LABORATOIRE SION
BIOLOGICAL ANALYSIS AND MEDICAL IMAGING
Specialized tests – Ultrasound – specimen collection at home or at the office.

Improving calcium measurement

IONISED CALCIUM MEASUREMENT IS THE GOLD STANDARD METHOD, BUT IN ITS ABSENCE, CORRECTED CALCIUM IS THE BEST ESTIMATOR OF THE PATIENT'S TRUE CALCIUM LEVEL.

Saturday 02 June
2018

Abstract

Total calcaemia consists of slightly more than 50% ionised calcium and slightly less than 10% complexed calcium, the remainder being carried by proteins, essentially albumin. Hypoalbuminaemia or hyperalbuminaemia leads respectively to a fall or a rise in total calcium without any change in ionised calcium, the only physiologically active fraction. Biologists and clinicians are therefore regularly reminded that, in the absence of an ionised calcium assay, the interpretation of total calcium must take into account the serum albumin concentration, according to the formula: ["corrected" Ca (mmol/L) = measured Ca (mmol/L) + 0.020 or 0.025 (40 – albumin (g/L))]

Correction with this commonly recommended formula may, however, lead to an increasing underestimation of calcaemia when albumin is above 40 g/L, and is therefore liable to mask a true hypercalcaemia.

This readjustment, clinically justified for a low calcium level caused by hypoalbuminaemia, should not be extended to other clinical situations, in particular when albumin is raised. In that case, ionised calcium remains the parameter of choice for the diagnosis of a hypocalcaemia or of a hypercalcaemia.

Introduction

Calcium is the fifth most abundant inorganic element in the body. Ionised calcium is essential for many intracellular and extracellular biological processes. Ca^{2+} plays an important role in the regulation of cell functions:

- transmission of hormonal messages (second messenger)
- haemostasis: coagulation factor IV
- nerve conduction
- electromechanical coupling of striated, smooth and cardiac muscle contraction
- sperm motility
- actions on numerous enzymes.

Ca^{2+} accounts for 2% (about 1.3 kg) of body weight; 99% is found in the skeleton and 1% is dissolved in body fluids. The amount of calcium present in the vascular space is one gram. Because of this major and ubiquitous physiological role, calcaemia must be maintained within very narrow limits, between 2.2 and 2.6 mmol/L. In plasma:

- 50% of calcium is in the active ionised form,
- 10% is in a complexed form, in particular calcium citrate and calcium bicarbonate,
- 40% is bound to proteins. This binding depends on blood pH. It increases during alkalosis.

Biological measurement of calcium must take this plasma distribution into account for greater effectiveness in the management of disorders related to calcium imbalance. Three approaches to calcium measurement are thus commonly used: total calcaemia, ionised calcium and corrected calcaemia. Which of these three approaches best reflects the real calcaemia?

1. Phosphocalcic metabolism

Calcium exists in the living organism either in a bound state or in a free state. Most calcium is bound and associated with bone structures. Free or ionised calcium is found in the intracellular and extracellular compartments. Total calcaemia varies with the total protein level: half of total calcium is normally bound to plasma proteins, notably albumin. The degree of ionisation and of protein binding of calcium also depends on the pH of the medium and, to a lesser degree, on the other plasma electrolytes.

Regulation of phosphocalcic metabolism takes place as follows:

- 3 levels of regulation: intestinal absorption, exchanges between bone tissue and the internal milieu, renal excretion
- 3 hormones: PTH (parathyroid hormone), 1,25 dihydroxyvitamin D3 (calcitriol), calcitonin

PTH raises calcaemia by promoting its intestinal absorption, its renal reabsorption and bone decalcification. Vitamin D increases the intestinal absorption of calcium and the mineralisation of the skeleton.

Calcitonin (of thyroid origin) responds to hypercalcaemia. It increases the renal excretion of calcium and the incorporation of calcium into the skeleton. Parathyroid hyperplasia leads to hyperparathyroidism with hypercalcaemia, renal stones and renal failure.

2. Hypercalcaemia

Hypercalcaemia is defined by a total calcium above 2.6 mmol/L. When it is symptomatic, hypercalcaemia is a medical emergency whose degree depends on the severity of the clinical impact. The discovery of a hypercalcaemia requires a second, confirmatory assay, without delaying treatment if threatening signs are present (rule out assay and sampling errors). The clinical signs of a hypercalcaemia include:

- **Asymptomatic hypercalcaemia**

40% of cases of hypercalcaemia are asymptomatic and are discovered incidentally on a serum electrolyte panel performed as a matter of routine.

- **Symptomatic hypercalcaemia**

The clinical signs of hypercalcaemia vary widely in their severity and in their presentation. In general, the clinical signs are all the more severe and frequent as the hypercalcaemia develops rapidly and/or as its level is high. Moreover, the clinical signs of hypercalcaemia are sometimes overshadowed by the signs of the causal disease. **Digestive signs:** anorexia, nausea, vomiting (sometimes intractable) or constipation, epigastric pain. **Neurological and psychiatric signs:** headache, physical or mental asthenia, « pseudopolyneuritic » symptoms (hyporeflexia or even areflexia and distal paralysis), « pseudomyopathic » symptoms (hypotonia), mental confusion, drowsiness and coma, psychiatric symptoms (agitation or depressive syndrome, etc.). **Renal manifestations:** polyuria–polydipsia syndrome (20% of cases), renal failure, arterial hypertension. **Cardiovascular manifestations:** ECG signs: shortening of the ST segment and of the QT interval, rhythm disturbances (tachycardia, ventricular extrasystoles, ventricular fibrillation) or conduction disturbances (atrioventricular block), arterial hypertension. **General signs:** weight loss with extracellular dehydration, fever. **Associated biological signs:** calcaemia generally > 3.5 mmol/L; extracellular dehydration (hyperproteinaemia, raised haematocrit); metabolic alkalosis (except in chronic renal failure or hyperparathyroidism); hypochloraemia and hypokalaemia.

3. Hypocalcaemia

Hypocalcaemia is defined by a value of: total calcaemia < 2.20 mmol/L or < 88 mg/L, ionised calcaemia < 1.10 mmol/L or < 44 mg/L. It manifests itself through: paraesthesia, hypoaesthesia, fasciculations, muscle spasms, tetany, myopathy, anxiety, irritability, depression, dementia, generalised seizures, focal seizures, depigmentation, dental abnormalities, etc.

The work-up directed at a hypocalcaemia must include calcaemia with albuminaemia or total protein, 24-hour urinary calcium, PTH, vitamin D2D3, magnesaemia, phosphataemia, serum electrolytes, renal function and bicarbonate.

4. Reminder! Mineral and bone metabolism disorders related to chronic renal failure (CKD–MBD):

This new terminology brings together:

- Biological disturbances: hypocalcaemia, hyperphosphataemia, raised PTH, vitamin D deficiency
- Bone remodelling abnormalities: mineralisation, volume, growth, fragility
- Vascular and soft-tissue calcifications: a major risk factor for cardiovascular mortality and morbidity.

Patients with chronic renal failure may present 1, 2 or 3 of the abnormalities listed above. The hypocalcaemia of chronic renal failure is multifactorial; hypocalcaemia/hyperphosphataemia leads to continuous stimulation of the parathyroid glands and to an increase in PTH secretion, with the progressive appearance of a secondary hyperparathyroidism. The rise in PTH leads to an increase in bone resorption, which is responsible for the abnormalities observed in chronic renal failure.

5. Calcium measurement

Total calcaemia consists of slightly more than 50% ionised calcium and slightly less than 10% complexed calcium, the remainder being carried by proteins, essentially albumin.

Hypoalbuminaemia or hyperalbuminaemia leads respectively to a fall or a rise in calcaemia without any change in ionised calcaemia, the only physiologically active fraction. Biologists and clinicians are therefore regularly reminded that, in the absence of an ionised calcium assay, the interpretation of total calcaemia must take into account the serum albumin concentration.

The correction regularly proposed in the literature is the following: [“corrected” Ca (mmol/L) = measured Ca (mmol/L) + 0.020 or 0.025 (40 – albumin (g/L))].

Indeed, in most clinical situations, in the absence of an ionised calcium that is not always accessible, this corrected calcium is sufficient. However, it must be borne in mind that correction with this commonly recommended formula may lead to an increasing underestimation of calcaemia when albumin is above 40 g/L, and is therefore liable to mask a true hypercalcaemia. This readjustment, clinically justified for a low calcium level caused by hypoalbuminaemia, should not be extended to other clinical situations, in particular when albumin is raised. In that case, ionised calcium remains the parameter of choice for the diagnosis of a hypocalcaemia or of a hypercalcaemia.

Conclusion

While it is true that ionised calcium remains the element of choice in the assessment of calcaemia, corrected calcium can provide important information on the measurement of the true calcaemia. Clinicians are therefore strongly encouraged to take these variations into account when assessing calcaemia. Laboratoire Sion has the technical platform required to measure ionised calcium with precision and also determines, at the prescriber's request, the corrected calcium with great efficiency.

References

1. Vassault A. Calcium total et ionisé. Encyclopédie Médico-Chirurgicale, Biologie clinique. Paris : Elsevier, 2006 : 90-10-0260.

2. Houillier P, Nicolet Barousse L, Maruani G, Paillard M. Comment la calcémie est-elle maintenue stable ? Revue du rhumatisme 2003 ; 70 :1054-61.

3. Houillier P, Paillard M. Désordres du métabolisme du calcium et du phosphate (en dehors de l'insuffisance rénale chronique). Encyclopédie Médico Chirurgicale, Néphrologie-Urologie. Paris : Elsevier, 2000, 18-034-F-10.

4. Cormier C. Anomalies du métabolisme phosphocalcique et osseux. Feuillets de biologie 2008 ; 49 : 19-27.

5. Garnero P, Souberbielle JC. Exploration du métabolisme phosphocalcique. Cahiers de formation Bioforma n° 39 - les dosages biologiques dans l'ostéoporose - 2007 ; 40-1.

Contact: 6 99 74 92 47 / 6 76 16 33 53 / 672 26 63 86; Email: contact@laboratoiresion.org