

Parathyroid function index does not differentiate between normocalcaemic primary hyperparathyroidism and Vitamin D deficiency associated secondary hyperparathyroidism

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Background: Normocalcaemic primary hyperparathyroidism (NPHPT) can be considered as an early biochemical manifestation of hypercalcaemic primary hyperparathyroidism (PHPT). Vitamin D repletion and exclusion of other conditions is recommended before diagnosing NPHPT. It is often challenging to distinguish Vitamin D deficiency associated secondary hyperparathyroidism (SHPT) from NPHPT and the two conditions may coexist. A parathyroid function (PF) index [(Parathyroid hormone (PTH) in pmol/l * Corrected Calcium in mmol/l)/ Phosphate in mmol/l] has been previously proposed as a reliable marker in distinguishing the two conditions. However, the patients in NPHPT group in that study were vitamin D deficient. We have evaluated the utility of PF index and other biochemical markers in a larger cohort of patients with or without Vitamin D replacement.

Methods: Patients were selected from electronic health records based on their consistently abnormal metabolic bone profile after exclusion of chronic kidney disease (eGFR < 60 ml/min/1.73 m²), concomitant pregnancy, interfering drugs and conditions that could cause hypercalcemia. Patients were categorised into four groups: Classic PHPT (*n*=60), NPHPT in those with serum 25(OH)D > 50 nmol/l (*n* = 329), Vitamin D deficiency related SHPT (*n* = 259) and age matched healthy controls (*n* = 118). ROC analyses was performed to determine a reliable PF index cut-off between NPHPT and SHPT.

Results: The PF index was highest in the classic PHPT group in comparison to others [Mean(SD) was 37.95± 20.1 PHPT vs 21.51±6.90 NPHT, 21.27±6.91 SHPT, 9.36±3.00 controls]. When comparing NPHPT with SHPT, AUROC was 0.51. In a separate analysis, when comparing pre-treatment PFindex between those who normalised their PTH after vitamin D repletion and those who did not, AUROC was 0.62. Thus, in patients with normocalcaemia, vitamin D deficiency and elevated PTH, PF index did not usefully predict which individuals would normalise PTH after vitamin D repletion and therefore did not distinguish patients with NPHPT from those with SHPT. Moreover, serum phosphate between the two groups was not significantly different.

Conclusion: After Vitamin D repletion, PF index did not discriminate NPHPT from those with Vitamin D deficiency related SHPT. Hence as recommended in recent guidelines, it is imperative to replace Vitamin D before diagnosing patients with NPHPT. Further studies are warranted to identify better markers for NPHPT so that they can be closely monitored for PHPT related bone and renal complications and thus referred for timely surgical intervention.