

Emerging data on cardiovascular risk in primary hyperparathyroidism

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The cardiovascular risk profile of patients affected by primary hyperparathyroidism (PHPT) has been an issue of debate over the last years. Studies regarding the potential damages caused by increased serum levels of parathyroid hormone (PTH) and/or calcium, have yielded controversial results, suggesting either the presence or the absence of damage [1, 2].

It is interesting to note that the answer to this question is further complicated by the changing clinical presentation of PHPT over the last decade. Indeed, once considered a symptomatic disorder characterized by significant hypercalcemia with kidney stones and/or bone involvement [3–5], today PHPT is most commonly seen in asymptomatic individuals with milder hypercalcemia, due to the large availability of routine serum calcium measurements and developments in assay systems. A new presentation is now emerging, characterized by normocalcemia and elevated serum parathyroid hormone levels (the so-called “normocalcemic primary hyperparathyroidism”).

Recently in this Journal, Procopio et al. reported an increased prevalence of intermediate-high cardiovascular risk score (CRS), both in symptomatic and asymptomatic PHPT patients, as compared to healthy controls [6]. Their data are in line with several previous studies that reported an increased coronary artery and cerebrovascular morbidity in PHPT [7, 8]. By means of a multivariate analysis, they also showed that, PHPT status predicts the presence of intermediate-high CRS and metabolic syndrome [9], while

elevated calcium levels predict altered glucose tolerance among the components of metabolic syndrome.

Procopio et al. added new information on an emerging aspect of patients with this glandular disorder; however, there are also some limitations that should be kept in mind when interpreting the results obtained. For example, the classification of patients is somewhat arbitrary. Asymptomatic patients with complications should no longer be considered as such; indeed, future classifications should be based on the presence or absence of complications. Just to make an example, patients may be asymptomatic, but can be incidentally discovered to have a kidney stone by ultrasound; in such a case she/he is asymptomatic but already has a complication of the disease. In essence, the term asymptomatic does not mean without complications; in this context, also a vertebral fracture may be asymptomatic but represents a complication. Secondly, the paper does not include any follow-up after surgery; this could have added meaningful information about the possible reversible effects of a restored biochemical calcium metabolism on cardiovascular risk factors. The current data conflict on this last issue [10, 11], possibly due to the different timing of surgery. For example in the case of hypertensive patients, it is entirely possible that parathyroidectomy would be effective only if performed in an early phase of the disease, when structural abnormalities are not present. A similar situation can be observed in other endocrine disorders determining arterial hypertension, such as primary hyperaldosteronism [12].

It has been shown that, in the general population, cardiovascular risk factors can result in cardiac organ damage which might be detected by echocardiographic measurements. Conflicting results are present in the current literature in relation to the finding of left ventricular (LV) hypertrophy and LV systolic and diastolic dysfunction in

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PHPT patients; these discrepancies might be related, among other things, to the heterogeneity in the clinical features of patients, the echocardiography criteria and the devices used [13, 14]. The latest study on this issue, by Ozdemir et al., shows that patients with PHPT, but without cardiac symptoms or documented cardiovascular disease, have subclinical systolic and diastolic myocardial dysfunction [15]. Patients were tested with new and very sensitive methods thus improving the standard echocardiography accuracy. In fact, the Authors investigated patients by means of Tissue Doppler Imaging (TDI) that measures myocardial wall velocities with respect to timing and amplitude and quantifies the global and regional systolic and diastolic functions. Moreover, strain (S) and strain rate (Sr) echocardiography, parameters derived from color Doppler myocardial imaging able to evaluate regional myocardial wall motion and deformation, were also used. The results obtained show that PHPT patients when studied with TDI, S and Sr echocardiography (in addition to conventional echocardiography) have a subclinical cardiac involvement, which was not revealed using standard echocardiography alone [15]. Serum calcium and PTH values were negatively correlated with both S and Sr values, further indicating their unfavorable effects on systolic functions. In this study as in the previous one, the classification of patients might generate confusion; furthermore, also in this case, the study lacked a follow-up after parathyroidectomy. However, a previous study on mild PHPT, which did not demonstrate that mean S values were different between patients and control, showed that S values significantly decreased after parathyroid surgery [16].

Bearing in mind the limits deriving from patients classification, the studies of Ozdemir and Procopio clearly demonstrated cardiovascular and metabolic involvement in PHPT patients; in particular, Ozdemir and coworkers showed that patients with apparently normal standard echocardiography, might have subtle abnormalities if investigated with more sophisticated measurements. Accordingly, clinicians should investigate accurately patients with PHPT; the utilization of more sophisticated procedures might generate more consistent results in the future.

The investigation of cardiovascular aspects in patients with primary hyperparathyroidism is of utmost importance, because it has been shown that an increased mortality in PHPT patients is mainly due to cardiovascular complications [17]; in this context, data on asymptomatic patients without complications are still limited. In addition, considering the well-known effects of calcium on cardiac contractility and conduction, some other aspects, such as for example the cardiac arrhythmias, could play a role when considering cardiovascular mortality. Indeed, an increased occurrence of ventricular premature beats and a

different QT interval adaptation, which suggests an electrical myocardial instability, were observed during exercise test [18] in PHPT patients. These electrocardiographic abnormalities, representing risk factors for major arrhythmias, were significantly reduced after parathyroidectomy [19].

Even though, the current guidelines for surgical treatment of primary hyperparathyroidism do not mention cardiovascular risk factors or the presence of arrhythmias among the criteria needed for elective surgery [20], these issues should be taken into consideration in the future agenda. The main limitation in order to draw definitive conclusion on the extent and nature of cardiovascular involvement is given by the lack of randomized controlled trials of adequate power and duration; more importantly, a uniform classification of patients enrolled (patients with complications vs truly mild asymptomatic patients without any organ damage) should be pursued. The same concerns should be considered for other non-classical symptoms of PHPT, such as gastrointestinal or neuropsychological complaints [21, 22].

In conclusion, new emerging data from Procopio [6] and Ozdemir [15] seem to underline a possible increased cardiovascular risk profile in patients with primary hyperparathyroidism. If these data are confirmed by well-designed studies of long duration with an adequate number of patients and, more importantly, if the risk is reversed after parathyroidectomy, cardiovascular risk profile might represent an additive criterion for submitting patients to surgery.

Conflict of interest The authors state they have no conflict of interest.

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