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Commentary

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# Clinical Presentation of Hypoparathyroidism

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**Abbreviation:** PTH, parathyroid hormone.

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Hypoparathyroidism is a rare endocrine disorder whose clinical manifestations and complications involve the perturbation of several organs and systems that are specifically related to the target organs of parathyroid hormone (PTH). Chronic hypoparathyroidism is characterized by hypocalcemia and deficient PTH secretion. Levels are usually below detection limits of clinical assays for PTH. Hypoparathyroidism occurs most often as a complication of anterior neck surgery but can also occur as a genetic, autoimmune, or idiopathic disorder.

Hypocalcemia, hyperphosphatemia, and low or undetectable PTH levels are the hallmark laboratory findings in hypoparathyroidism; hypercalciuria may be present, as well. The clinical presentation of hypoparathyroidism is characterized not only by these biochemical abnormalities but also by a wide range of complications that relate specifically to the chronic effects of these metabolic abnormalities on different organs [1-3]. The neuromuscular and cardiovascular systems may be involved, with effects ranging from acute, life threatening manifestations (eg, tetany, seizures, arrhythmias) to long-term complications (eg, cerebral, vascular, renal or other ectopic calcifications) [2]. The organs that can be affected include, but are not limited to, the skeleton, kidneys, skin, and gastrointestinal, ocular, and dental systems [2, 3]. Related to many of these complications or perhaps as a separate entity, quality of life is typically adversely impacted [4].

In the last decade, several studies have focused on the prevalence, natural history, and pathophysiology of hypoparathyroidism and its complications. This research has offered new insights into a disease with protean manifestations [3]. Moreover, and similar to primary hyperparathyroidism [5], published observations from different geographical areas gain an advantage by comparing and contrasting the clinical profiles of hypoparathyroidism as they present around the world.

The study by Zanchetta et al, published in this issue of the *Journal of the Endocrine Society* [1], adds importantly to our knowledge of how hypoparathyroidism presents in Argentina and thus complements other similar cross-sectional studies published elsewhere. A strength of this report is the impressively large number of patients with hypoparathyroidism from 7 specialized centers in Buenos Aires, Argentina, from 1985 to 2018. Of the 322 subjects who constituted the cohort, post-thyroidectomy hypoparathyroidism predominated as the most common etiology.

One of the understandable drawbacks to a retrospective, observational study, such as this one, is that information about many different features of hypoparathyroidism were not uniformly available. Specific observations were made on numbers typically much smaller than the large cohort. Nevertheless, the report is insightful.

Neuromuscular manifestations were most common, reported in 40% of cases. Among those in whom basal

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ganglia calcifications were sought, almost the same percentage was reported. Thus, neuromuscular and neurological complications manifesting as both acute or chronic conditions were very common in this cohort. It is possible that if data on cognitive impairment and psychiatric disturbances were available, the incidence of neurological and neuropsychiatric manifestations of hypoparathyroidism would have been even higher.

Renal manifestations were also reported in a substantial proportion of Zanchetta's cohort. Even though renal ultrasound was performed in fewer than the half of the patients, the incidence of renal stones and/or nephrocalcinosis was as high as 15%. Renal failure was observed in 22%. These data underscore recommendations that kidney imaging should be included in the routine evaluation of all subjects with hypoparathyroidism, regardless of historical information [3].

Since the skeleton is another target organ of PTH, one would expect deficiencies to surface here as well. Although bone mineral density was normal, on average, by T-score at the lumbar spine and hip regions, 39% had low bone mass and 13% had frank osteoporosis. These findings make an important point, namely, that one cannot assume that a state typically associated with normal or above average bone mineral density will not harbor a substantial proportion of subjects with low bone mass. From the article, it is not clear whether these individuals developed their hypoparathyroidism after the menopause [1]. If so, the effects of estrogen deficiency on bone loss, prior to the onset of the hypoparathyroid state, might be reflected in these numbers. The 3 individuals who sustained a vertebral fracture had low bone density and were elderly. It is not clear from the report whether the other fractures were associated with low bone mass. In hypoparathyroidism, fractures could be explained by excessive stiffness even with normal or above normal bone mineral density [1, 6] It would have been helpful to know the bone mineral density of the subjects who sustained non-vertebral fractures.

With the advent of recombinant human PTH (rhPTH[1–84]), guidelines have been proposed to help clinicians decide who might benefit from replacement therapy [6]. Zanchetta et al apply these guidelines to their large cohort [1]. It is fascinating that a full 70% would meet guidelines for PTH replacement therapy. Even more interesting, one of the major criteria, hyperphosphatemia or an elevated calcium × phosphate product, was seen in almost 40% of subjects. The average serum phosphorus concentration was 4.7 mg/dL. This is a point not sufficiently emphasized in terms of the long-term complications of hypoparathyroidism as they relate to the risk of ectopic calcifications. Many experts feel that hyperphosphatemia alone and/or an elevated calcium × phosphate product are major risk factors for ectopic calcifications in hypoparathyroidism [1].

If confirmed by other large series, our expectations about how many people with hypoparathyroidism would benefit from rhPTH(1–84) therapy might serve to be adjusted upwards. Further documenting the attractiveness of rhPTH(1–84) in hypoparathyroidism is another observation of Zanchetta et al, namely that one-fourth of patients experienced episodes of hypocalcemia requiring hospitalization [1].

This paper helps to place in an international context not only descriptive characteristics of hypoparathyroidism but also gives insight into the extent to which subjects are suffering long-term with signs and symptoms of the disease. These insights will help to refine guidelines for conventional management and more recent advances in treatment with rhPTH(1–84).

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## Additional Information

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