The hungry bone syndrome (HBS), also referred to as bone hunger syndrome, is a rare yet increasingly recognized metabolic bone disorder, that may be dangerous and even life-threatening for patients with diverse disease conditions. It is a peculiar form of secondary hyperparathyroidism, in which persistent and harmful hypocalcemia does not depend on low calcium absorption or high calcium excretion but on calcium avidity of new forming bone. In the vast majority of cases, HBS is a complication of otherwise successful treatments for the diagnosed disease; in some cancer patients, on the other hand, it is a rather neglected feature that characterizes metastatic progression in the skeleton. First described in the ’70s in patients who had undergone surgical removal of a parathyroid adenoma for primary hyperparathyroidism, HBS has become more popular among nephrologists than endocrinologists due to the practice of parathyroid surgery for secondary and tertiary hyperparathyroidism refractory to medical treatment in patients with chronic renal failure. In the most recent years, HBS has been described in patients successfully treated for thyrotoxicosis, severe metabolic acidosis, Paget’s disease and in patients with metastatic cancer bone disease, notably those bearing prostate cancer1-5. These apparently distant conditions share a common way to alter bone metabolism, either systemically or locally: recruitment and/or activation of basic multicellular units (BMU) which in turn are responsible for high bone turnover rate and clinical appearance of bone lesions.

It is held that bone integrity depends on continuing remodeling. All remodeling is carried out by temporary anatomic structures, first identified by Frost6 at the end of ’60s and named by him BMU, to which, in the adult non-injured skeleton, substantially all osteoclasts and osteoblasts belong. In 3-4 months of life span and in a coupled sequence of activation, resorption and formation, each BMU turns over ~0.05 mm³ of bone. When a BMU makes less bone than it resorbs, this tends to remove bone permanently. When a BMU makes more bone than it resorbs, this tends to build up bone permanently. Adult humans create about 3 million new BMU annually, and more than 1 million function at any moment in the whole skeleton. A new BMU is a separate functional unit with regulatory mechanisms for the recruitment, differentiation and activity of precursor cells, osteoclasts, osteoblasts, supporting cells and microvascular bed. It functions in the same sense as nephrons in the kidney7.

Osteoclasts and osteoblasts, the most important cell types of BMU, are continuously receiving endocrine, paracrine and autocrine signals in order to perform their programmed and coupled activity. Among osteotropic hormones, the parathyroid hormone (PTH) is essential for both cell types. Osteoblasts are a primary target of PTH. It is now clear that PTH is a fundamental anabolic signal that promotes differentiation and prevents apoptosis of osteoblasts8. It has also the capability of increasing gene expression and synthesis of receptor activator of nuclear factor κB ligand (RANKL), which is a major stimulus for the differentiation of active mature osteoclasts. When PTH production is excessive and sustained over time as it occurs in primary and long-standing secondary hyperparathyroidism, RANKL synthesis from cells of the osteoblastic lineage may rise up to levels higher than physiological of two orders of magnitude9. Under these circumstances, the osteoclast-mediated bone resorption overrides the osteoblast-mediated bone formation and bone loss becomes clinically apparent.

Turning to HBS, osteoblast number and activity may be increased as a logical consequence of osteoclast-mediated excess resorption, e.g. in hyperparathyroidism or thyrotoxicosis. Uncoupling of osteoblast to osteoclast function, with overwhelming bone apposition even in the presence of supranormal resorption, may be a function of paracrine signals (cytokines, growth factors) that specifically activate differentiation of the osteoblastic lineage in the bone microenvironment, e.g. in Paget’s lesions or prostate cancer metastases. Since decades, clinicians are well acquainted with increased serum levels of a marker of osteoblastic activity, the alkaline phosphatase (AP) (more recently, bone-specific alkaline phosphatase, BAP), in all the above-mentioned conditions.
As expected, after surgery for hyperfunctioning parathyroid adenoma(s), osteoclast-mediated bone resorption rapidly declines; in such circumstances osteoblast activity proceeds substantially unopposed. Mineralization of the new matrix calls for circulating calcium and phosphorus. The HBS becomes apparent with hypocalcemia, hypophosphatemia and hypomagnesemia. The fall of these analytes may be rapid and severe; it causes neuromuscular and cardiac dysfunctions, sometimes of great concern. Arrhythmias and left ventricular failure are conceivably favored by previous hyperparathyroidism that often involves the cardiovascular system. In patients with parathyroidectomy-induced HBS, notably in those with renal failure, hypocalcemia and hypophosphatemia are also accounted for by 1,25(OH)₂-vitamin D deficiency. Independently of suberving mechanisms, hypocalcemia leads to hyperfunction of the remaining parathyroid tissue. The levels of serum PTH rise remarkably as a hallmark of this secondary hyperparathyroidism, and may attain exceedingly high values. The reasons of such a rebound phenomenon, that may be already apparent within weeks after surgery, are not clear. An explanation could be viewed in the down-regulation of PTH receptors by previous hormonal excess, with irreversible or slowly reversible target cell resistance similar to pseudohypoparathyroidism type I. The role of the calcium-sensing receptor and relevant transducing pathways awaits investigation, since serum PTH levels may remain high after long-term supplementation of oral calcium, while they usually fall to the normal range after intravenous calcium loading. The point deserves attention also in the light of the most recent availability for clinical use of calcimimetic drugs, which are positive modulators of the calcium-sensing receptor, such as cinacalcet.

In any case, post-parathyroidectomy HBS once properly treated with calcium and vitamin D preparations should have an autolimiting course in relation to the number of actually active BMU, presumably in a time span of weeks or maximum few months. Intriguingly this does not hold true in a number of patients, in whom difficulties also arise in the treatment. Hypocalcemia may be refractory to calcium supplementation, and huge amounts of exogenous calcium may be required, up to hundreds of cumulative grams, to face unexpected prolongation of osteoblast hyperactivity and new bone mineralization. In the present issue of our Journal, the case report by Morrone et al. focuses on abnormal levels of calcium and BAP long time after parathyroidectomy, hence on the possibility of long-standing HBS. Restoring adequate activity of the vitamin D system in order to attain good phosphorus balance as well, and monitoring levels of serum PTH should help clinicians to tailoring treatment on an individual basis. Furthermore, longitudinal evaluation of bone turnover markers should allow prediction of the course ahead.

Unfortunately, we do not have before surgery prognostic factors of severity and duration of the potential HBS. Information from the literature relies on small series of patients and a number of anecdotal observations on single cases. Taken together available sources, the risk of subsequent HBS seems to be higher in patients with large parathyroid adenomas, higher serum PTH, symptomatic hypercalcemia, appearance of bone lesions and renal failure. Little if any information is available about the preventive role of preoperative administration of bisphosphonates, which has been advocated as potentially effective for more than one decade. It is known that these antiresorptive agents reduce the bone turnover rate. Another relevant point is that they reside unmetabolized in the bone microenvironment for a long time, after administration.

On the other hand, the increasing use of intravenous bisphosphonates in clinical oncology has prompted attention to HBS as a potential complication of their use. In a non-negligible percentage of prostate cancer patients bearing osteoblastic metastases (10-20%), serum PTH levels are supranormal and witness a condition of secondary hyperparathyroidism. This is due to the increased number of BMU with osteoblast prevalence, in other words to subclinical HBS in that hypocalcemia is not apparent. Under such circumstances also osteoclast number and activity are increased, accounting for bone pain and excess matrix resorption. Both altered bone architecture and higher bone turnover rate predispose to fractures. In such patients, the antiresorptive therapy with highly active bisphosphonates has a clear rationale. In particular cases, however, the bisphosphonate-induced fall of osteoclast activity further shifts the balance between formation and resorption toward the former, thus favoring the entrapment of great amounts of calcium and phosphorus in the newly mineralized bone. It is logical to think that at higher risk of this particular HBS be those patients with advanced prostate cancer who have huge tumoral burden in the skeleton, hence a high number of activated BMU (bone scintiscan positive), high levels of serum AP or BAP, secondary hyperparathyroidism and impaired renal function.

Paradoxically enough, administration of potent intravenous bisphosphonates such as pamidronate or zolendronic acid, can improve and not deteriorate HBS in such patients. A plausible explanation could be viewed in the action of bisphosphonates, potentially involving not only
the osteoclasts but the cancer cells themselves. As a consequence, production of paracrine factors crucial for differentiation and activation of osteoblasts at the metastatic sites would be down-regulated and bone formation hampered. The concept of a double-edged sword able to accelerate or contrast HBS in cancer patients also holds for chemotherapy in sparse breast cancer patients who bear mixed or osteoblastic bone lesions. In such cases, the key mechanism should be the impact upon production of PTH-related peptide, that is an anabolic signal for osteoblasts at the same extent of PTH, on the one hand, and also recruits osteoclasts and enhances resorption through hyperexpression of the RANKL, on the other one19.

To summarize, subclinical HBS may be more frequent than previously thought. The use of antiresorptive drugs may lead to uncoupled osteoblast activity within actually operating BMU similarly to what it may occur after parathyroidectomy in patients bearing parathyroid adenomas, and account for unexpected appearance of overt HBS. Not surprisingly, the most recent observation in this respect regards the use of recombinant osteoprotegerin in cases of juvenile Paget’s disease/familial hyperphosphatasia, a rare disease which arises from inactivating mutations in the gene that encodes osteoprotegerin20. The message for clinicians is inherent to the potential severity of the syndrome and its duration, occasionally much longer than expected. Therapy with calcium and vitamin D needs individual monitoring. Much more awareness of the syndrome is needed. The message for researchers in the field of bone metabolism is inherent to unavailability of multicenter controlled studies on prevalence and outcomes, and to many unresolved issues about pathophysiology and management. HBS is also an attractive model for better understanding effects of osteotropic drugs in different clinical settings.

References