

Endocrinology Research Review

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Issue 34 - 2017

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Abbreviations used in this issue:

ACTH = adrenocorticotrophic hormone; **(a)OR** = (adjusted) odds ratio;
GD = Graves' disease; **GO** = Graves' ophthalmopathy;
HPA = hypothalamic-pituitary-adrenal; **HR** = hazard ratio;
OS = overall survival; **QoL** = quality of life; **RAI** = radioactive iodine;
TSH = thyroid-stimulating hormone; **TPO** = thyroid peroxidase.

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Welcome to the 34th issue of Endocrinology Research Review.

Highlights of this Review include a promising clinical trial of the IGF-1 receptor antagonist teprotumumab for Graves' ophthalmopathy, although more evidence is needed to assess the long-term safety and durability of effect with this agent. We report on a small prospective study which evaluated the use of the overnight metyrapone test for assessment of HPA axis function following pituitary surgery. Findings suggest that this is a safe and simple alternative to insulin hypoglycaemia testing provided liquid chromatography tandem mass spectroscopy assays are used. We feature a retrospective analysis providing evidence of the utility of temozolomide in aggressive pituitary tumours, and finish up with a study demonstrating that thiazide therapy may be of benefit in a subset of patients with primary hyperparathyroidism.

We hope you find the selection for this month's issue useful in your practice, and we look forward to receiving your comments or feedback.

Kind Regards,

Professor Duncan Topliss

duncan.topliss@researchreview.com.au

Teprotumumab for thyroid-associated ophthalmopathy

Authors: Smith TJ et al.

Summary: This multicentre, controlled, double-masked, clinical trial randomised 88 patients with active, moderate-to-severe ophthalmopathy to 3-weekly IV teprotumumab (total of 8 infusions) or placebo. The primary endpoint was clinical response encompassing ≥ 2 -point reduction in Clinical Activity Score (range 0-7) and ≥ 2 mm reduction in proptosis in the study eye at week 24. The proportions of patients with a response at week 24 were 69% with teprotumumab vs 20% with placebo ($P < 0.001$, intention-to-treat analysis). Respective proportions of responders at week 6 were 43% vs 4% ($P < 0.001$). No drug-related adverse events were noted other than hyperglycaemia in patients with diabetes which was managed by medication adjustment.

Comment: Currently validated drug treatments for Graves' ophthalmopathy (GO) include high dose glucocorticoid therapy especially by the EUGOGO protocol, with or without orbital irradiation or cyclosporin. Mild GO may respond to selenium supplementation. Rituximab remains unproven because of conflicting trial results, but may be considered as a second line agent, and treatments of marginal or unproven value include somatostatin analogues, azathioprine, ciamexone, and IV immunoglobulins. (The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy, [Bartelena et al. Eur Thyroid J. 2016;5:9-26](#)). This randomised controlled study of the IGF-1 receptor antagonist, teprotumumab, is based upon *in vitro* studies showing attenuation of the action of IGF-1 and thyroid stimulating antibodies on orbital fibroblasts. Eight doses given every 3 weeks over 24 weeks to patients with active GO improved proptosis, Clinical Activity Score, and quality of life scores for vision, appearance, and diplopia. Serious adverse events were more common with teprotumumab (5/43 versus 1/45) but only two were assigned as possibly treatment-associated: single cases of diarrhoea and mental confusion. It is disappointing that this therapy, like glucocorticoid therapy, has a hyperglycaemic effect, in 12% versus 5% for placebo, but this was only clearly seen with pre-existing diabetes and was easily controlled. The durability of the effect and long-term safety remain to be assessed, but this may become a major option in the treatment of active GO.

Reference: *N Engl J Med.* 2017;376:1748-61

[Abstract](#)


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PP-TE-AU-0025. Date of preparation: January 2017.
FR7056/ERR1/2/17.



Mortality in Graves' orbitopathy is increased and influenced by gender, age and pre-existing morbidity

Authors: Schwensen CF et al.

Summary: These Danish investigators conducted a cohort study based on nationwide registry data in order to determine whether mortality rates differed amongst patients with Graves' disease (GD), with or without ophthalmopathy (GO). Subjects were all adults diagnosed with GD ($n = 28,461$) and GO ($n = 3,965$) between 1995 and 2012 (mean follow-up 7.9 years); each were age- and sex-matched with 4 controls. Adjusted mortality rates were increased vs controls amongst patients with GD (HR 1.19; 95% CI 1.16, 1.22) and GO (HR 1.23; 1.12, 1.35). Males with GD and GO had significantly higher mortality rates than females. GD patients had higher mortality rates than those with GO (HR 0.64; 0.59, 0.69), which attenuated following adjustment for age, gender and co-morbidity.

Comment: The study provides evidence of a modest adverse effect of GO and GD on mortality especially in men which was cumulative over the duration of the study. These authors have previously published evidence of a 42% increase in mortality in Graves' disease compared to the general population ([Brandt F et al. Thyroid. 2013;23:408-413](#)) but did not distinguish between those with GO and those without. The presence of GO is known to be associated with taking more sick leave and significant reduction of quality of life so the authors hypothesised that those with GO would be particularly adversely affected. Males with GD more frequently experience failure of medical treatment, are less likely to enter long-term remission and have more severe GO. The reason may be poorer compliance and biochemical control, given that men are less frequent users of the healthcare system than women. However, unexpectedly and unexplained, decreased mortality in GO was found compared to that of patients with GD alone. This difference was attenuated after adjustment for age, gender and pre-existing morbidity, indicating that the two phenotypes do not with certainty differ significantly in mortality risk. The study does not provide information about the causes of increased mortality in men. Perhaps in the absence of this information it is reasonable to focus on maintaining adherence to therapy and on reducing cardio- and cerebro-vascular risk including thromboembolic stroke.

Reference: *Eur J Endocrinol.* 2017;176:669-676
[Abstract](#)

The second antithyroid drug treatment is effective in relapsed Graves' disease patients

Authors: Kim YE et al.

Summary: This Korean study sought to determine long-term prognosis and factors predicting relapse amongst patients with Graves' disease (GD). Subjects ($n = 187$) were recently diagnosed with GD, treated with anti-thyroid drugs (ATD) and had ≥ 4 years' follow-up (median 11.1 years) available. Remission (euthyroid status maintained for ≥ 1 year post ATD withdrawal) was achieved by 51.9% of study participants. Remission (ten-year rates) with 1st ATD course were 34.2%, compared to 25.5% with 2nd ATD course and decreased thereafter with further ATD courses. Factors associated with persistent disease status included greater number of relapses (OR 4.7; 2.3, 9.8; $p < 0.001$), moderate-severe Graves' ophthalmopathy (OR 4.1; 1.1, 15.2; $p = 0.032$) and greater length of ATD therapy (OR 1.4; 95% CI 1.2, 1.7; $p < 0.001$).

Comment: This study provides useful information to aid decision-making in Graves' hyperthyroidism treatment selection. In follow-up of Korean patients with GD, the relapse rate after a second antithyroid drug course was very similar to that after the first course, but the relapse rate after the third course was clearly worse. Thus it is reasonable to consider a second course, but if another relapse occurs then selection of ablative therapy, or perhaps chronic drug therapy, is more appropriate than a third course. While we all recognise this sequence is reasonable, the study provides factual information that should assist in counselling patients.

Reference: *Thyroid.* 2017;27:491-496
[Abstract](#)

Preconception TSH and pregnancy outcomes: a population-based cohort study in 184 611 women

Authors: Chen S et al.

Summary: This Chinese, population-based, cohort study examined associations between pre-conception maternal TSH concentrations and pregnancy outcomes. Subjects were volunteer couples recruited via the free National Pre-pregnancy Checkups Project between 2010 and 2012. The study cohort comprised 184,611 women who became pregnant. TSH was measured ≤ 6 months prior to conception. Adverse pregnancy outcomes occurred in 28.6% of the study cohort. Multivariable logistic regression analysis found associations between adverse pregnancy outcomes of spontaneous abortion (aOR 1.10; 1.03, 1.18), pre-term birth (aOR 1.09; 1.04, 1.15) and operative vaginal delivery (aOR 1.15; 1.09, 1.21) with pre-conception TSH 2.50-4.29 vs TSH 0.48-2.50 mIU/L. In subjects with the highest TSH concentrations (4.29-10.0 mIU/L), increased rates of spontaneous abortion (aOR 1.15; 1.10, 1.22), still birth (aOR 1.58; 1.10, 2.28), preterm birth (aOR 1.20; 1.08, 1.34), caesarean section (aOR 1.15; 1.10, 1.22) and large for gestational age infants (aOR 1.12; 1.04, 1.21) were observed vs those TSH < 2.5 .

Comment: The maternal TSH value above which adverse pregnancy effects may be seen remains unclear. Most data have been accumulated in the first trimester during which maternal TSH is changing so that early and late first trimester value may differ significantly with TSH up to 4-6 weeks of gestation similar to preconception values. The American Thyroid Association now recommends a cut-off of approximately 4.0 mIU/L for first trimester TSH. This is a low-risk population-based cohort study in China of pre-conception TSH within 6 months of conception which finds modest but significant adverse associations of TSH > 2.50 mIU/L, and of TSH 4.29-10 mIU/L. Of course, a one-off TSH abnormality should ideally be confirmed and the TPO antibody status checked as well, as positivity carries an independent risk of premature delivery. Only 20% of women with initial normal-high TSH are confirmed to have hypothyroidism. Furthermore identifying an increased risk is one thing and initiating levothyroxine treatment in women planning a pregnancy with TSH > 2.5 mIU/L is another. Not all studies have found an association between normal high TSH and adverse pregnancy outcomes. A large prospective prenatal screening study in the USA identified an association between maternal hypothyroidism and pregnancy-related hypertension, but this increased risk was seen only in women with initial TSH > 4.5 mIU/L ([Bryant, SN et al. Am J of Obstet & Gynecol. 2015;213\(4\):565 e1-6](#)) Prospective randomised controlled trials examining the role of levothyroxine supplement in mildly hypothyroid women before pregnancy are needed.

Reference: *Clin Endocrinol (Oxf).* 2017;86(6):816-824
[Abstract](#)



Selection and review of the research has been carried out independently by Professor Duncan Topliss, MB BS Hons, MD, FRACP, FACE.

Professor Duncan Topliss is Director of the Department of Endocrinology and Diabetes at the Alfred Hospital Melbourne, Professor of Medicine in the Department of Medicine Monash University and a past-President and Life Member of the Endocrine Society of Australia. He has served on the editorial board of the Journal of Thyroid Research and Clinical Endocrinology and is a frequent reviewer for Clinical Endocrinology, Thyroid, and other endocrine journals. Professor Topliss heads the Diabetes Clinic at the Alfred Hospital, has a long-term interest in diabetes prevention and management and has been an investigator on several major international diabetes trials. He has a wide interest in clinical endocrinology including osteoporosis, pituitary and adrenal disease and endocrine hypertension, and has over 25 years of experience in the management of thyroid disease and thyroid cancer. His other interests are drug regulation and safety, he is a member of the Australian Advisory Committee on Medicines of the Therapeutic Goods Administration, and a frequent consultant to the Australian Advisory Committee on Therapeutic Devices.




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References: 1. Arlot M *et al.* *J Bone Mineral Res.* 2005;20:1244–1253. 2. FORTEO (teriparatide) Product Information, 2 November 2015. 3. Forteo PBS listing, available at: <http://www.pbs.gov.au/medicine/item/9411H> accessed September 2016.

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 PP-TE-AU-0026. Date of preparation: January 2017. FR7056/ERR2/2/17.

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Extent of surgery did not affect recurrence during 7-years follow-up in papillary thyroid cancer sized 1-4 cm: preliminary results

Authors: Kim MJ et al.

Summary: This retrospective observational study examined the impact of hemithyroidectomy vs thyroidectomy on recurrence rates in patients with papillary thyroid cancer sized 1-4 cm. Subjects who underwent hemithyroidectomy (n = 147) were matched for age, sex, tumour size, multiplicity, extrathyroidal extension status and lymph node metastasis status with controls who underwent thyroidectomy (n = 298). During a mean follow-up of 7 years the proportion of patients with recurrence was 6.1% with hemithyroidectomy and 5.7% with thyroidectomy. No between-group differences in recurrence-free survival were observed with regard to variant, multifocality, lymph node metastasis or RAI therapy, however subgroup analysis found that patients with contralateral nodules on preoperative imaging had a significantly greater risk of recurrence with hemithyroidectomy.

Comment: The 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer, Recommendation 35, states that: For patients with thyroid cancer >1 cm and <4 cm without extrathyroidal extension, and without clinical evidence of any lymph node metastases (cNO), the initial surgical procedure can be either a bilateral procedure (near- total or total thyroidectomy) or a unilateral procedure (lobectomy). Thyroid lobectomy alone may be sufficient initial treatment for low-risk papillary and follicular carcinomas; however, the treatment team may choose total thyroidectomy to enable RAI therapy or to enhance follow-up based upon disease features and/or patient preferences. (Strong recommendation, Moderate-quality evidence). This study presents follow-up data for a retrospective analysis of patients with papillary thyroid carcinomas of 1-4 cm diameter in whom either total or hemithyroidectomy was performed. As this was not a randomised study, propensity score matching was performed but this may not correct for unrecognised factors causing bias. In general hemithyroidectomy was performed if no lymph node metastases were suspected, and total thyroidectomy if there was a nodule in the contralateral thyroid lobe. The overall recurrence rate was not significantly different over 7 years but if there was a contralateral lobe nodule the recurrence rate after hemithyroidectomy was higher (OR 6.39). The complication rate of total thyroidectomy was high, with 7.7% permanent hypoparathyroidism and 4.4% vocal cord palsy versus nil for hemithyroidectomy. Certainly if the complication rate of total versus hemithyroidectomy differs so much then strong consideration to hemithyroidectomy should be given, but these rates seem much higher than in expert Australian centres where the benefit of enhanced follow-up of total thyroidectomy generally continues to hold sway. These data, however, certainly suggest that routine conversion to total thyroidectomy if a patient is referred to a tertiary centre is generally not necessary.

Reference: *Clin Endocrinol (Oxf)*. 2017 Mar 24. [Epub ahead of print] [Abstract](#)

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Prospective evaluation of a week one overnight metyrapone test with subsequent dynamic assessments of hypothalamic-pituitary-adrenal axis function after pituitary surgery

Authors: English K et al.

Summary: This prospective, single centre study aimed to determine the utility of the overnight metyrapone test (OMT) for assessment of hypothalamic-pituitary-adrenal (HPA) axis function within 1 week of pituitary surgery. Forty patients undergoing pituitary surgery had morning cortisol measured on postoperative days 3 and 4, OMT on days 5 to 7 and week 6, short Synacthen test at week 6 and insulin tolerance test (ITT) at week 7. The concordance of week 1 OMT with week 7 ITT and 6-month glucocorticoid requirement was 78% and 81% respectively, and was similar to that observed with postoperative morning cortisol. Amongst participants with an abnormal OMT at day 6, 37% had normalised by week 6.

Comment: The OMT to assess the HPA axis is a convenient, well-tolerated test. Metyrapone inhibits 11-beta-hydroxylase, which catalyses the conversion of 11-desoxycortisol to cortisol. Metyrapone has no intrinsic glucocorticoid action and does not inhibit ACTH release. Thus the fall in cortisol should normally generate a rise in ACTH and stimulate a rise in 11-desoxycortisol. The 11-desoxycortisol response in the OMT correlates with the insulin hypoglycaemia test response and may even be more sensitive for the detection of impaired adrenal response ([Gibney J et al. J Clin Endocrinol Metab. 2008;93:3763-8](#)). The OMT needs to be validated in follow-up after pituitary surgery and this study provides important information in this circumstance. One potential source of confounding is the cross-reaction of 11-desoxycortisol with cortisol in standard radioimmunoassays, but this study avoids this by use of liquid chromatography tandem mass spectroscopy (LC MS/MS) assays for both cortisol and 11-desoxycortisol. Although the overnight metyrapone test within the first week after pituitary surgery was no better than an early morning cortisol level at predicting glucocorticoid requirement at 6 months, OMT at week 6 and insulin hypoglycaemia testing (IHT) at week 7 showed a similar concordance when compared to glucocorticoid requirement at 6 months (80-85%). OMT at week 6 compared to ITT at week 7 had a concordance of 66% (21/32), with most (10/11) of the discordant results arising from participants with a normal OMT but abnormal ITT. The authors carefully discuss the issue of which test may be most clinically accurate. This study reinforces the long-held view that it is necessary to wait 6 weeks after pituitary surgery to assess function and provides evidence that the OMT is a safe and simple alternative to IHT, provided LC MS/MS assays are used.

Reference: *Clin Endocrinol (Oxf)*. 2017 Mar 22. [Epub ahead of print] [Abstract](#)

Impaired quality of life in patients with treated acromegaly despite long-term biochemically stable disease: results from a 5-years prospective study

Authors: Kyriakakis N et al.

Summary: These researchers aimed to determine the factors influencing QoL in patients with acromegaly. Subjects were treated patients with biochemically controlled acromegaly (n = 58), healthy, matched controls (n = 116), and a longitudinal cohort of 28 treated-patients who completed the follow-up (5.7 ± 0.6 years). QoL was assessed at 11.6 ± 8.2 years post-diagnosis and treatment using the PGWBS (Psychological General Well-Being Schedule), SF-36 (36-item Short-Form), EQ-5D (EuroQoL) and the disease-specific AcroQoL questionnaire. In comparison to controls, patients with acromegaly rated lower for QoL on all scales and sub-scales except for the anxiety subscale of the PGWBS. In the adjusted analysis there was no significant change in QoL from baseline in patients with acromegaly.

Comment: Cross-sectional studies have reported reduced QoL in patients with acromegaly. Treatment of active acromegaly improves QoL. In the only other long-term prospective study of patients with controlled acromegaly, no change was found in QoL scores in most of the questionnaires subscales during 4 years follow-up, and a significant deterioration in the QoL scores in five QoL subscales, including physical and social functioning, physical fatigue, psychological well-being and personal relationships ([van der Klaauw AA et al. Clin Endocrinol. 2008;69:123-128](#)). This study indicates that the focus of clinical care should be not only on aggressive biochemical disease control, but also on trying to improve the physical and psychosocial comorbidities associated with acromegaly.

Reference: *Clin Endocrinol (Oxf)*. 2017;86(6):806-815 [Abstract](#)



Temozolomide treatment can improve overall survival in aggressive pituitary tumors and pituitary carcinomas

Authors: Lasolle H et al.

Summary: This retrospective, multicentre study included 43 patients with pituitary tumours treated with temozolomide (TMZ) between 2006 and 2016. Most patients received a standard regimen with a median treatment duration of 6.5 cycles (range 2-24); six patients received TMZ combined with radiotherapy. Post-treatment follow-up was a median of 16 months (0-72). The response rate (decrease in maximal tumour diameter > 30% and/or decrease in hormonal rate by > 50%) at the end of treatment was 51.2% (22/43). Responders had significantly prolonged overall survival ($P = 0.002$). Relapse occurred in 10 patients at median 5 months (range 0-57) post-treatment; TMZ was reintroduced unsuccessfully in 5 patients.

Comment: TMZ is an alkylating agent used in the treatment of gliomas and, more recently, aggressive pituitary adenomas and carcinomas including Cushing's disease and Nelson's syndrome. TMZ methylates DNA and, thereby, has antitumor effects. O^6 -methylguanine-DNA methyltransferase (MGMT), a DNA repair enzyme, removes the alkylating adducts that are induced by TMZ, thereby counteracting its effects so that a high-level of MGMT immunoexpression correlates with an unfavourable response. Ortiz LD et al. *Clinics (Sao Paulo)*. 2012;67(Suppl 1):119-123 summarised previous publications: 46 cases of adenohypophysial tumors were treated with TMZ, including 30 adenomas and 16 carcinomas, and eighteen of the 30 (60%) adenomas and 11 of the 16 (69%) carcinomas responded favourably to treatment. Ji Y et al. (*J Clin Oncol*. 2015;33 (Suppl): abstract e13014) reported an overall response rate (complete plus partial response) to TMZ of 67.8% in aggressive pituitary adenomas and a 60% response in pituitary carcinoma. McCormack has reported an overall 67% response rate to TMZ in aggressive pituitary adenomas and that low or negative MGMT expression predicts a high chance of response (83%) (*US Endocrinol*:2012;8(2):112-117). This study is of the retrospective experience of members of the French Society of Endocrinology and reports a similar response rate, and a better survival amongst responders. TMZ should be considered in aggressive pituitary adenoma and pituitary carcinoma where surgery and radiotherapy have failed to achieve control.

Reference: *Eur J Endocrinol*. 2017;176(6):769-777

[Abstract](#)

Primary aldosteronism as a risk factor for vertebral fracture

Authors: Notsu M et al.

Summary: The aim of this cohort study was to determine whether primary aldosteronism (PA) is a risk factor for vertebral fracture. Patients with PA ($n = 56$) were age- and sex-matched with healthy controls ($n = 56$), and underwent evaluation of serum and urinary biological parameters, bone mineral density and presence of vertebral fracture. Significant between-group differences were observed in systolic and diastolic blood pressure, haemoglobin A1c, triglycerides and calcium:creatinine ratios; all increased in PA ($P < 0.05$ for each). HDL cholesterol was lower in PA subjects vs controls ($P < 0.05$). Vertebral fractures were more common in PA patients vs controls (44.6% vs 23.2%; $P < 0.05$), as were severe fractures. PA was significantly associated with vertebral fracture (OR 3.13; 95% CI 1.30, 7.51; $P < 0.05$) under multivariate logistic regression analysis adjusted for age, sex and body mass index. The association remained significant under further adjustment to include systolic and diastolic blood pressure, haemoglobin A1c, triglycerides and HDL cholesterol. Significance was lost with the inclusion of calcium:creatinine ratio and bone mineral density.

Comment: In recent years, studies have suggested that osteoporotic fractures are associated with hypertension and cardiovascular disease and a population-based case-control study identified hypertension as a risk factor for hip fracture. Chronic stimulation of the renin-angiotensin-aldosterone system is associated with hypertension and cardiovascular disease and is reported to negatively affect bone metabolism due to the effect of angiotensin II. Aldosterone excess induces urinary excretion of calcium, leading to bone mineral density loss and increased levels of parathyroid hormone, and there is evidence that patients with PA are at higher risk of osteopenia and osteoporosis than patients with essential hypertension. Patients with PA have been reported to have a higher prevalence of vitamin D deficiency but the role of vitamin D deficiency in this study was not defined. A surprising difference in vertebral fracture prevalence was found in this small study. Confirmation in larger studies is needed.

Reference: *J Clin Endocrinol Metab*. 2017;102(4):1237-1243

[Abstract](#)

Thiazide treatment in primary hyperparathyroidism—a new indication for an old medication?

Authors: Tsvetov G et al.

Summary: This retrospective analysis of patient records sought to investigate the safety and efficacy of thiazide therapy in patients with primary hyperparathyroidism (PHPT). Participants with PHPT who were treated with thiazides ($n = 48$ female, $n = 14$ male) were recruited from an endocrine clinic at a tertiary hospital. Hydrochlorothiazide therapy was associated with a decrease in mean urinary calcium from 427 ± 174 mg/d to 251 ± 114 mg/d ($P < 0.001$), and a decrease in parathyroid hormone from 115 ± 57 ng/L to 74 ± 36 ng/L ($P < 0.001$). Serum calcium was unaffected ($P = 0.04$). No effect of dose on these findings was observed.

Comment: We are all aware that thiazide treatment can be associated with hypercalcaemia and reduced urinary calcium excretion. Although the hypercalcaemia may improve or remit on cessation of the thiazide, persisting PHPT is common. Thiazides are the treatment of choice for idiopathic hypercalcaemia. There are reports of severe hypercalcaemia in thiazide-treated patients with PHPT but also reports that thiazide diuretics may be safe in patients with PHPT (*Riss P et al. Clin Endocrinol* 2016;85:196-201). In this retrospective study, hydrochlorothiazide, 12.5 to 50 mg/d, in patients with PHPT and hypercalcaemia who were ineligible for surgery or for whom surgery was not successful, successfully decreased urinary calcium excretion without inducing a substantial change in serum calcium level. One-third had past nephrolithiasis but no symptomatic disease in follow-up over a mean of 3.1 years. So rather than thiazide being universally contraindicated in PHPT, this drug class may be helpful in patients with inoperable disease and sufficient hypercalcaemia to be at risk of nephrolithiasis.

Reference: *J Clin Endocrinol Metab* 2017;102(4):1270-1276

[Abstract](#)

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