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How can I improve the management of bone disease?



With a portfolio of bone metabolism assays that facilitate informed decision-making

In Vitro assays for bone turnover and calcium regulation

Answers for life.

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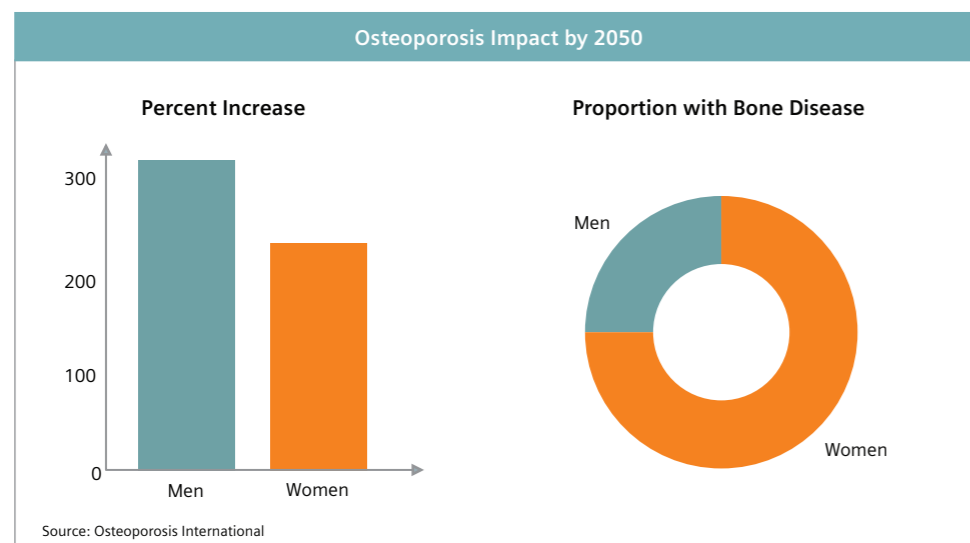
For Patients. For Life. For Improved Bone Metabolism Management.



Helping clinicians manage the growing number of bone metabolism diseases will require a portfolio of tests that measure both calcium regulation and bone turnover. Siemens Healthcare Diagnostics offers a comprehensive portfolio of bone metabolism immunoassays to help your hospital, reference laboratory, or renal center better manage and improve patient outcomes.

The Global Impact of Osteoporosis

In the past decades, the global incidence of osteoporosis has increased dramatically with rising life expectancy, and over 200 million people suffer from osteoporosis worldwide.¹ Women have a 40-50% risk of having a fracture during their lifetime, while men have a 13-22% risk.² The annual incidence is greater than breast cancer, heart attacks, and strokes combined. By 2050, the global cost of osteoporosis is expected to exceed \$130 billion and the annual hip fracture incidence is expected to increase to 6.3 million.^{1,3} The highest risks of hip fracture are currently found in Norway, Sweden, Iceland, Denmark, and the United States, but by 2050 Asia is expected to account for almost one half of all global fractures.^{4,5}



The Life Cycle of Bone Metabolism

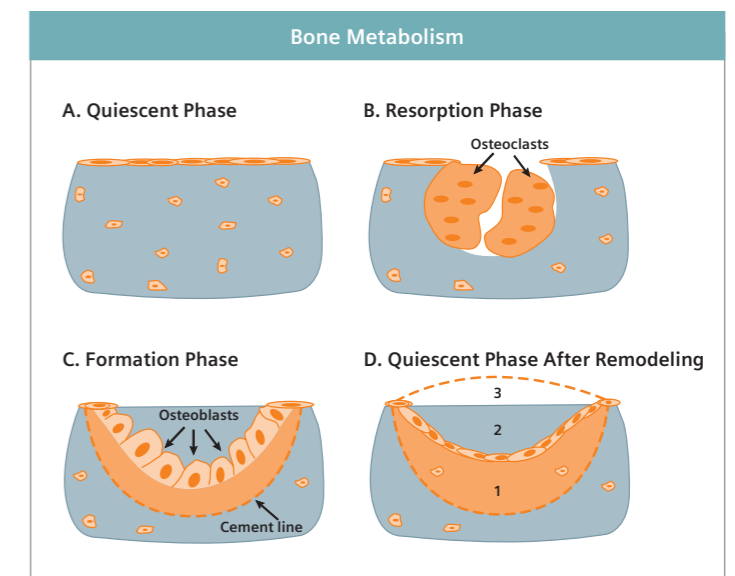
Osteoporosis ("porous bone") is a bone disease which increases the risk for fracture. It is caused by a loss of bone density from losing too much, not making enough, or a combination of both. Bone metabolism is the constant process of the body removing old bone ("bone turnover") and replacing it ("bone resorption"). These processes take place in the osteoblasts, which form new bone, and osteoclasts, which break down old bone. As long as these processes are in balance, bone mass remains on a constant level.

As a person reaches mid-life, they begin to lose bone quicker than they are able to replace it due to calcium metabolism, calcium and vitamin D deficiency, and hormonal factors, such as estrogen. Bone resorption accelerated during menopause leads to a high turnover-osteoporosis. In contrast, a reduced creation of new bone in conjunction with a normal resorption causes a low turnover-osteoporosis.

Bone mineral density (BMD) is measured to determine the strength of bones. Dual energy X-ray absorptiometry (DEXA) is considered the gold standard and most accurate way to measure bone density. BMD provides a static snapshot of the skeletal area assessed, but does not indicate the level of bone turnover activity which could affect the strength of the bone in the future. When combined with BMD, bone turnover markers provide additional insight into bone turnover to help predict fracture risk. Low BMD

is associated with high turnover, and high turnover impacts the structure and fragility of bone.

Measuring proteins produced by the osteoblasts and osteoclasts provides a real-time evaluation of bone turnover, especially in the management of post-menopausal osteoporosis. Bone resorption markers can monitor progress of therapeutic interventions within a few weeks or months, whereas bone formation markers can take six to 12 months. This is still an improvement over BMD, which can take as long as one to two years to determine the effectiveness of treatment.



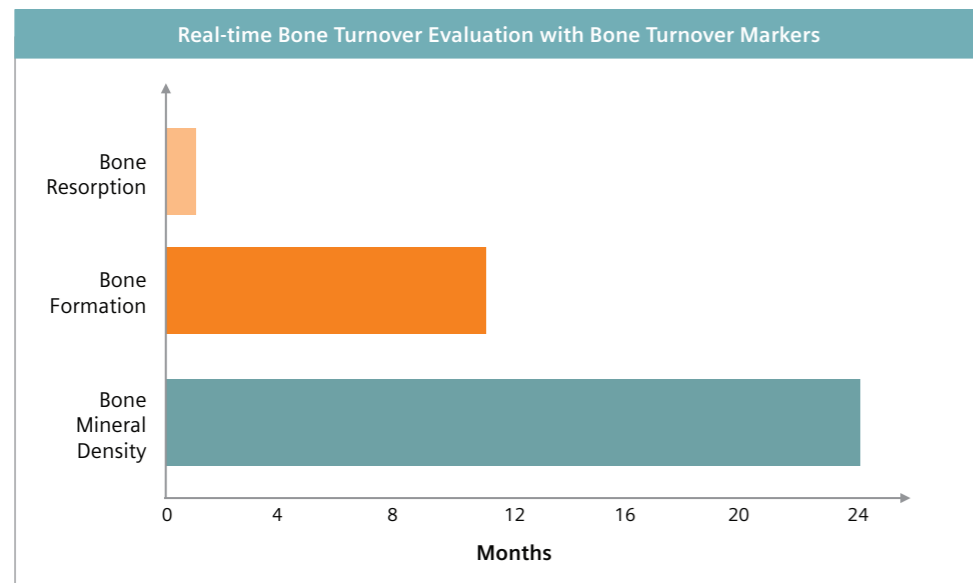
Bone Turnover Measurement: Osteocalcin and Crosslinks Desoxypyridinoline

Measuring Bone Formation: Osteocalcin

- A protein found in the bone and dentin manufactured by the osteoblasts that binds to calcium
- A highly specific marker of late stage osteoblastic activity
- Elevated serum levels may occur in osteomalacia, Paget's disease of the bone, hyperthyroidism, primary hyperparathyroidism, and renal osteodystrophy
- Depressed levels have been reported in hypothyroidism and during long-term corticosteroid therapy

Measuring Bone Resorption: Crosslinks Desoxypyridinoline

- A urine test that helps establish baseline bone turnover
- Significantly more elevated in post-menopausal women with osteoporosis than in normal post-menopausal women
- It monitors changes in urinary (deoxypyridinoline) DPD excretion associated with aminobiphosphonate antiresorptive therapy
- DPD is excreted unmetabolized in urine and is unaffected by diet, making it suitable for assessing resorption



Calcium: Building Strong Bones

Calcium and phosphorous are the most abundant minerals found in the body, and the majority of both minerals are found in the skeletal system. Almost 99% of the body's calcium is stored in bone and teeth. Calcium regulation is required for many basic body functions, such as cell function, bone structure, blood clotting, and neural transmission. Insufficient calcium or loss of calcium is called hypocalcemia, whereas too much calcium in the blood, often a result of malignancy or primary hyperthyroidism, is called hyperthyroidism. The body regulates calcium through the parathyroid hormone (PTH) and vitamin D, and to a lesser extent, calcitonin.

Enhancing Calcium Absorption with PTH and Vitamin D

PTH

- Enhances calcium absorption in the intestines by stimulating the renal synthesis of 1.25(OH)₂D
- Increases the amount of calcium in the blood through the release of PTH and the removal of calcium from the bone
- Decreases the amount of calcium by releasing less PTH

Vitamin D

- Helps to form and maintain strong and healthy bones by increasing the amount of dietary calcium absorbed by the intestines
- Stops the parathyroid gland from secreting parathyroid hormone, which would increase levels of calcium in the blood
- Protects against osteoporosis, cancer, and hypertension

Clinical Utility of Calcium and PTH for Differential Diagnosis

Physicians use the combination of calcium and PTH measurements to aid in the differential diagnosis of several diseases. Intact PTH is increasingly becoming an important assay since more than 10-20% of cancer patients will develop hypercalcemia during their disease, and the associated mortality with malignant disease is very poor.⁶

Disease	Calcium Level	PTH Level	Description
Hyperparathyroidism	High	High	Usually caused by a benign tumor on the parathyroid gland; surgical removal of tumor is confirmed using intraoperative PTH
Hypoparathyroidism	Normal	Low	Cause of hypocalcemia since the thyroid gland is sometimes damaged during surgery and unable to produce PTH
Hypercalcemia of malignancy	High	Low	High levels of calcium caused by bone metastasis that destroy the bone and release calcium into the bloodstream
Secondary hyperparathyroidism in renal disease	Low	High	Renal patients often have low circulating calcium levels, which cause PTH levels to rise. Dietary calcium supplements help the PTH levels return to normal. Persistently elevated PTH levels in renal patients can lead to bone disease, causing muscle pain, bone deformity, and increased incidence of fracture

PTH and End Stage Renal Disease

Chronic kidney disease (CKD) is a global disease that affects approximately 500 million people worldwide.⁷ When kidney disease progresses, normal concentrations of calcium and phosphorous are disrupted, which leads to elevated levels of PTH and decreased levels of vitamin D. As a consequence, this leads to abnormalities in the bone turnover process. Patients with CKD stages three to five often experience secondary hyperthyroidism and bone abnormalities. Measuring PTH is of increased importance as a patient progresses from CKD stage three through to end-stage renal disease (ESRD).

Siemens Portfolio of Bone Metabolism Assays

Siemens is dedicated to providing quality assays that improve patient care, and allow laboratories of any size to consolidate testing on the ADVIA Centaur®, IMMULITE® or Dimension Vista® systems.

Siemens offers calcium measurement on all of its clinical chemistry and integrated systems, including the ADVIA® Chemistry, Dimension® and Dimension Vista systems.

SYSTEM	ADVIA Centaur CP	ADVIA Centaur XP	IMMULITE 1000	IMMULITE 2000	IMMULITE 2500
Bone Metabolism	Intact PTH	Intact PTH	Intact PTH	Intact PTH	Intact PTH
	–	–	Turbo PTH*	–	Stat PTH*
	–	–	Osteocalcin**	Osteocalcin**	Osteocalcin**
	–	–	Pyrilinks-D	Pyrilinks-D	Pyrilinks-D
	Vitamin D***	Vitamin D***	Vitamin D***	Vitamin D***	–

* Approved for intraoperative use
 ** Not available for sale in the U.S.
 *** In development

Assay and Reference Ranges

System	Assay	Reportable Range	Reference Range (95%)
ADVIA Centaur CP / XP	Intact PTH	2.5 – 1,900 pg/mL	14 – 72 pg/mL (EDTA)
	Intact PTH	3.0 – 2,500 pg/mL	16 – 87 pg/mL (EDTA) 11 – 67 pg/mL (Serum)
IMMULITE 1000/2000/2500	Osteocalcin	2.0 – 100 ng/mL	< 2.0 – 22 ng/mL
	Pyrilinks-D†	6.0 – 300 nM	2.3 – 5.4 nM DPD/mM (males)* 3.0 – 7.4 nM DPD/mM (females, premenopausal)*
IMMULITE 1000 Turbo	Intact PTH (Intraoperative)	5 – 2,500 pg/mL	8 – 74 pg/mL (EDTA)
IMMULITE 2500 Stat	Intact PTH (Intraoperative)	5 – 2,500 pg/mL	11 – 72 pg/mL (EDTA)

* Based on a reference range of 90%

† Pyrilinks-D is an assay for Crosslinks Desoxypyridinoline



ADVIA Centaur XP



IMMULITE 2000 XPI

Helping Clinicians Improve Patient Outcomes

Siemens Healthcare Diagnostics offers a breadth of assays that measure both calcium regulation and bone turnover. Our comprehensive bone metabolism portfolio facilitates informed decision-making across the clinical continuum, helping healthcare professionals to maximize the quality of care they provide for patients.

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