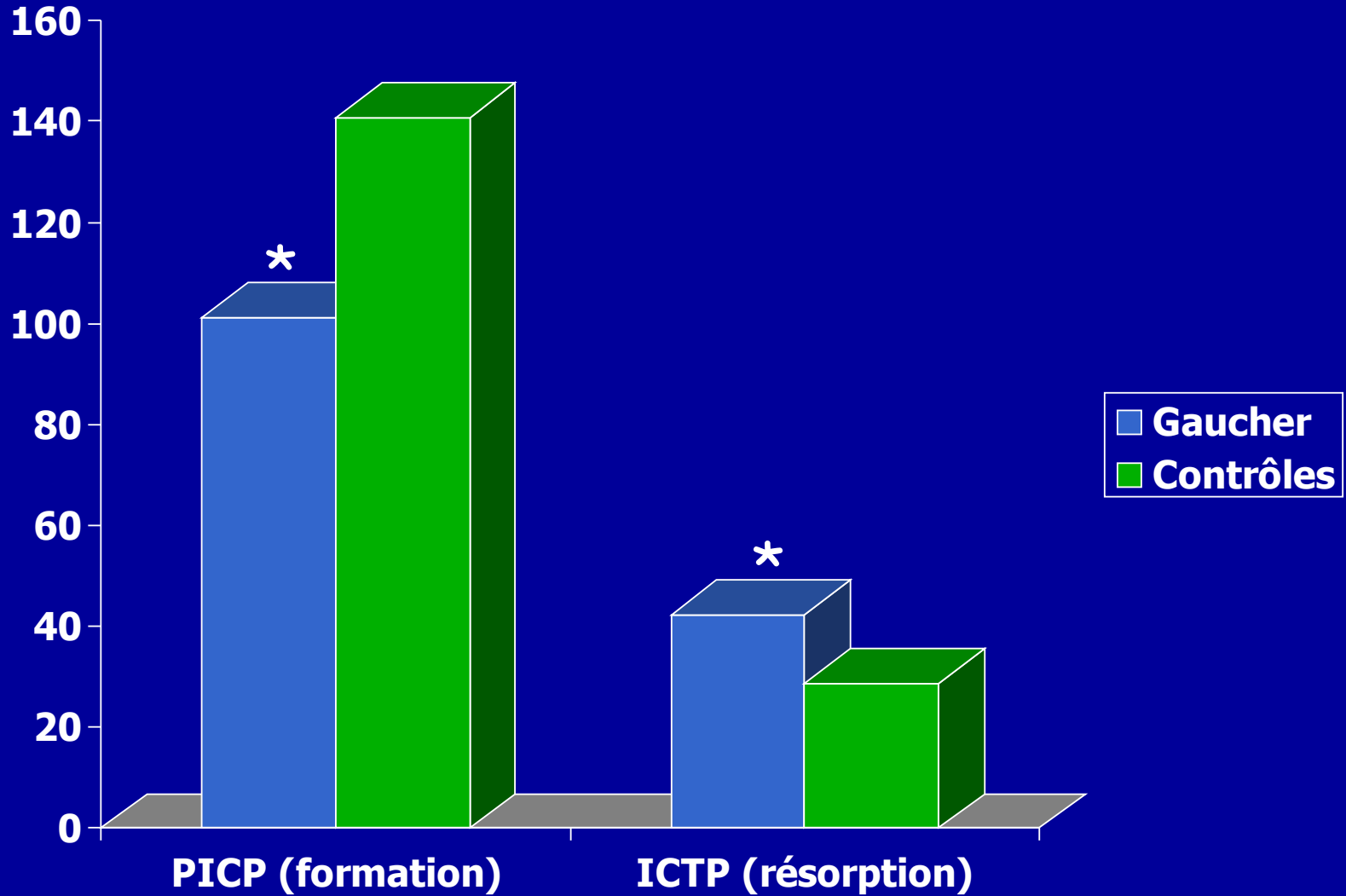
Marqueurs de remodelage osseux et Gaucher



16 Gaucher type I (27.4 ans) vs 29 contrôles appariés pour l'âge

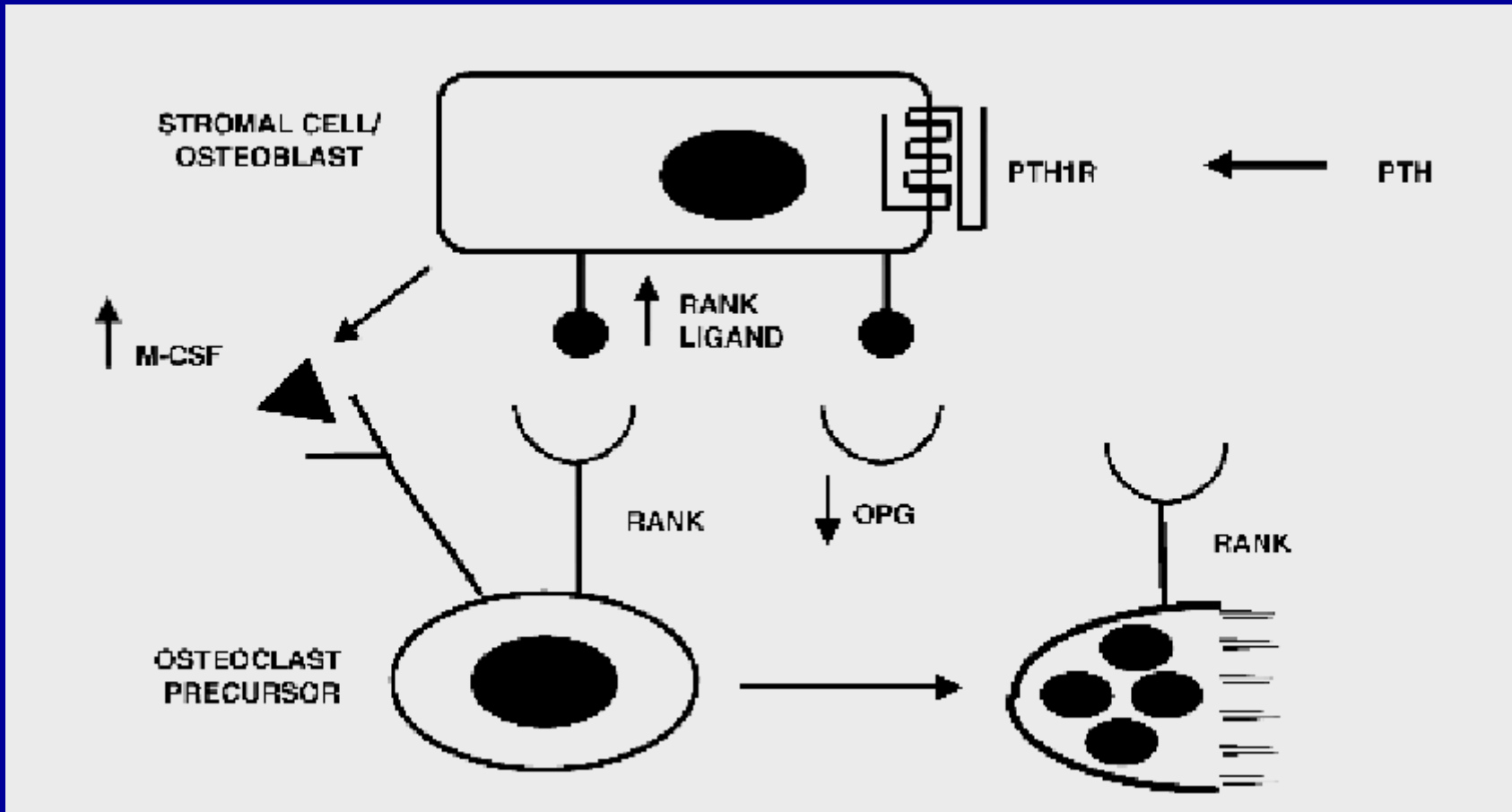
Marqueurs de remodelage osseux et Gaucher

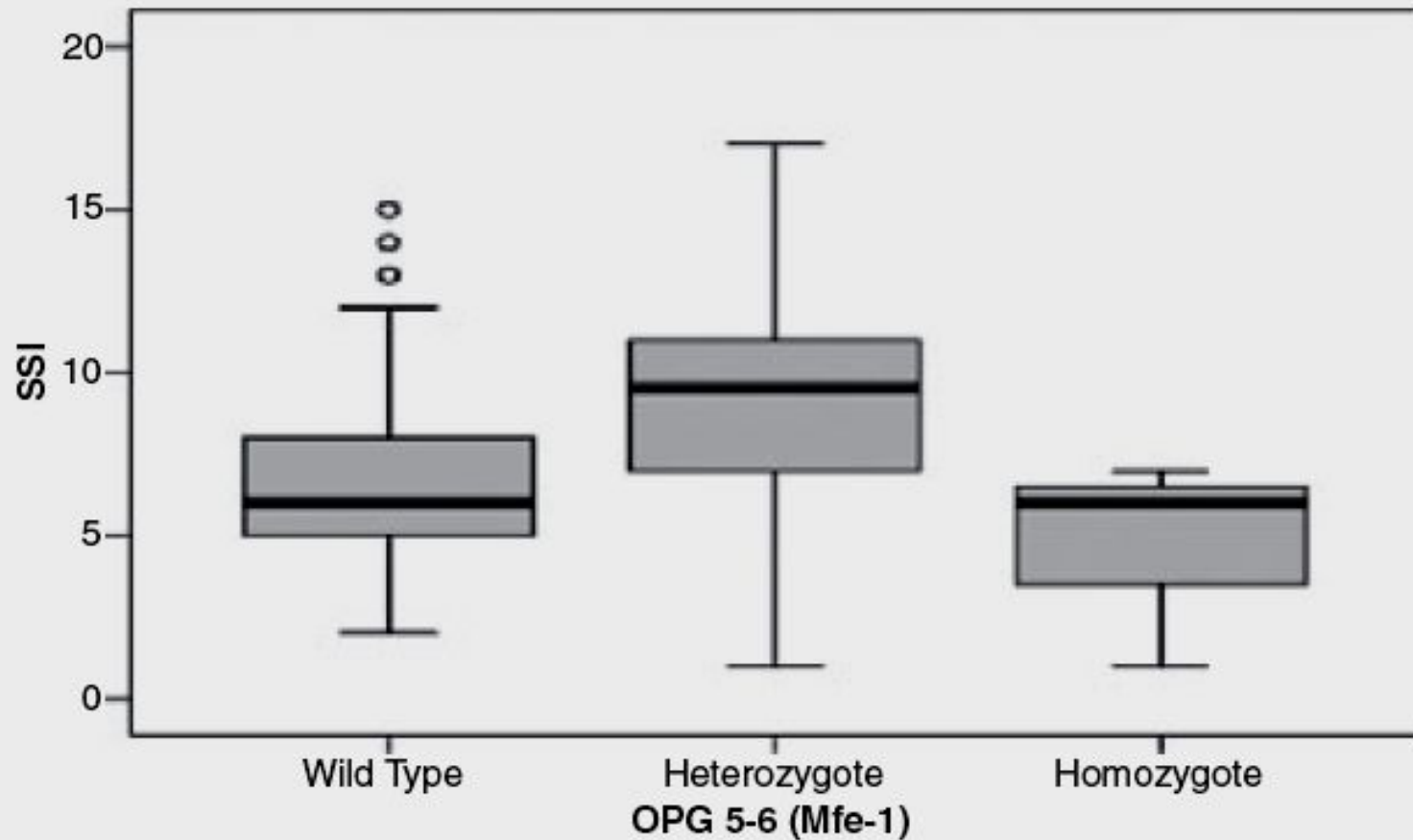




10 Gaucher type I

RANK/RANKL/OPG ?

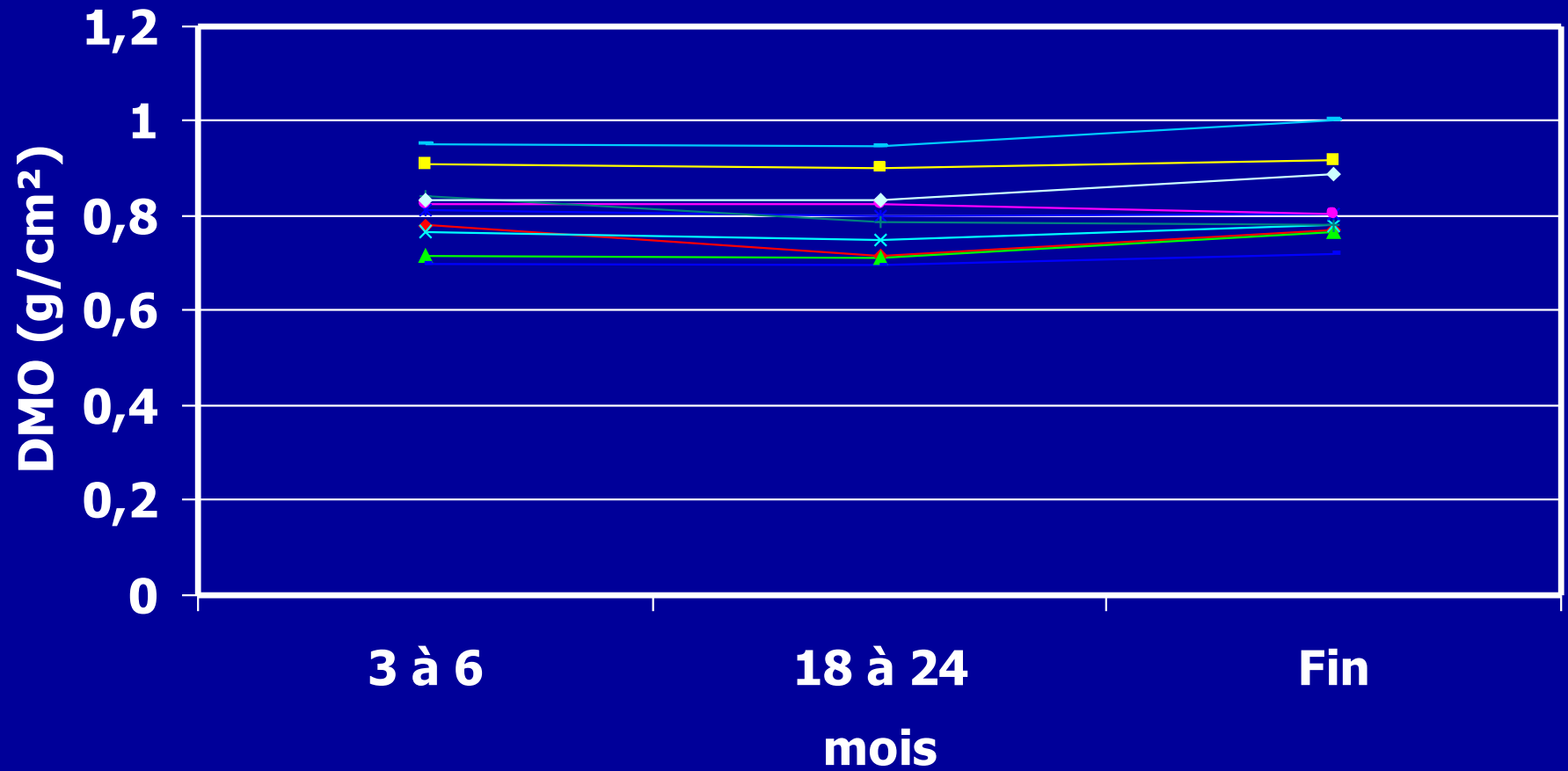




- Absence de corrélation entre taux d'OPG, DMO, génotype et marqueurs d'activité
- Corrélation entre génotype OPG 5-6 et sévérité

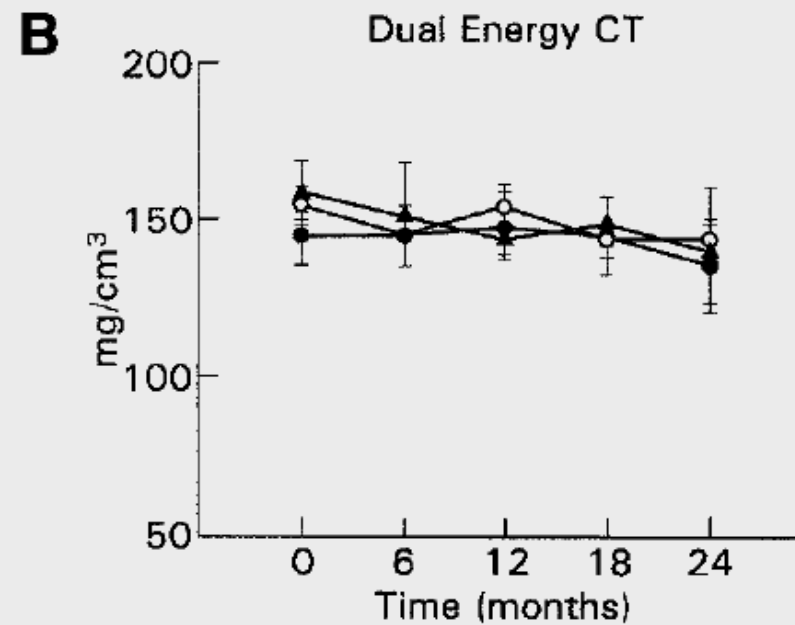
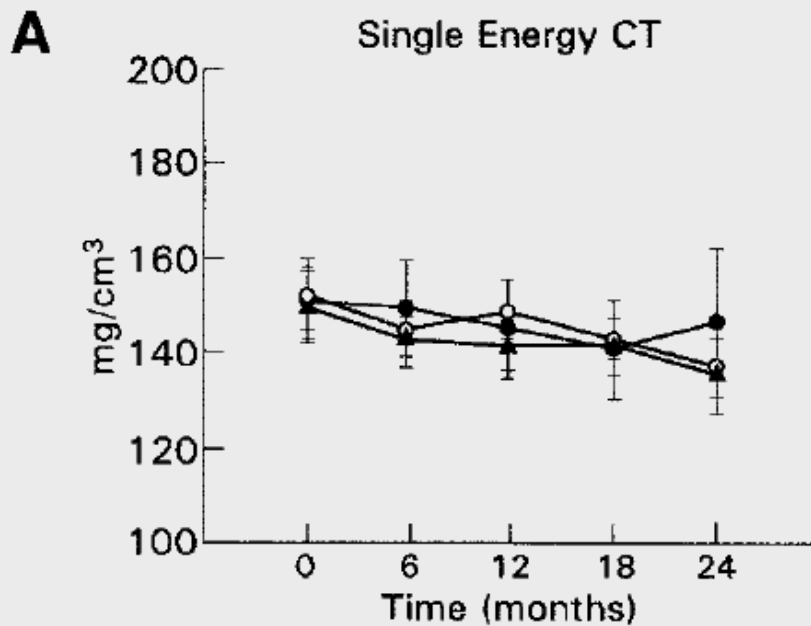
Evolution de la DMO sous traitement substitutif

- **10 patients suivis de 60 à 108 mois**
 - 8 femmes (18-46 ans)
 - 2 hommes (35 et 44 ans)
- **Inclus dans essais thérapeutiques**
- **DMO (Z-score)**
 - **Lombaire: -2.27 ± 0.9 DS**
 - **Col fémoral: -1.78 ± 0.52 DS**

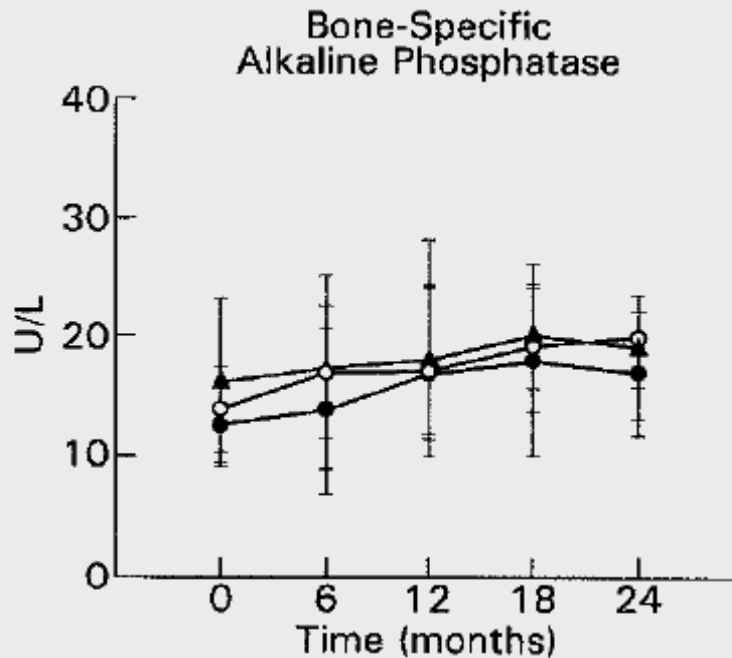
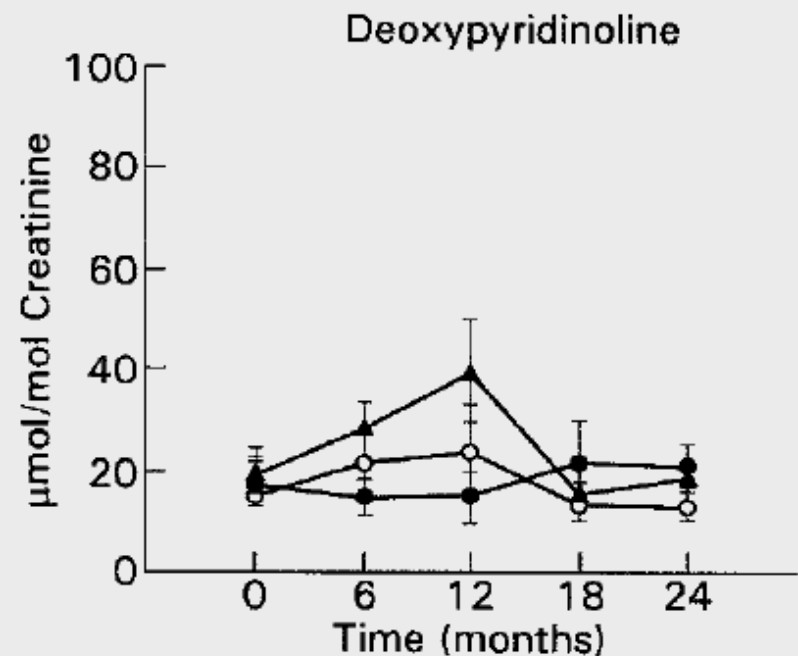


• Absence de douleurs osseuses, fractures, ostéomyélite ou nouvelle ON

DXA après splénectomie et traitement substitutif (n=29)



DXA après splénectomie et traitement substitutif (n=29)

D**G**

Gaucher disease and bone: Laboratory and skeletal mineral density variations during a long period of enzyme replacement therapy

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- **12 Gaucher type I**
 - 6 hommes et 6 femmes
 - N370S
 - Âge moyen 32.3 ans (25-40)
 - Evaluation avant ERT
- **12 contrôles**
- **Suivi 4.5 ans**

Table 2 Serum biochemical and urinary parameters of bone resorption/formation in the 12 GD I patients compared to 12 healthy adult subjects. Data are expressed as mean values with standard deviation (SD)

	<i>Patients (n = 12)</i> [mean (SD)]	<i>Controls (n = 12)</i> [mean (SD)]	<i>p-Value</i> ^a
Bone ALP isoenzyme (U/L)	29.75 (18.85)	30.90 (12.93)	NS
PICP ^b (ng/ml)	100.52 (30.70)	142.45 (63.51)	0.017
ICTP ^c (ng/ml)	3.93 (1.40)	2.72 (0.47)	0.004
PTH (pg/ml)	30.01 (13.17)	45.76 (29.46)	NS
Hydroxyproline (mg/g creatinine)	17.30 (5.26)	17.9 (4.45)	NS
Free deoxypyridinoline (pmol/ μ mol creatinine)	6.4 (2.66)	5.38 (1.81)	NS
Ca/creatinine (mg/mg creatinine)	0.062 (0.009)	0.082 (0.009)	0.07

Student's two sided *t*-test; *p*-values < 0.05 regarded as statistically significant; NS, non-significant

^bCarboxyterminal propeptide of type I procollagen

^cCarboxyterminal telopeptide of type I collagen

Table 3 Serum and urinary bone markers changes during the follow-up period. Data are expressed as mean values \pm standard deviation (SD)

	<i>Patients (n = 12)</i>					<i>p-Value^a</i>
	<i>At baseline</i> [mean (SD)]	<i>After 4–6 months</i> [mean (SD)]	<i>After 1 year</i> [mean (SD)]	<i>After 2 years</i> [mean (SD)]	<i>After 4.5 years</i> [mean (SD)]	
Bone ALP isoenzyme (U/L)	29.75 (18.85)	28.69 (19.85)	29.68 (18.79)	25.31 (11.77)	23.25 (10.27)	NS
PICP ^b (ng/ml)	100.87 (30.31)	102.94 (65.01)	123.72 (65.80)	115.20 (61.87)	118.43 (30.23)	NS
ICTP ^c (ng/ml)	3.94 (1.40)	3.96 (1.52)	3.80 (1.26)	3.74 (1.32)	3.84 (0.94)	NS
PTH (pg/ml)	30.39 (13.53)	26.94 (9.29)	34.76 (21.36)	31.73 (17.68)	39.07 (18.41)	NS
Hydroxyproline (mg/g creatinine)	18.77 (5.18)	21.65 (9.86)	23.58 (9.01)	22.13 (8.17)	20.56 (6.72)	NS
Free deoxypyridinoline (pmol/ μ mol creatinine)	6.49 (2.58)	6.05 (2.07)	5.87 (2.06)	7.37 (3.91)	6.99 (3.68)	NS
Ca/creatinine (mg/mg creatinine)	0.06 (0.033)	0.064 (0.035)	0.093 (0.058)	0.096 (0.058)	0.191 (0.15)	0.0014

^aRepeated-measures ANOVA; *p*-values < 0.05 regarded as statistically significant; NS, non-significant

^bCarboxyterminal propeptide of type I procollagen

^cCarboxyterminal telopeptide of type I collagen

Table 4 Individual changes in lumbar BMD, expressed in g/cm², percentage change at the last examination from baseline and mean BMD variations with standard deviation, expressed in g/cm², during ERT follow-up

<i>Patient no., sex, age (years)</i>	<i>Baseline</i>	<i>4–6 months</i>	<i>1 year</i>	<i>2 years</i>	<i>4.5 years</i>	<i>Change from baseline (%)</i>
1, F, 25	1.050	1.052	1.096	1.023	1.091	+3.9
2, M, 27	0.990	0.999	1.010	1.049	1.050	+5.1
3, M, 27	1.001	0.979	0.957	1.013	1.012	+1.09
4, M, 31	0.952	0.986	1.019	0.982	0.995	+4.5
5, F, 30	1.103	1.115	1.130	1.140	1.173	+6.34
6, F, 23	0.859	0.859	0.876	0.875	0.952	+10.82
7, M, 34	1.146	1.178	1.165	1.146	1.164	+1.57
8, M, 40	0.898	0.952	0.872	0.905	0.880	−2.0
9, M, 38	0.932	0.940	0.950	0.962	0.981	+5.25
10, F, 36	0.852	0.847	0.879	0.881	0.836	−1.87
11, F, 26	0.944	0.944	0.954	0.952	0.961	+1.8
Mean	0.978	0.986	0.991	0.993	1.008	$p = 0.039^a$
(SD)	(0.09)	(0.09)	(0.10)	(0.09)	(0.10)	

^aANOVA; p -values < 0.05 regarded as statistically significant

Effet du pamidronate

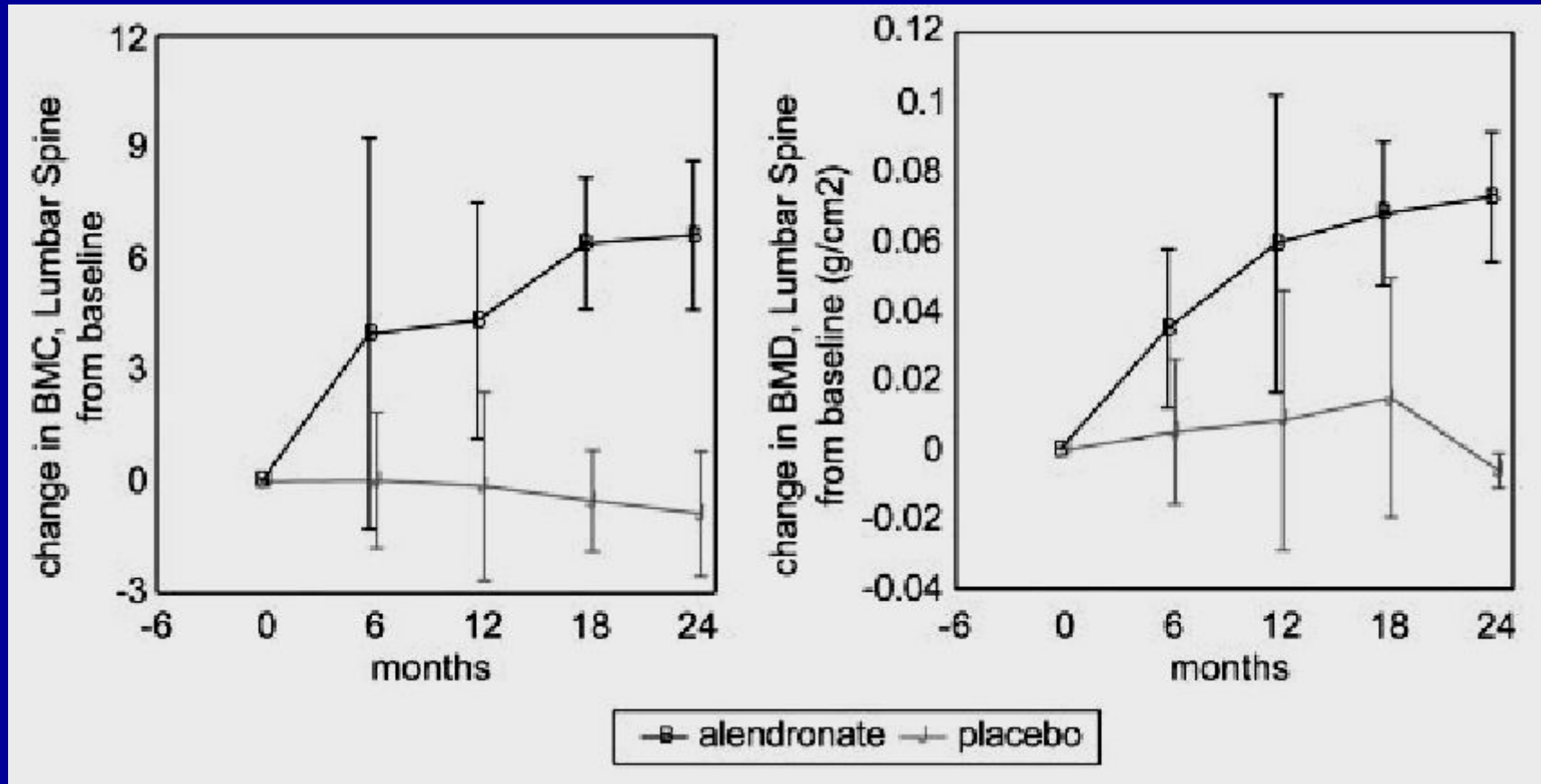
- **5 patients gaucher Type I**
 - 3 femmes et deux hommes
 - 24 à 60 ans
 - Atteinte osseuse sévère
- **45 mg pamidronate/3 sem – 5 mois**
- **Amélioration des douleurs**
- **Diminution des marqueurs de remodelage**
- **↑ DMO : 0.79 ± 0.07 à 0.84 ± 0.05 g/cm² (p=0.04)**

Traitement par alendronate

Design aspect	Description
General design	Double-blind, 2-arm; alendronate versus placebo
Duration	Up to 24 months
Study interval	6 months
Treatment	<u>Alendronate: 40 mg once per day versus placebo</u> Vitamin D: 400 U once per day Calcium carbonate (Tums): 1.5 g once per day
Key inclusion criteria	Gaucher disease, on ERT more than 24 months Older than 18 years and less than 50 years of age Lumbar spine Z score less than -1
Key exclusion criteria	Pregnancy Prior use of antiresorptive agents Active gastric or duodenal ulcer disease
Endpoints	
Primary	Changes in lumbar spine BMD in g/cm ² Reduction in focal changes in long-bone x-rays
Secondary	Reduction of biochemical indices of bone turnover

Traitement par alendronate

	ALN; N = 17	Placebo; N = 17	P
Baseline			
Male sex, %	29	29	
Age, y	39.50 ± 7.38	32.99 ± 9.91	.0374
Enzyme dose, U/kg	28.88 ± 8.66	37.59 ± 15.09	.049
BMC, g	59.13 ± 15.60	60.62 ± 13.92	.7707
BMD, g/cm ²	0.95 ± 0.14	0.95 ± 0.14	.9527



- **Arrêt de l'étude à 24 mois AIn>>PCB**
- **↑ DMO dès 6 mois**
- **Pas d' ↑ significative sous enzyme seule**
- **Marqueurs de remodelage osseux**
 - ↓ ostéocalcine et PAO
 - ↓ NTXu mais pas des pyridinolines...
- **Pas de variations radiographiques**
 - Lésions focales inchangées
- **Diminution des fractures ?**
- **Problème de la dose ?**