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EDITORIAL

Glucose intolerance and primary hyperparathyroidism: an unresolved relationship

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Abstract Primary hyperparathyroidism (PHPT) can be characterized as either symptomatic or asymptomatic, or, most recently, as normocalcemic. In the current issue of the journal, Cakir et al. report that insulin resistance and glucose intolerance is not an aspect of normocalcemic PHPT. However, both the current study as well as the literature are compromised by the lack of appropriate classification of normocalcemic PHPT subjects. Rigorously characterized cohorts are necessary to determine whether glucose intolerance is in fact present in normocalcemic PHPT.

Keywords: Primary hyperparathyroidism · Glucose intolerance · Insulin resistance · Normocalcemic primary hyperparathyroidism

Introduction

In early descriptions of primary hyperparathyroidism (PHPT), patients were always symptomatic with kidney stones, bone disease, and marked hypercalcemia. In addition to the cardinal renal and skeletal features, aspects of the metabolic syndrome were reported, including increased body weight, [1] hypertension, dyslipidemia, glucose intolerance [2], insulin resistance [3], and an increased incidence of Type 2 diabetes mellitus [4]. Such a link between PHPT and glucose metabolism is in fact biologically plausible, as higher serum calcium levels could stimulate higher insulin levels by regulating intracellular free calcium concentrations. Whether parathyroidectomy improves glucose abnormalities in symptomatic PHPT is unclear; studies have reported worsening [5], improvement [6, 7] or no change [8] in glucose tolerance after curative surgery.

With the advent of the multichannel autoanalyzer, the clinical phenotype of PHPT changed to a disorder characterized by mild hypercalcemia and the absence of classical features of the disease. Whether abnormalities in glucose metabolism are also present in modern, asymptomatic PHPT is unclear. Contradictory data are available in observational studies regarding insulin resistance, glucose tolerance, and diabetes [9]. The data suggest that glucose abnormalities, if present in asymptomatic PHPT, are likely subtle. Importantly, if such abnormalities exist, they do not appear to resolve with cure. In the only randomized controlled trial data available on metabolic parameters in PHPT, a cohort of 116 mild PHPT patients (serum calcium 10.7 ± 0.4 mg/dl), were randomized to parathyroidectomy or observation. BMI, glucose, and insulin levels did not change over the 2 years of study follow-up in either group [10].

We are now entering a third era in the history of PHPT in which patients are being discovered with normal serum calcium concentrations, but with parathyroid hormone levels that are consistently elevated. This new entity, normocalcemic PHPT, can only be diagnosed in patients who meet rigorous criteria [11]. Both total and ionized serum calcium must be consistently normal, and secondary causes for PTH elevation must also be meticulously excluded. Most important of these is vitamin D deficiency, in which case repletion of vitamin D would be associated with either normalization of the PTH level or unmasking of hypercalcemic PHPT. Other causes of secondary elevations in PTH that need to be ruled out include hypercalciuria,

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malabsorption, and use of medications (lithium and thiazides) that can alter calcium homeostasis.

In the current issue of the Journal, Cakir et al. [12] report a case–control study in which 18 patients with elevated PTH levels and normal serum calcium levels and 18 matched controls had comparisons of glucose metabolism as assessed by oral glucose tolerance testing. The patients and controls were matched with regard to age, gender, and BMI; both groups were obese (BMI of 32 kg/m^2) and had unfavorable lipid profiles. In both groups, impaired glucose tolerance was similarly found (in 8 patients and in 6 controls). The authors conclude that insulin resistance and glucose intolerance are not present in normocalcemic PHPT.

The authors should be commended for pursuing this question. Indeed, this is an important clinical issue, as glucose intolerance may be linked to known cardiovascular abnormalities in PHPT, and if present in normocalcemic PHPT, could impact the cardiovascular risk as well as surgical recommendations. However, enthusiasm for this study is limited by several issues. First and foremost, is its characterization of the normocalcemic cohort. Two criteria required for the diagnosis of normocalcemic PHPT–normal levels of ionized calcium and urinary calcium excretion–were not assessed. Pitfalls in diagnostic classification also limit interpretation of prior studies of carbohydrate metabolism in normocalcemic PHPT. One study reported abnormal glucose tolerance, but 25-hydroxyvitamin D levels were not available on all patients, there were no ionized calcium levels and 20 % had hypercalciuria [13]. Another found increased BMI, glucose levels, and proathrogenic lipids, but had no data on vitamin D levels [14]. It is essential to the development of a secure literature on normocalcemic PHPT that diagnostic criteria be rigorously followed. Thus, both the current study as well as the literature are compromised by the lack of appropriate classification of normocalcemic PHPT cohorts. A second limitation of the study of Cakir et al. is its small sample size. Finally, it is possible that matching by BMI prevented the authors from seeing an association that may be mediated by fat mass. Meta-analysis suggests that body weight is increased in PHPT and data support an association of PTH levels with fat mass, possibly mediated by leptin [15], in non-PHPT subjects.

Further studies are necessary to determine whether glucose intolerance is in fact present in normocalcemic PHPT. Intuitively, one would expect that glucose abnormalities would correlate with the severity of the PHPT and the degree of hypercalcemia, such that classical PHPT would be associated with the most glucose intolerance and normocalcemic PHPT with the least. However, this assumes that normocalcemic PHPT subjects are simply a forerunner of hypercalcemic PHPT patients. In fact, we now understand that normocalcemic PHPT subjects may actually represent a more severely affected cohort, with a greater incidence of kidney stones, low bone density, and fracture [16]. Most of these patients have been identified when seen for referral in specialized bone units for low bone mass and found on evaluation to have high PTH levels, even when the serum calcium is normal. This phenotype is indeed consistent with the cohort described in the current study, in whom 40 % had osteoporosis. One could thus argue that perhaps such normocalcemic PHPT patients would be more severely affected with regard to glucose metabolism as well. Although the current data are inconclusive, more data with regard to both mild PHPT as well as rigorously characterized normocalcemic PHPT cohorts would shed light in this regard.

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Conflict of interest The authors have no conflicts of interest.

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