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Treatment indications of mild primary hyperparathyroidism in old age; a challenge for research

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ABSTRACT

Primary hyperparathyroidism (PHPT) is common in older people, but it does not usually develop classical symptoms or long-term complications in the last years of life. The non-specific symptoms are often indistinguishable from age-related complaints and illnesses, and the patients are generally left in surveillance. Trials are needed to show, whether the non-classical symptoms of PHPT so far deemed as contraindications are rather indications for treatment in old age.

In clinical practice, physicians often encounter mildly hypercalcaemic older patients. In most cases concomitantly elevated concentration of parathyroid hormone (PTH) confirms the diagnosis of primary hyperparathyroidism (PHPT). Several population-based studies have shown that the prevalence of PHPT increases with age, being at least twice as common in women as in men [1]. However, it is not clear how the oldest PHPT patients should be treated and monitored. The diversity of clinical symptoms in older PHPT patients, the poor association of these symptoms with the degree of hypercalcaemia and parathyroid hormone (PTH) levels as well as the uncertainty of treatment results emphasize the need for future trials.

1. The clinical presentation of PHPT has changed

At present, PHPT is commonly diagnosed without the classical manifestations such as hypertension, renal calculi, nephrocalcinosis, renal dysfunction, osteopenia or osteoporosis, osteitis fibrosa cystica, and severely altered neurologic function with obtundation, delirium or coma [2]. In fact, case-control studies based on questionnaires have revealed that PHPT patients often report non-specific milder complaints like, weakness, easy fatigability, depression, intellectual weariness, cognitive impairment, loss of initiative, anxiety, irritability, sleep disturbances and features of somatisation [3]. These patients with milder phenotype of PHPT have been also called "asymptomatic". A third phenotype of the disease, "normocalcaemic PHPT", has been also described [4]. It is defined by elevated PTH concentration, normocalcaemia and sufficient vitamin D status.

2. Effects of parathyroidectomy on non-classical symptoms of PHPT

Parathyroidectomy (PTX) is effective and safe also in older patients [5]. PHPT accompanied by frank elevation of serum calcium with obvious clinical symptoms is a clear treatment indication even in the oldest. Moreover, non-classical symptoms of PHPT are being accepted as indication for PTX especially in younger patients. These symptoms often resemble age-related illnesses and aging itself, i.e., "senility", inevitably resulting in delayed or deferred referral of older PHPT patients for PTX [6]. Clinical experience on selected cases and a plethora of sporadic case reports suggest that PTX can sometimes improve this "pseudosenility" [7]. Thus, the effects of PTX on quality of life and functional capacity, particularly, are emphasized in the management of older patients with biochemically mild PHPT.

Randomized controlled trials (RCT) addressing the effects of PTX in PHPT were retrieved in April 2011 from Pubmed with the following search phrase: "Primary hyperparathyroidism AND (parathyroidectomy[title] OR surgery[title] OR surgical[title]) AND (randomly[title/abstract] OR randomized[title/abstract] OR randomised[title/abstract] OR random[title/abstract])". The search included 48 papers which were evaluated and their reference lists reviewed. To date three larger and one RCT have addressed the

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effects of PTX on quality of life or physical functioning in PHPT patients without classical indications for surgery (Table 1). In these trials PTX improved bone mineral density (BMD), walking distance, some domains of quality of life, and sleep quality [8–13]. However, none of these trials addressed the effectiveness of PTX in old age. Nevertheless, Talpos et al. found that surgery improved social and emotional role functioning [8]. In the extension of the study, a modest benefit was still found [9]. In the series of Böllerslev et al. the patients were collected from primary care in three Scandinavian countries and referred to five surgical centres [10]. The patients did have more neuropsychiatric complaints as compared to the Swedish normative data, but PTX did not improve neuropsychological functions. However, in the single-centre study by Amborgini et al., surgery improved some domains of quality of life such as physical function, bodily pain, general health, mental health, and vitality [11]. One small RCT has shown a clinically meaningful improvement in 6-minute walking distance in the PTX-group [12]. In another report from the same patient group, PTX seemed to improve sleep quality [13].

It should be noted that the placebo effect of surgery cannot be excluded in these studies (Table 1). It is also important to recognize that the patients were highly selected and young in all of these trials. Furthermore, patients with mental disorders and mental symptoms seem to have been often excluded. In fact, also the referral practices in primary care may have been too conventional and conservative leading to under-utilization of surgical possibilities and resulting in surgical study groups with relatively few frail older PHPT patients with "non-classical" symptoms [6].

3. Indications for parathyroidectomy in old age are not clear

For several reasons the present trial evidence does not allow normative definitions of indications for surgery in PHPT in old age. Neither serum calcium nor PTH correlates well with severity of symptoms [14]. Thus, treatment decisions solely based on the serum calcium and/or PTH levels seem not to be appropriate.

Secondly, old age alters the relative significance of bone disease. The PHPT induced bone loss is partly reverted by PTX which may also prevent fractures [15]. Thus, BMD measurements have been recommended in the follow-up of PHPT patients [3]. However, all older persons have at least osteopenia and the relevance of repeated BMD measurements in surgical decision-making for older PHPT patients remains unclear. Even though PHPT can be associated with neuromuscular weakness and the incidence of fractures is increased in young PHPT patients [16], no study has addressed bone fracture risk of oldest PHPT patients. Actually, with advancing age, the fracture incidence of PHPT patients seems to become equal to that of the general population [17], perhaps due to attenuation of disease progression.

Thirdly, concerning morbidity and mortality, the prognostic importance of biochemically mild PHPT in old age is unclear. Epidemiologic findings indicate that PHPT increases cardiovascular mortality, which is also decreased by PTX [18]. This evidence from relatively hypercalcaemic patients has been used to advocate PTX in biochemically mild PHPT without classical symptoms. Recently, also mild PHPT has been associated with increased mortality in a population-based cohort of relatively old (mean age = 69 years) PHPT patients [19]. In addition, there are several large-scale prospective studies showing association of elevated PTH with all-cause and cardiovascular mortality even in normocalcaemic populations [20]. High PTH has been associated with mortality also in late life [21], but the 17-year follow-up of these older people (age cohorts of 75-, 80-, and 85-year old general population, N = 567) living in Helsinki did not suggest excess mortality of persons with PHPT (Fig. 1).

Apart from co-morbidities and disease severity, old age alone diminishes the likelihood of PTX. In contrast to young PHPT patients, older patients with biochemically mild PHPT typically do not develop classical long-term complications [4] and are generally left in surveillance only. However, the actual present-day impact of PHPT on quality of life and activities of everyday living may be far more relevant in the last years of life.

4. Other treatment options

Bisphosphonates can protect bones for years but do not correct hypercalcaemia permanently [22]. The calcimimetics e.g. cinacalcet lower both serum calcium and PTH and thus seem promising in those PHPT patients who are not candidates for PTX [22]. Estrogens or raloxifene, a selective estrogen receptor modulator have not been tested in the treatment of the non-classical symptoms of PHPT, thus far.

5. Future research perspectives

Follow-up studies based on calcaemic screening of large unselected older population could shed light on the evolution and natural history of PHPT. Such studies could show that in old

Table 1
Randomized parathyroidectomy vs. observation trials addressing quality of life and physical functioning in primary hyperparathyroidism patients without classical symptoms.

Author	Patients	Recruitment population, N	Eligible, N	Mean age, years	Mean calcium, mmol/L	Mean PTH, ng/L	Follow-up	Drop-outs, %	Main positive results related to PTX
Talpos et al. 2000 [8] Rao et al. 2004 [9]	Asymptomatic PHPT patients (USA)	Hypercalcemic patients within computerized health system, 1201	53	65 ± 7	2.59	82	24–64 months	0	BMD, QoL (modest), Anxiety/phobia (modest)
Böllerslev et al. 2007 [10]	Asymptomatic PHPT patients (Sweden, Norway, Denmark)	Referred PHPT patients, N not reported	191	64 ± 7	2.69	97	2 years	48	BMD
Ambrogini et al. 2007 [11]	PHPT patients not meeting guidelines for PTX (Italy)	Referred PHPT patients, 412	50	65 ± 6	2.54	112	1 year	0	BMD, QoL (modest)
Perrier et al. 2009 [12] Morris et al. 2010 [13]	PHPT patients not meeting guidelines for PTX (USA)	Consecutive referred PHPT patients, 54	21	66 ± 10	2.58	122	6 months	14	Walking distance, Day time sleepiness (modest)

PTX: Parathyroidectomy; PHPT: Primary hyperparathyroidism; PTH: parathyroid hormone; BMD: Bone mineral density; QoL: Quality of life.