

Parathyroids: Pandemic update

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ABSTRACT

Parathyroid glands-related issues (also involving calcium-phosphorus metabolism) amid pandemic are represented by: complicated recovery after COVID-19 infection in cases with severe vitamin D (VD) deficiency or uncorrected hypocalcemia (hCa); the cases with primary hyperparathyroidism-related hypercalcemia who are postponed for parathyroid adenoma removal might be complicated with arrhythmia if the patient becomes COVID-19 positive; lockdown restrictions limited the physical activity, a situation which might aggravate sarcopenia and bone mineral density loss; subjects with renal hyperparathyroidism who do not have controlled values of serum calcium are at higher risk of severe COVID-19 infection due to a wide area of chronic renal failure-associated complications, including Ca, VD and PTH disturbances. This is an update concerning parathyroid glands in relationship to two-year pandemic experience. The mini-review of literature is based on PubMed navigation using a combination of key words like "parathyroid glands", "parathyroid", "parathormone", "vitamin D", "calcium" and "COVID-19" or "coronavirus" or "pandemic". During the first months of COVID-19 pandemic there was a massive reduction of parathyroidectomies volume which was elective for severe forms associating life threatening values of serum calcium. The number of parathyroidectomies increased during the second year of pandemic Hypocalcemia remains a poor prognostic factor in severe COVID-19 infections while underlying mechanisms are complex and might not be exclusively related to vitamin D deficiency which is a topic still on trends. Direct hypoparathyroidism is a new entity amid coronavirus-induced puzzle. E-health is mandatory to follow calcium correcting medication and associated life style intervention in cases with anomalies of calcium/PTH/VD levels.

Keywords: COVID-19, pandemic, parathyroid, parathyroidectomy, vitamin D, calcium

INTRODUCTION

Parathyroid glands-related issues (also involving calcium-phosphorus metabolism) amid pandemic are represented by: complicated recovery after COVID-19 infection in cases with severe vitamin D deficiency or uncorrected hypocalcemia; also, the cases with primary hyperparathyroidism-related hypercalcemia who are postponed for parathyroid adenoma removal might be complicated with arrhythmia if the patient becomes COVID-19 positive; lockdown restrictions limited the physical activity, a situation which might aggravate sarcopenia and bone mineral density loss; subjects with renal hy-

perparathyroidism who do not have controlled values of serum calcium are at higher risk of severe COVID-19 infection due to a wide area of chronic renal failure-associated complications (1-5) (Figure 1).

METHOD

This is an update concerning parathyroid glands in relationship to two-year pandemic experience. The mini-review of literature is based on PubMed navigation using a combination of key words like "parathyroid glands", "parathyroid", "parathormone", "vitamin D", "calcium" and "COVID-19" or "coronavirus" or "pandemic".

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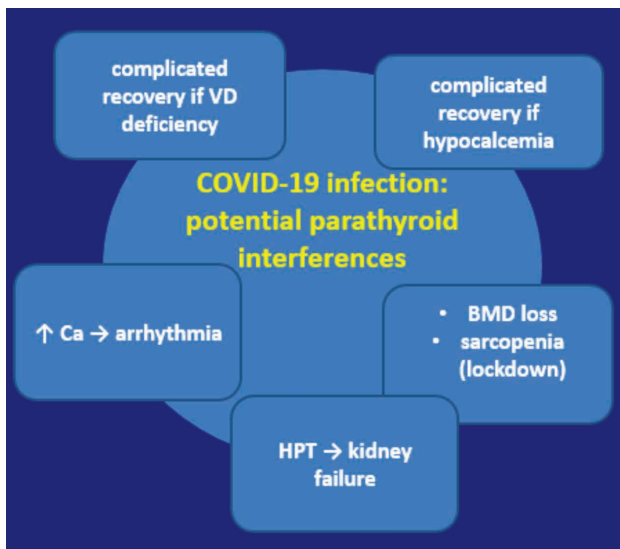


FIGURE 1. Parathyroid glands issue amid COVID-19 pandemic. VD = vitamin D; Ca = calcium; BMD = bone mineral density; HPT = hyperparathyroidism (1-40)

PARATHYROIDECTOMY AMID PANDEMIC

During the first months of COVID-19-related 2020 pandemic there was a massive reduction of parathyroidectomies volume which was elective for severe forms associating life threatening values of serum calcium (2,6). After that, a recovery in procedures number was detected, while for the second pandemic year, “the new normal” means performing parathyroid surgery whenever is needed based on each hospital protocol (7,8,9). One study comparing 2020 versus 2019 in terms of parathyroid surgery found a reduction of 54% (7). High levels of calcium before surgery as well as post-operative hypocalcemia might be a subject of a telemedicine evaluation and patient’ selection in order to decide admission to hospital (10-20).

However, uncontrolled hypocalcemia due, for instance, to an incidental COVID-19 infection might

require the switch from oral calcium supplements to intravenous replacement while uncontrolled hypercalcemia because of infection- related dehydration or diarrhea, might require hospitalization for fluids replacement, diuretics, intravenous bisphosphonates, denosumb, etc. to control calcium levels (21,22).

HYPOCALCEMIA ACCOMPANYING SEVERE FORMS OF COVID-19 INFECTION

Low levels of serum calcium have been identified during severe infections with coronavirus (2,23,24,25). COVID-19-related hypocalcemia is generally regarded as a poor prognostic factor (2,23,24,25).

Several underlying mechanisms have been reported like low vitamin D levels, impaired renal response to parathormone action concerning calcitriol production due to the final hydroxylation step; also hypoalbuminemia might contribute to low total calcium levels; relative and direct hypoparathyroidism as well as impaired absorption of calcium at intestinal level due to severe infection, and probably to associated medication like glucocorticoids (2,26,27) (Figure 2).

Hypoalbuminemia is caused by poor nutrition during infection and potential liver damage (2,28). Direct coronavirus invasion was described at the level of parathyroid glands which might explain their hypofunction (2,29).

One study on COVID-19 positive subjects (N = 78) identified a median of total calcium levels of 2.15 mmol/l, a percent of 67% of patients with hypocalcemia (defined as a value of total calcium below 2.2 mmol/l); also, 67% of patients had hypovitaminosis D (which was defined as a value of 25-hydroxyvitamin D below 20 ng/ml) with secondary increase of parathormone above 65 pg/ml only in one

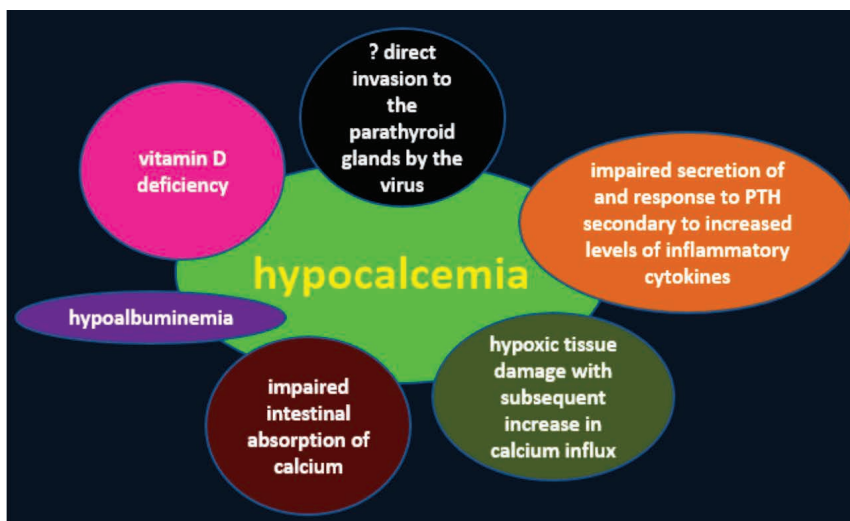


FIGURE 2. Proposed mechanisms of hypocalcemia during COVID-19 infection. PTH = parathormone (1-40)

out of five persons with hypocalcemia and low vitamin D, proving that apparently inefficient response of PTH to vitamin D deficiency might act as the driving force of hypocalcemia amid active infection (30).

A single centric Italian study on 348 COVID-19 positive patients showed that low vitamin D levels (as considered for the study – a level of 25-hydroxyvitamin D less than 12 ng/ml) is statistically significant associated with acute respiratory insufficiency, independent of age, sex, calcemic level, inflammatory syndrome elements, while secondary hyperparathyroidism combined with hypovitaminosis D is also correlated with acute hypoxemic respiratory insufficiency, as well as the need of ventilation (31).

A case-control study (on 91 subjects with COVID-19 infection versus 169 healthy persons) showed a rate of hypocalcemia when first admission of 59% versus 32%; mortality was statistically significant higher in patients with hypocalcemia when compare to infected persons with normal calcium levels (and similarly for admission at Intensive Care Unit); the levels of vitamin D and PTH were similar between the two groups; the percent of severe infection was of 74% versus 24% among persons with hypocalcemia versus those with normal calcium levels (32). This study reveals the role of hypocalcemia as a poor prognostic factor amid coronavirus infection, while low levels of calcium might not be completely attributed to the power games between vitamin D and parathormone (32).

A retrospective study published in 2020 on 241 people with positive COVID-19 infection detected 74% of them with hypocalcemia (a serum calcium median of 2.12 mmol/l), also associating in addition to low calcium decreased 25-hydroxyvitamin D of 10.2 ng/ml (median); subjects with calcium less than 2 mmol/l had the higher incidence of septic shock and multi-organ failure (33).

VITAMIN D AND CORONAVIRUS

As expected, multiple data were released concerning the massive role of vitamin D in immunomodulation, while vitamin D deficiency is seen all over the world (34,35). Evidences that adequate levels of 25-hydroxyvitamin D offer a certain level of protection against coronavirus are heterogeneous; for what it worth so far, vitamin D should be offered in cases with deficiency, not routinely (36,37). However, due to the major epidemiological impact of hypovitaminosis D based on pre-pandemic data,

there is big chance that amid pandemic days, this should be ongoing reality, as well (38,39). Moreover, the daily doses of replacement are mostly harmless thus the massive recommendations of supplementation in general population amid pandemic seem a logical step (40,41). A prospective study on 410 patients admitted for COVID-19 infection showed that 48% of them had vitamin D deficiency on terms of lower levels of 25-hydroxyvitamin D than 20 ng/ml; paradoxically, the patients with hypovitaminosis D were statistically significant younger and had fewer co-morbidities and, as expected, they had a higher level of PTH, but the infection-related mortality, oxygen necessary, severe presentation, outcome, inflammatory picture were not different among groups with versus without vitamin D deficiency (42).

DISCUSSIONS

From an endocrine point of view, a patient with primary hyperparathyroidism-related hypercalcemia might associate other endocrine and neuroendocrine tumors like acromegaly (multiple endocrine neoplasia syndrome type 1, neurofibromatosis type 1) or an adrenal secretor tumor and a thyroid carcinoma (for instance, in multiple endocrine neoplasia type 2A) thus the risk of having a more severe COVID-19 infections comes from the association with diabetes mellitus, high blood pressure, obesity etc. (43-47). On the other hand, post-thyroidectomy hypocalcemia (especially related to malignant conditions requiring large neck dissections) might be managed through digital health platforms in most of cases; an additional supplementation of calcium intake is recommended in COVID-19 positive cases (48-51).

CONCLUSIONS

Hypocalcemia remains a poor prognostic factor in severe COVID-19 infections while underling mechanisms are complex and might not be exclusively related to vitamin D deficiency which is a topic still on trends. Direct hypoparathyroidism is a new entity amid coronavirus-induced puzzle. The volume of parathyroidectomies is resumed during the second year of pandemic after a massive drop during the first months. E-health is mandatory to follow calcium correcting medication and associated life style intervention in cases with anomalies of calcium/PTH.

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