

# Bases de l'interprétation du bilan phospho-calcique et de l'ostéodensitométrie osseuse

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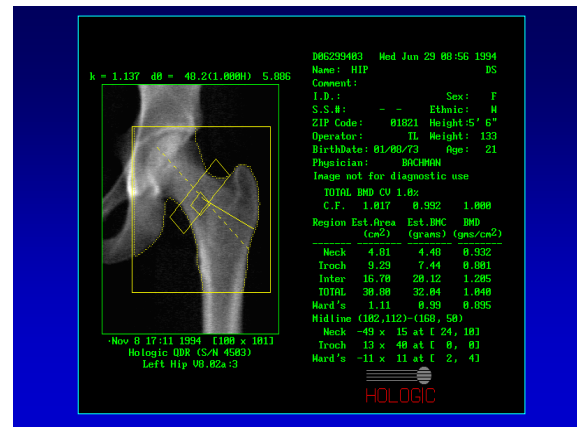
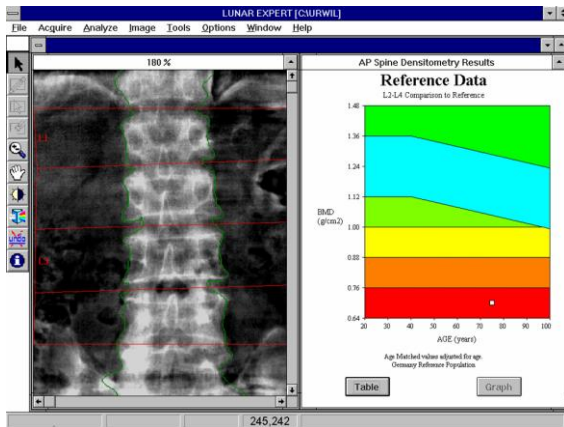
Service des maladies osseuses  
Département des Spécialités de Médecine  
Hôpitaux Universitaires de Genève

Colloque de Néphrologie, HUG. Le 27 septembre 2013

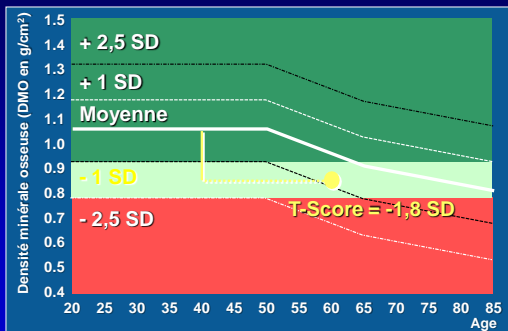
## Densitométrie osseuse



Bone Mineral Density (BMD) is best assessed by computerized central densitometry (DEXA Scan) comparing the spine and hip to peak bone mass at age 30 (T-Score).



## T-Score comme valeur diagnostique

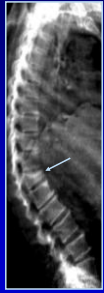


## Définition de l'ostéoporose chez la femme selon l'OMS (critères diagnostiques)

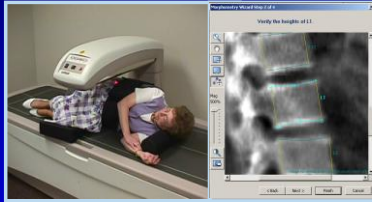
Définition	Densité osseuse	Stratégie
Normal	jusqu'à 10% de perte de densité osseuse (T-score jusqu'à -1 DS)	Prévention
Ostéopénie	10 à 25% de perte de densité osseuse (-1 DS > T-score > -2,5 DS)	
Ostéoporose	25% ou plus de perte de densité osseuse (T-score ≤ -2,5 DS)	Traitement
Ostéoporose sévère	Ostéoporose avec fracture(s)	

WHO Technical Report Series: 843; 1994

## DXA-based Vertebral Fracture Assessment (VFA)

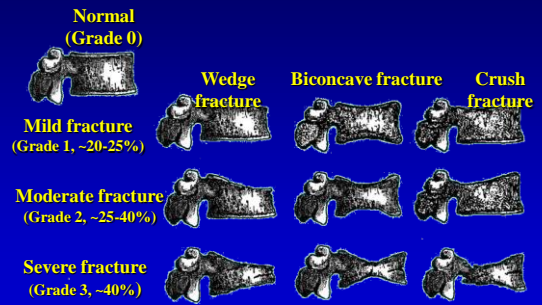


Lateral Decubitus and Point-of-Care tools



7

## Semiquantitative visual grading of vertebral fractures



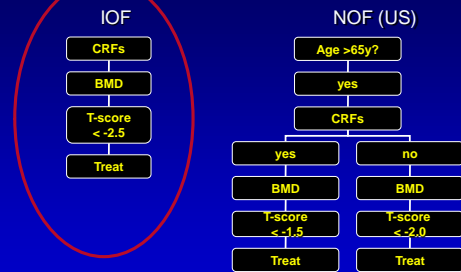
Genant & Wu

## Remaining Lifetime Fracture Probability at age 50 In Switzerland

Fracture site	Gender	Remaining lifetime probability at age 50 (%)	
		Sweden	USA
Hip	Men	7.0	6
	Women	22.6	18
Any	Men	20.2	13
	Women	51.3	40

Lippuner K, Johansson H, Kanis JA, Rizzoli R, Osteoporosis Int 2009

## Case finding strategies



CRF: Clinical Risk Factor

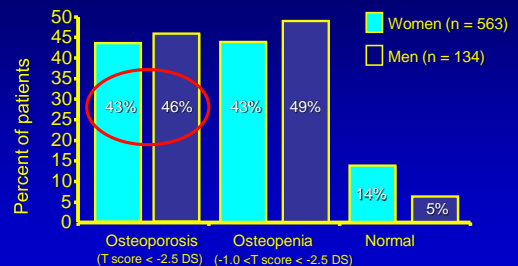
## Ostéodensitométrie : indications remboursées (Ordonnance du 1er janvier 2003)

### Remboursement

- Ostéoporose clinique manifeste & fracture
- Hypogonadisme
- Traitement par glucocorticoïdes
- Hyperparathyroïdie primitive
- Ostéogenèse imparfaite
- Maladies digestives & malabsorption
- Au maximum une fois tous les 2 ans  
DXA seulement : colonne et/ou hanche,  
VFA non remboursée

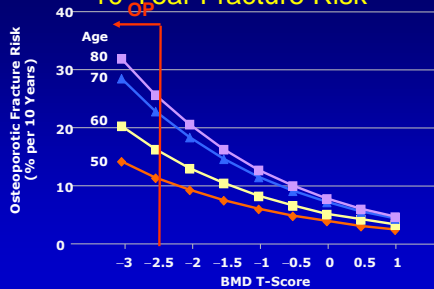
## Geneva Osteoporosis Clinical Pathway

Prevalence of Osteoporosis\* and osteopenia\* in 697 fractured patients (76%) with DXA



\*DXA at the lumbar spine and/or at the hip Chevalley et al Osteoporos Int 2002

## Relationships Between BMD, Age, and 10-Year Fracture Risk



Kanis JA, et al. *Osteoporos Int.* 2001;12:989-995.

**Ten-Year Fracture Probability**

1. Major Osteoporotic Fractures: Vertebrae, Hip, Humerus, Forearm,
2. Hip

-> Indication to Treatment

February 2008

www.SVGO.ch  
www.iofbonehealth.org

→ www.shef.ac.uk/FRAX

**FRAX<sup>®</sup> WHO Fracture Risk Assessment Tool**

Country: Switzerland Name / ID:

**Questionnaire:**

1. Age (between 40 and 90 years) or Date of birth:  /  /
2. Sex:  Male  Female
3. Weight (kg):
4. Height (cm):
5. Previous fracture:  No  Yes
6. Parent fractured hip:  No  Yes
7. Current smoking:  No  Yes
8. Glucocorticoids:  No  Yes
9. Rheumatoid arthritis:  No  Yes
10. Secondary osteoporosis:  No  Yes
11. Alcohol (3 or more units per day):  No  Yes
12. Femoral neck BMD (g/cm<sup>2</sup>):

Selected DXA:

Clear Calculate

TABLE 1. CLINICAL RISK FACTORS INCLUDED IN THE WORLD HEALTH ORGANIZATION FRACTURE RISK ASSESSMENT TOOL (FRAX<sup>®</sup>)

- Country of residence<sup>a</sup>
- Ethnicity (U.S. models only: Caucasian, black, Hispanic, and Asian)
- Age (allows ages between 40 and 90 years)<sup>b</sup>
- Sex
- Weight and height for calculating body mass index
- Prior fragility fracture, including radiographic vertebral fracture
- Family history of osteoporosis (parent with hip fracture)
- Current smoking
- Glucocorticoid use (prednisolone  $\geq 5$  mg daily for  $\geq 3$  months, current or past)
- Rheumatoid arthritis (physician-confirmed diagnosis)
- Alcohol use ( $\geq 3$  units daily)<sup>c</sup>
- Secondary osteoporosis<sup>d</sup>
- Bone mineral density<sup>e</sup>; model also works without bone mineral density

**FRAX**

Appropriate candidates for using FRAX to assist with a treatment decision:

men aged > 50 years and postmenopausal women

- (1) who are not on treatment
- (2) low bone mass (T-score between - 1.0 and - 2.5)
- (3) no prior hip or vertebral fracture
- (4) an evaluable hip for DXA.

Circumstances in which the FRAX tool is not appropriate

- Only applicable to untreated patients
- Unnecessary in patients for whom treatment is clearly indicated
- May not be appropriate for patients with T-scores better than - 1.0, as treatment has not been shown to be effective in this patient population

**WHO-FRAX Algorithm**

Age-adjusted relative risk of fracture

Previous fracture	2.1*
Corticosteroid use	2.3*
Family history	2.3*
Smoking / alcohol	1.6*
RA	1.7*
BMI	2.0†

\* Persistent effect after BMD adjustment  
† Effect lost after BMD adjustment

Kanis J. *WHO Study Group* (2005)

## Limitations of the FRAX Tool (1)

- Dose-response is not taken into account for several of the risk factors, (type/location/number of fractures, glucocorticoid dose and duration, and smoking and alcohol quantity and duration)
- Number of risk factors for fracture that are not incorporated into the algorithm (bone turnover, risk factors for falls, pharmacological intervention, vitamin D, and physical activity)
- BMD input to FRAX is limited to the femoral neck
- Combinations of secondary causes of osteoporosis
- FRAX has not been validated in randomized clinical intervention trials in patients who are included based on FRAX data

## Limitations of the FRAX Tool (2)

- the increased subsequent fracture risk after an initial fracture is considered constant over time in FRAX
- A low number of types of fractures are predicted by FRAX Hip, Spine, Wrist, Humerus
- NHANES III BMD Reference
- Country Disparity (Life Expectancy, Fracture Incidence)

- Ten year probability of hip fracture compared with Sweden

### Relative probability

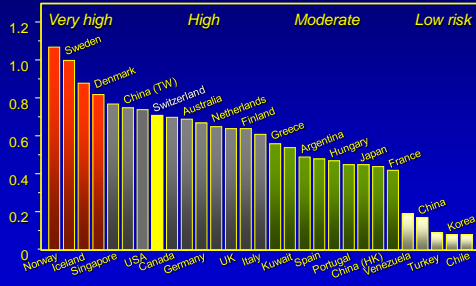


TABLE 1. CRITERIA FOR RECOMMENDING PHARMACOLOGIC TREATMENT FROM THE U.S. NOF GUIDELINES

*In women and men age 50 or older, pharmacologic therapy should be recommended for those with:*

- A history of hip fracture or clinical or radiographic spine fracture
- T-score  $\leq -2.5$  at femoral neck or spine\*
- Low bone mass (osteopenia), T-scores  $-1.0$  to  $-2.5$  at the femoral neck or lumbar spine and any of the following
  - $\geq 3\%$  10-yr probability of hip fracture OR
  - $\geq 20\%$  10-yr probability of a major osteoporotic fracture based on the WHO model for the United States

\* After excluding secondary causes.

## Estimates of the Proportion of Older White Women Who Would Be Recommended for Pharmacologic Treatment by the New U.S. National Osteoporosis Foundation Guidelines

TABLE 3. NOF CRITERIA FOR RECOMMENDING PHARMACOLOGIC THERAPY

	$\geq 65$ yr [% (n)] N = 6086	$\geq 75$ yr [% (n)] N = 1426
Hip fracture	1.6 (99)	3.3 (47)
Clinical spine fracture	5.8 (356)	8.1 (115)
T-score $\leq -2.5$ at		
Femoral neck	20.7 (1259)	24.6 (493)
Spine	33.4 (2033)	37.8 (533)
Femoral neck or spine	50.6 (3086)	50.7 (723)
Low bone mass (osteopenia) at the FN or spine and		
U.S. WHO 10-yr probability of hip fracture $\geq 3\%$	38.4 (2343)	59.1 (842)
U.S. WHO 10-yr probability of any major osteoporosis-related fracture $\geq 20\%$	40.4 (2465)	68.4 (975)
Low bone mass (osteopenia) only at the FN (not spine) and		
U.S. WHO 10-yr probability of hip fracture $\geq 3\%$	32.5 (1979)	48.4 (690)
U.S. WHO 10-yr probability of any major osteoporosis-related fracture $\geq 20\%$	33.3 (2030)	55.6 (793)
All NOF criteria combined*	72 (4377)	93 (1323)

JBMR 2009

## Estimates of the Proportion of Older White Men Who Would Be Recommended for Pharmacologic Treatment by the New US National Osteoporosis Foundation Guidelines

At least 34% of US white men aged 65 years and older and 49% of those aged 75 years and older would be recommended for drug treatment

JBMR 2010

### Germany: Intervention Threshold Depends on Fracture Probability (%)

Risk:   low (<20%)   intermediate (20-30%)   high ≥30%

No Fx	DXA T-score Spine or proximal Femur							
	-1.0	-1.5	-2.0	-2.5	-3.0	-3.5	-4.0	
50 Yrs	2	4	5	7	10	16	22	
55 Yrs	4	5	8	11	15	23	32	
60 Yrs	6	8	11	16	22	34	47	
65 Yrs	8	11	16	22	33	48	>65	
70 Yrs	12	16	23	32	46	>65	>65	
75 Yrs	16	22	31	43	63	>65	>65	
80 Yrs	19	27	39	54	>65	>65	>65	
Vertebral-Fx			Rapid intervention, risk for further fracture = high					

DVO-Leitlinien 2006

### Association suisse contre l'ostéoporse (ASCO)

**Traitement**

1. Fracture vertébrale ou de hanche ✓
2. ≤ - 2.5 T-Score ✓
3. Risque absolu de fracture (OMS-FRAX-Suisse) ✓  
 - Seuil variable en fonction de l'âge  
 (-> risque équivalent à celui associé à une fracture prévalente vertébrale ou de hanche)

**JUGEMENT CLINIQUE !**  
*Recommandations 2010*

[www.SVGO.ch](http://www.SVGO.ch)

Age	%
50	10
60	15
70	30
80	40

### Exploration du métabolisme phosphocalcique

- Physiologie et exploration du métabolisme du calcium
- Physiologie et exploration du métabolisme du phosphate
- Parathormone et vitamine D
- Evaluation du remodelage osseux: méthodes et indications

### Calcium: its role

```

  graph TD
    Calcium --> Bone
    Calcium --> Extraskeletal
    Bone --> BoneList["• Skeletal rigidity (hydroxyapatite)  
• Calcium store"]
    Extraskeletal --> ExtraskeletalList["• Enzymes  
• Muscles  
• Nerves  
• Secretion  
• Cell signalling"]
  
```

### Calcium in the body

- Cells: 10 g
- Extracellular fluid: 1 g
- Bone and teeth: 1200 g

## Circulating calcium

**Protein-bound**  
mostly albumin  
1.0 mmol/l  
40%

**Ionized**  
1.2 mmol/l  
50%

**Complexed**  
(citrate,  
bicarbonate,  
phosphate, etc)  
10%

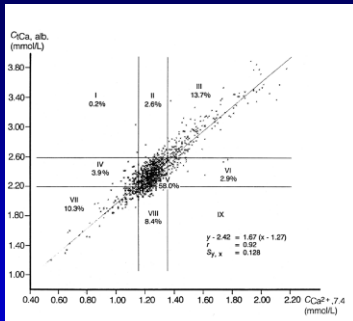
**Total calcium: 2.4 mmol/l**

## Protein-Corrected Plasma Calcium (mM)

$$= \text{Ca} / [\text{prot}/160 + 0.55]$$

## Albumine-Corrected Plasma Calcium (mM)

$$= \text{Ca} + [0.02 \times (40 - \text{Albumine})]$$



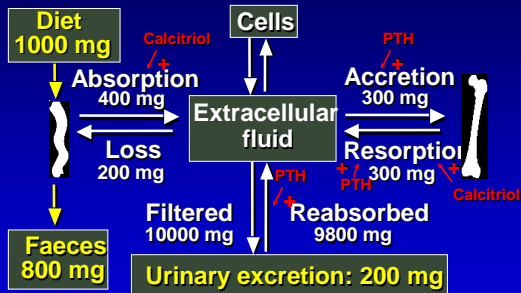
N = 1213  
Discordance rate 31%  
with Ca  
18% with Corr Ca

Thode J et al 1989

## Calcium Ionisé : conditions de prélèvement

- Membre au repos et sans garrot
- Seringue bien remplie (rôle de l'héparine)
- Conditions anaérobies

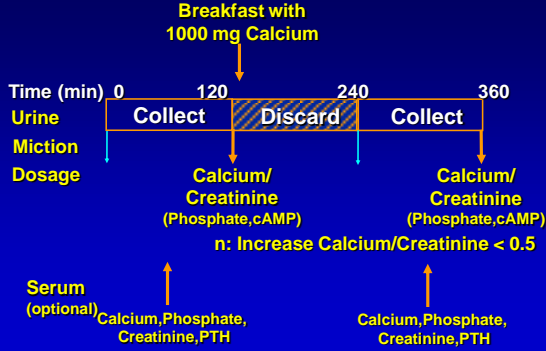
## Daily calcium fluxes controlling calcium homeostasis



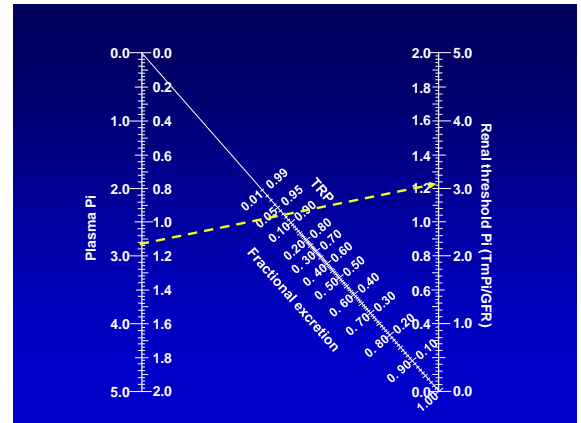
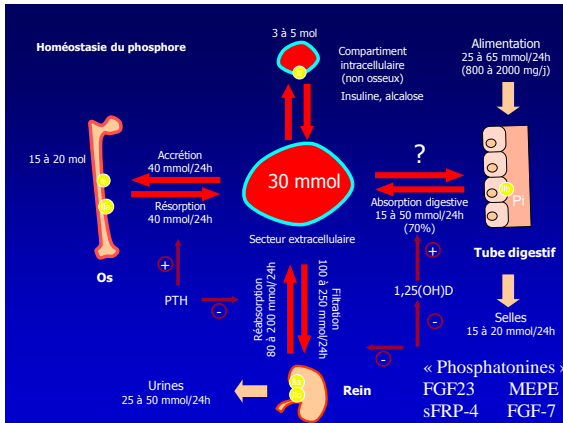
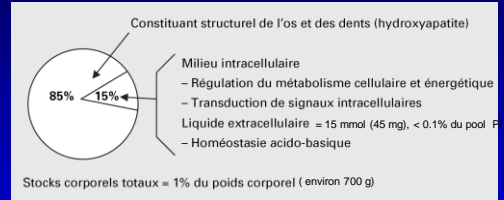
## Evaluation of Main Calcium Fluxes

Calcium Flux	Evaluation
• Net Intestinal Absorption	<b>24 h Urinary Calcium Excretion</b> [ n : < 7.5 mmol/d in Men ] [ n : < 6.25 mmol/d in Women ] Urinary Pi > 32 mmol/d → Dairy Products Origin Urinary Sodium > 200 mmol/d → High Salt Intake Origin
• Net Bone Resorption Calcium/Creatinine	<b>Fasting Urinary</b> [ n : < 0.5 mmol/mmol ]
• Renal Tubular Reabsorption	<b>Index of Renal Tubular Reabsorption</b> (derived from Fractional Excretion of Calcium and a Nomogramme) [ n : 2.40-2.90 mmol/l GFR ]

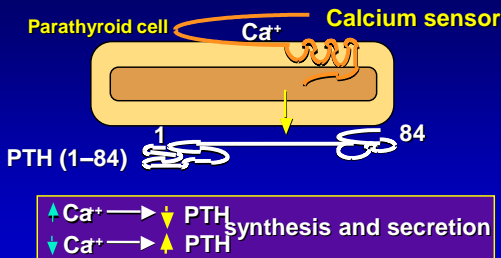
## Calcium Absorption Test (Pak's Test)



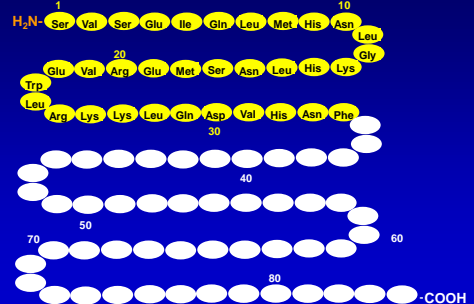
## Distribution et rôle du phosphate dans l'organisme

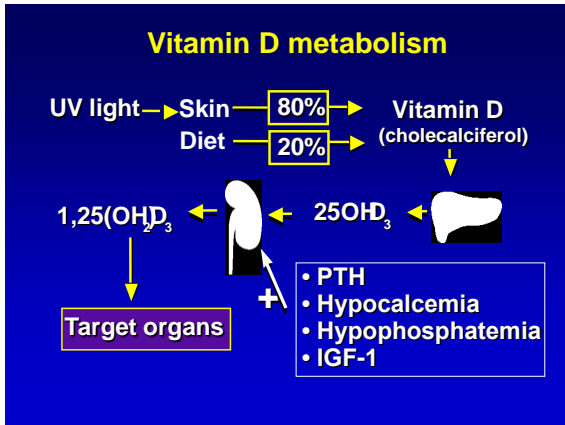
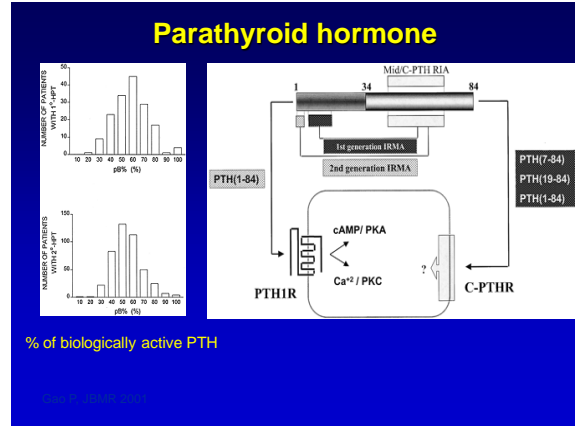
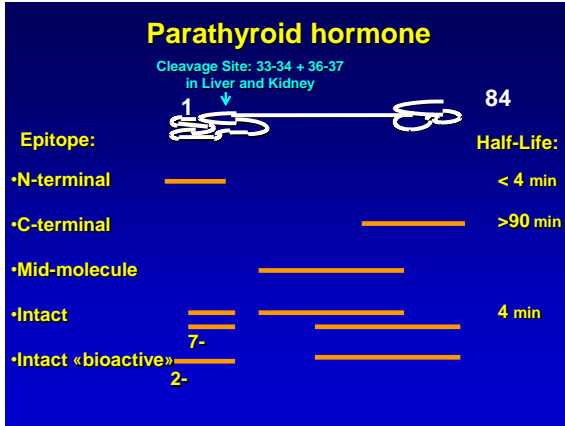


## Secretion of parathyroid hormone



## Human Parathyroid Hormone 1-34 and 1-84





### Circulating forms of vitamin D

	Half-life	Circulating levels
• Vitamin D	4 – 5 days	1 – 5 nmol/l
• 25OH D <sub>3</sub>	10 – 20 days	20 – 100 nmol/l*
• 1,25(OH) <sub>2</sub> D <sub>3</sub>	5 – 18 hours	50 – 150 pmol/l

\*Reflects vitamin D supply and status

### Méthode de dosage de la vitamine D

### Méthode de dosage de la vitamine D (1)

Nombreuses méthodes de dosage de la 25(OH)D:

- RIA,
- Chemiluminescence,
- ELISA,
- HPLC-UV,
- HPLC
- LC-MS/MS, (Liquid chromatography tandem mass spectrometry).

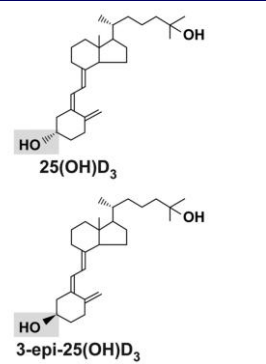
### Facteurs influençant le dosage de la 25(OH)D

- Nature lipophile de la molécule (interférence non-spécifique des autres lipides)
- Nécessité de déplacer l'analyte de la VDBP
- Capacité à reconnaître la vitamine D2 et D3
- Présence d'épimères

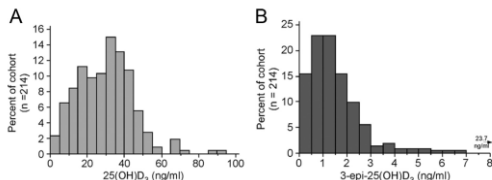
Reproductibilité proche < 10 %

Exactitude ?

### 3-epi-25OHD3



### The C-3 Epimer of 25-Hydroxyvitamin D<sub>3</sub> Is Present in Adult Serum

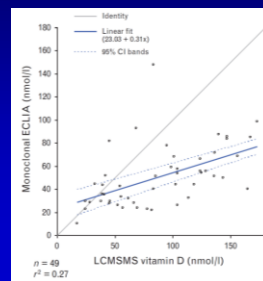


The 3 epimer concentration ranged from 0 to 25.5% of the 25(OH)D<sub>3</sub> concentration.

Lensmeyer et al, 2012

### Overreporting of vitamin D deficiency with the Roche Elecsys Vitamin D3 (25-OH) method

- Electrochemiluminescence immunoassay (ECLIA)



Quoi mesurer ?

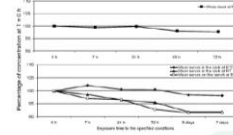
- 25-OHD3, 25-OHD2, les deux métabolites, ou la 1,25-OHD?

25-OHD3 et 25-OHD2 = 25-OHD totale

1,25-OHD : diagnostic de l'hypercalcémie  
et de formes rares d'hypophosphatémie

La 25-OHD et 1,25-OHD sont-ils stables durant le transport ?

« Preanalytical Stability of 25(OH)-Vitamin D3 in Human Blood or Serum at Room Temperature: Solid as a Rock. »

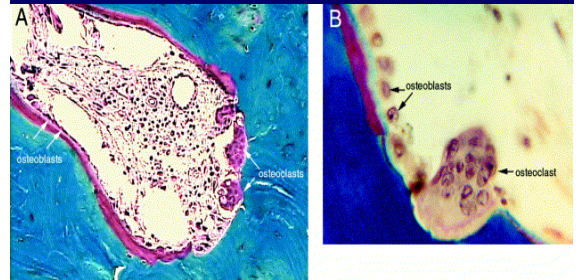


Wielders JP, Wijnberg FA, Clinical Chemistry, 2009

-Très stables même à température ambiante et après plusieurs cycles de congélation/décongélation

Quels tubes ?

Sérum ou plasma



## Bone Remodeling

1. Maintenance of Mechanical Strength  
(Replacement of Fatigued Bone,  
Prevention of Excessive Aging)
2. Supply of Bone Marrow with Growth Factors
3. Mineral Homeostasis (Calcium Release)

## Biochemical Markers of Bone Remodeling

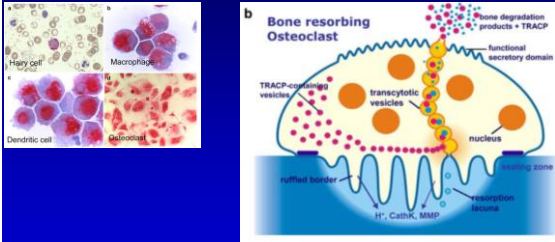
### Bone Formation

Total Alkaline Phosphatase  
Bone Specific Alkaline Phosphatase  
Osteocalcin  
Procollagen Type I Carboxyterminal Propeptide (PICP)  
Procollagen Type I Aminoterminal Propeptide (PINP)

### Bone Resorption

Hydroxyproline  
Deoxypyridinoline  
C-terminal I Collagen Cross-linking Telopeptide (CTX)  
N-terminal I Collagen Cross-linked Telopeptide (NTX)  
Hydroxyglycosides  
Bone Sialoprotein  
Tartrate-resistant acid phosphatase

## Emerging biochemical assessment: Type 5b tartrate-resistant acid phosphatase



Janckila et al., 2009

## Potential Uses of Markers of Bone Remodeling

Identify patients who need treatment

- Correlate with bone loss
- Correlate with fracture risk

Help in selecting therapeutic agent

Early indicator of response to treatment

Evaluate patients who are not responding to conventional treatment

**Table 3 | Serum bone turnover markers**

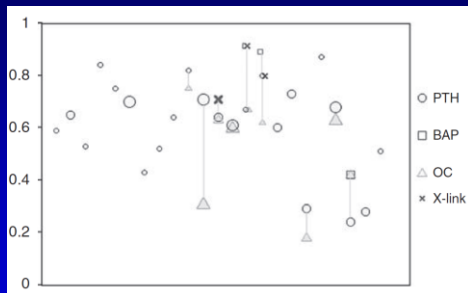
	Levels dependent on eGFR (cleared renally)?
<i>Serum markers of bone resorption</i>	
Serum amino-terminal crosslinking telopeptide of type 1 collagen (s-NTX)	Yes
Serum carboxy-terminal crosslinking telopeptide of type 1 collagen (s-CTX)	Yes
Carboxy-terminal crosslinking telopeptide of type 1 collagen (s-ICTP or CTX-MMP)	Yes
Serum tartrate-resistant acid phosphatase (TRAP5b)	No
<i>Serum markers of bone formation</i>	
Serum osteocalcin	Yes
Serum alkaline phosphatase	No
Bone-specific alkaline phosphatase	No
Procollagen type 1C propeptide (s-P1CP)	Yes
Procollagen type 1N propeptide (s-PINP)	No

Abbreviation: eGFR, estimated glomerular filtration rate.

**Table 1 | Uncontrollable and controllable sources of pre-analytical variability according to their importance**

Source	Importance	Nature of effect
<b>Uncontrollable sources</b>		
Age	Very important	BTM increase with age in men and women
Menopausal status	Very important	BTM increase within a few months after the last menstrual period
Gender	Very important	BTM are higher in older women than older men
Fractures	Important—limits evaluation of case control studies	BTM increase after a fracture (maximal at 2 to 12 weeks, but effect lasts for up to 52 weeks)
Pregnancy and lactation	Important	BTM are increased during pregnancy; highest levels during third trimester, even higher postpartum
Drugs	Important: corticosteroids, anticonvulsants, heparin, GnRH agonists	BTM may be decreased (glucocorticoids) or increased (anticonvulsants)
Disease	Important: thyroid disease, diabetes, renal impairment, liver disease	BTM often increased (thyrotoxicosis, chronic kidney disease)
Bed rest/immobility	Important	Bone formation markers decrease and resorption markers increase
Geography	Somewhat important	Small changes amongst countries, usually explained by differences in lifestyle
Ethnicity	Not important	Small changes, such as lower OC in African Americans vs. Caucasians
Oral contraception	Not important, except in women over 35 years	Lower values for BTM
<b>Controllable sources</b>		
Circadian	Extremely important	Most striking for bone resorption markers; highest values in second half of night and on waking; lowest values in afternoon and evening
Fasting status	Important for specific markers	Fasting results in a decrease in BTM; for example, s-CTX decreases by 20% after breakfast
Exercise	Important—chronic and acute effects	Changes occur but depend on type of exercise and age of subjects
Menstrual	Not important	Small decreases in bone resorption and increases in bone formation during luteal phase
Seasonal	Not important for individual, but maybe for longitudinal studies	Small decreases in BTM over winter
Diet	Not important	Small reduction in BTM immediately following calcium supplementation

## Correlation coefficients between bone formation rate as seen on bone biopsies and serum markers of PTH, bone-specific ALP (BAP)



KDIGO guidelines, KI 2009

## Conclusion

### Evaluation of bone turnover

- Isolated use of iPTH has poor diagnostic performance for the type of ROD
- Serum iPTH and bAP are complementary