Biochemical Testing Relevant to Bone

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KEYWORDS

• Metabolic bone disease • Calcium • Phosphorus • Vitamin D • Parathyroid hormone • Parathyroid hormone-related protein • Biochemical markers

KEY POINTS

- Laboratory biochemical testing is critical in the evaluation, diagnosis, and management of bone disorders.
- Assessment of mineral metabolism, including serum calcium and phosphorus, gives insight into the pathophysiology of bone diseases.
- The pathophysiology of vitamin D, parathyroid hormone, and parathyroid hormone-related protein directly impact skeletal disorders.
- Markers of bone turnover give direct insight into bone formation and resorption.

INTRODUCTION

Laboratory biochemical testing is critical to understanding bone disorders. The most common bone disorder, osteoporosis, is characterized by low bone mass and abnormal skeletal architecture caused by genetic or acquired biochemical abnormalities that result in impaired bone strength and increased risk of fragility fracture.[1] More than 20 million Americans are affected by this common disorder, with at least 1.5 million osteoporotic fractures occurring in the United States each year.[2] Less common metabolic bone diseases, such as primary hyperparathyroidism, hypoparathyroidism, osteomalacia or rickets, Paget disease of the bone, and rare bone diseases are also clinically important, and develop owing to unique changes in skeletal physiology. This review summarizes recent data on biochemical testing relevant to bone, focusing on minerals, vitamin D, parathyroid hormone (PTH), PTH-related protein (PTHrP), and bone turnover markers (BTMs).

MINERALS: CALCIUM AND PHOSPHORUS

Serum Total Calcium

The adult human is estimated to contain total body calcium of about 1 kg, representing about 2% of body weight. Of this, 99% is present as calcium hydroxyapatite in the

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skeleton, and less than 1% is present in nonosseous intracellular or extracellular fluid. Calcium in extracellular fluid is in dynamic equilibrium with the rapidly exchangeable fraction of bone calcium. About 45% of serum total calcium is bound to proteins, mostly albumin, with about 10% found in inorganic complexes, and 45% free or ionized calcium.[3] Calcium ions are crucial for mineralization of newly formed osteoid matrix that leads to new bone. Serum total calcium is typically measured using a photometric method.

Hypocalcemia most often results from absence or impaired function of the parathyroid glands or a low vitamin D level.[4] Chronic kidney disease (CKD) may be associated with hypocalcemia owing to decreased renal 1,25-dihydroxyvitamin D (1,25-diOHD) synthesis, as well as hyperphosphatemia and skeletal resistance to the action of PTH. Hypocalcemia may cause tetany or osteomalacia.

Hypercalcemia results from either increased calcium mobilization from the skeleton or intestinal increased absorption.[5] The majority of hypercalcemia is owing to primary hyperparathyroidism or breast, prostate, thyroid, or lung carcinomas metastatic to the skeleton. Patients with primary hyperparathyroidism associated with osteoporosis or osteitis fibrosa cystica, kidney stones, nephrocalcinosis, or symptoms of hypercalcemia are candidates for parathyroidectomy.[6] Increased serum total calcium may be owing to increased albumin levels, and decreased serum calcium owing to decreased albumin levels, so albumin-corrected serum calcium should be assessed. Ideally, calcium should be measured fasting to minimize the influence of dietary or supplemental intake on the serum level.

Treatment of chronic hypocalcemia involves long-term oral therapy tailored to the specific disease causing the hypocalcemia. The therapeutic target for serum calcium level is usually 8.0 to 8.5 mg/dL, because this prevents tetany and minimizes other symptoms. For acutely symptomatic hypocalcemia, calcium is administered intravenously.[7]

Hypercalcemic symptoms develop at variable levels in different patients. Symptoms are common when serum calcium is greater than 11.5 mg/dL, although patients may still be asymptomatic at this level. Levels greater than 12.0 mg/dL are considered critical and possibly life threatening. Severe hypercalcemia greater than 15.0 mg/dL is usually considered a medical emergency.[8]

Ionized Calcium

Ionized calcium, which accounts for about 45% of serum total calcium, is the biologically active form of calcium. Low serum ionized calcium values may be seen in CKD, severely ill patients, or patients rapidly transfused with citrated whole blood or blood products. Increased serum ionized calcium may be seen in primary hyperparathyroidism, ectopic PTH-producing tumors, excess intake of vitamin D or vitamin A, or malignancies involving the skeleton.[9] Nomograms are used to calculate serum ionized calcium from total calcium, albumin, and blood pH. Because calculated ionized calcium results may be unreliable, ion-selective electrodes are used to directly measure this in body fluids. Serum ionized calcium is used to assess calcium levels in critically ill patients with fluid shifts, acid–base imbalances, or multiple comorbidities. It is generally considered a second-order test in the evaluation of abnormal calcium values. Serum ionized calcium concentrations 50% below the lower limit of normal may result in severely reduced cardiac function. Ionized calcium is higher in children and young adults. Ionized calcium values vary inversely with pH by approximately 0.2 mg/dL per 0.1 pH unit change.

Twenty-Four–Hour Urine Calcium

Ordinarily, about 25% to 30% of dietary calcium is absorbed, and 98% of filtered serum calcium is reabsorbed by the kidney. Trafficking of calcium between the