REVIEW ARTICLE

Hormone Replacement After Thyroid and Parathyroid Surgery

by Andreas Schäffler

SUMMARY

Background: Hypothyroidism and hypocalcemia are common after thyroid and parathyroid surgery. In this article, the authors provide clinically-oriented recommendations to help surgeons, general practitioners, internists, and endocrinologists give their affected patients adequate hormone replacement therapy.

Methods: Selective evaluation of original articles and reviews that were retrieved by a PubMed search over the years 1980 to 2010, as well as of the recommendations of medical societies including the Endocrine Society (USA), the German Society for Endocrinology (Deutsche Gesellschaft für Endokrinologie), and the American and European Thyroid Associations.

Results: Important issues in L-thyroxine replacement therapy include: the selection of the hormone preparation (T4 or T4/T3), combination with iodine (yes/no), the definition of therapeutic TSH ranges (particularly after surgery for thyroid cancer), the extent of remaining thyroid tissue after goiter surgery and its significance, underlying diseases, and drug interactions. The major issues in the treatment of postoperative hypoparathyroidism are: the selection of suitable calcium and vitamin D preparations, the definition of therapeutic goals, the treatment of hypercalciuria and hyperphosphatemia, and the option of recombinant parathormone therapy.

Conclusion: Effective treatment requires an appropriate choice of medication and an understanding of its pharmacokinetics as well as of the possible effects of the patient's underlying disease, comorbidities, and other medications on its absorption and metabolism.

▶ Cite this as:
Schäffler A: Hormone replacement after thyroid and parathyroid surgery. Dtsch Arztebl Int 2010; 107(47): 827–34. DOI: 10.3238/arztebl.2010.0827

Klinik und Poliklinik für Innere Medizin I, Universität Regensburg:
Prof. Dr. med. Schäffler

Hormone replacement after thyroid and parathyroid surgery is a common clinical challenge. The initiation of hormone replacement therapy is not always a simple matter (e1), as it often overlaps with the transition from inpatient to outpatient care (i.e., from surgery and the immediate postoperative period to the period of ambulatory follow-up), and hormone replacement is either begun or continued by physicians from multiple specialties (surgery, internal medicine, family medicine). Permanent hypothyroidism arises not only after total or subtotal thyroidectomy, but also in 11% to 28% of patients that have undergone hemithyroidectomy (e2–e4). Risk factors for permanent hypothyroidism include seropositivity for TPO (thyroid peroxidase) antibodies, high normal preoperative TSH (thyroid stimulating hormone) levels, and histologically confirmed thyroiditis, but not age, sex, family history, or weight of the resected tissue (e1, e4). Patients who were in euthyroid status before they underwent elective surgery may need a change of their hormone dose afterward depending on the extent of the procedure, even if they are receiving replacement therapy that is closely adapted to body weight: this is true in 17% to 42% of cases (for hemithyroidectomy and subtotal thyroidectomy, respectively) (1, e1).

Objectives

The goal of this review article is to give practical recommendations for hormone replacement therapy that will be of use to physicians from all of the involved specialties, including surgery, general practice, internal medicine, and endocrinology.

Methods

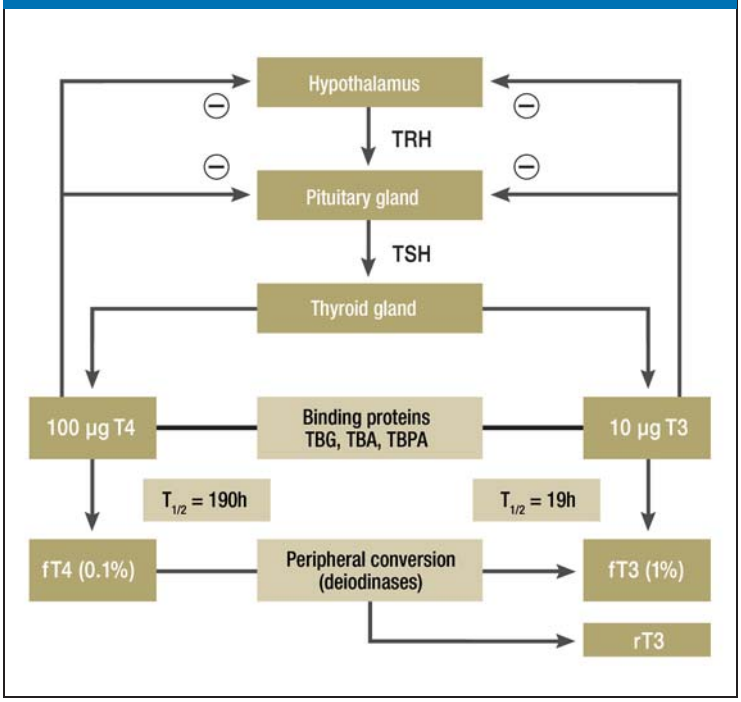
The recommendations given here are based on an assessment of selected scientific publications and review articles retrieved from the PubMed database, and of the recommendations of the following medical societies: the Endocrine Society (United States), the German Society for Endocrinology (*Deutsche Gesellschaft für Endokrinologie,* DGE), the American Thyroid Association (ATA), and the European Thyroid Association (ETA).

Principles of hormone replacement in primary hypothyroidism

Physiology and clinical biochemistry

For a physiological understanding of the recommendations on hormone replacement therapy (2), one must

FIGURE



The hierarchical functional organization of the thyrotropic axis. The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary lobe to secrete thyrotropin, also known as thyroid-stimulating hormone (TSH). TSH, in turn, regulates the synthesis and release of the thyroid hormones T4 (ca. 100 µg/day) and T3 (ca. 10 µg/day). This regulation occurs by way of negative feedback of the T4 and T3 concentrations on the secretion of TRH and TSH. Nearly all of the T4 and T3 in the bloodstream is bound to the binding proteins thyroxine-binding globulin (TBG), thyroxine-binding albumin (TBA), and thyroxine-binding prealbumin (TBPA). The free hormones fT4 and fT3 account for only 0.1% and 1% of circulating T4 and T3, respectively. Deiodinase enzymes in the peripheral tissues catalyze the conversion of fT4 to the biologically more active hormone fT3, while a small amount of inactive reverse T3 (rT3) is also produced. An important consideration for the design of an effective treatment regimen is the half-life of the two main thyroid hormones: ca. 190 hours for T4 and ca. 19 hours for T3

bear in mind the hierarchical functional arrangement of the thyrotropic axis, as shown in the *Figure*. The indispensable basis of effective thyroid hormone replacement therapy is the clinical biochemical measurement of TSH and, in some cases, of fT4 and fT3. *Table 1* provides an aid to the interpretation of various constellations of hormone levels. TSH levels should be measured exclusively with modern third- and fourth-generation assays (e5) whose analytic sensitivity is under 0.01 mIU/L; such assays are universally available in Germany today. For TSH and the free thyroid hormones, attention should be paid to the relevant normal ranges and units (3).

The pharmacokinetics of thyroid hormones

A proper understanding of the pharmacokinetics of thyroid hormones (4) is essential for treatment planning. When T4 is taken orally, up to 80% of it is absorbed, and the peak serum concentration is reached two to four hours after ingestion. The serum concentration then rises by 20% to 40%. The half-life of T4 is relatively long, at 190 hours. A fatty meal lowers its absorption by 40% (e6), and even drinking coffee lowers its absorption by 27% to 36% (e7). Consequently, thyroid hormone must be taken in the fasting state, with water, 30 to 60 minutes before breakfast (e6). The absorption of T3 is 90%, and peak levels are reached one to two hours after ingestion. The serum concentration may rise by 250% to 600%. T3 has a relatively short half-life of only 19 hours.

The required amount of L-thyroxine

In estimating the required quantity of L-thyroxine replacement (2, 4) in postoperative hypothyroidism, one should know the patient's physiological requirement for L-thyroxine. This depends on a number of factors (2), mainly the patient's age, weight, pregnancy status, medications, and diseases that either increase the requirement for L-thyroxine or affect its absorption (e8). *Table 2* contains an overview of the physiological requirement for L-thyroxine per kilogram of body weight. In general, the T4 requirement is more closely correlated with the patient's lean body mass than with his or her total body weight (e9). The T4 requirement varies considerably from one person to another. The diseases and medications that are associated with an elevated L-thyroxine requirement are listed in *Table 4*.

L-thyroxine replacement

In view of the physiological, pharmacokinetic, and clinical biochemical considerations outlined above, ten tips can be given for clinical practice (2, 5–8):

- With regard to the frequency of TSH measurements after a change in the hormone dose or in the clinical circumstances, rechecking at four- to six-week intervals is recommended. For benign diseases of the thyroid gland, the target range for TSH is 1 to 2 mU/L (2, 8).
- Blood drawing for fT4 should be done early in the morning before the daily dose of L-thyroxine.
- Measuring fT3 is usually unnecessary for the monitoring of replacement therapy but can be useful for the detection of T3 hyperthyroidism in special situations, e.g., thyroid carcinoma.
- L-thyroxine should be taken by mouth early in the morning, in the fasting state, 30 to 60 minutes before breakfast, with water. The standard dose is 15 µg/kg body weight (BW). If the patient forgets to take one daily dose, this can safely be neglected and should not be "made up for" by additional intake the next day (2, 8).
- Giving T3 for replacement is unphysiological and less well tolerated and is thus not recommended as a routine measure. The monodeiodization of T4 normally occurs as needed in the peripheral tissues, so that there is no need to take T3 (liothyronine) as well. In a total of 10

randomized double-blind clinical trials, including six crossover trials and four parallel-group trials (9, e10–e17), treatment with a combination of T3 and T4 was found to provide a convincing benefit with respect to well-being, cognitive functioning, or quality of life for some individual patients, but not in the overall group of patients studied, and this remained the case after multiple meta-analyses (e18, 10). There will be some patients who report having a better mental and cognitive state when receiving combination therapy and therefore want it. To this end, preparations are available that contain T3 and T4 in a fixed ratio of 10 or 20 µg of T3 to 100 µg of T4. If the clinical manifestations of hypothyroidism persist under L-thyroxine replacement therapy despite normalized TSH levels, this may be due to genetic variation (e19–e21) in the peripheral 5´-deiodinases (e22–e24), which are selenoprotein enzymes that catalyze the conversion of T4 to active T3 as needed (11, e25). Patients with low peripheral 5´-deiodinase activity may be unable to metabolize T4 to T3 in adequate amounts and may therefore respond better to combined replacement therapy than to T4 alone. There is, however, no routinely available clinical biochemical or genetic test to determine whether this is the case.

- There is a widespread misconception that the various thyroid preparations on the market are identical in bioavailability. This is not so (e26), and therefore the preparation currently being taken should not be switched if the patient is tolerating it well. The area under the curve (AUC) of different preparations' absorption profiles can differ so greatly (e27) that their relative bioavailability varies from 0.8 to 1.25, and this is a clinically relevant variation (e28).
- After thyroid hormone replacement is initiated at a low dose, the dose should be raised in individualized fashion. For patients who are elderly, suffer from heart disease, or have longstanding hypothyroidism, the dose should be raised slowly, e.g., in weekly increments of 25 µg, after an initial dose of 25 µg. On the other hand, patients in good general health who undergo thyroid surgery can have the dose rapidly raised to the target postoperative dose (within a maximum of five days after surgery) (1). The need for postoperative thyroid hormone replacement is a function of the residual volume of thyroid tissue (2). Hormone replacement is always necessary when less than 6 mL of thyroid tissue is left. A practical approach would be to start postoperatively at a dose of 1 µg/kgBW and then measure the TSH level again in four to six weeks.
- Patients who are dysphagic or are receiving a special enteral diet can be given L-thyroxine as a liquid preparation (e.g., L-thyroxine drops [Henning], where 1 drop contains 5 µg of the hormone).
- Note: In this review, we do not discuss the treatment of secondary or tertiary hypothyroidism caused by diseases affecting the hypothalamic-pituitary axis (12). Nevertheless, we take this opportunity to point out that TSH cannot be used as a guide to therapy in such cases, as the TSH concentration may be in the normal range, or low, despite peripheral hypothyroidism. Thus, treatment monitoring must be performed by measurement of fT4.
- A potential pitfall: patients with other serious illnesses in addition to primary hypothyroidism can develop NTIS ("non-thyroidal illness syndrome") and therefore have low values of both fT3 and TSH. In such cases, too, hormone replacement therapy must be monitored by fT4 measurement.

TABLE 1

Interpreting typical constellations of peripheral thyroid hormones and TSH

fT3	fT4	TSH	Interpretation
Normal	Normal	Normal	Euthyroidism
High	High	Low	Overt hyperthyroidism
Low	Low	High	Overt hypothyroidism
Normal	Normal	High	Latent hypothyroidism
Normal	Normal	Low	Latent hyperthyroidism
Low	Low	Normal/ Low	hypothalamic/pituitary hypothyroidism or non-thyroidal illness syndrome (NTIS)
High	High	High	Thyrotropin-secreting tumor or resistance to thyroid hormone

TABLE 2

The physiological L-thyroxine requirement: rules of thumb for replacement in primary hypothyroidism

Age	T4 requirement
Neonates	10–15 µg/kg BW
Children. 8-12 months	8–10 µg/kg BW
Children. 2-10 years	4–6 µg/kg BW
Adolescents	2–3 µg/kg BW
Adults	1.5 µg/kg BW
Elderly persons	1–1.2 µg/kg BW
Pregnant women	1.8–2 µg/kg BW

TABLE 3

Diseases, conditions, and medications associated with an elevated L-thyroxine requirement

Diseases/conditions	Mechanism of elevated L-thyroxine requirement
Malabsorption	Diminished absorption
Short bowel syndrome	Diminished absorption
Sprue	Diminished absorption
Chronic atrophic gastritis*1	Elevated gastric pH, diminished solubility
Helicobacter pylori infection*1	Increased formation of NH_3
Pregnancy	Elevated TBG,*2 gestational deiodization, elevated renal iodine clearance
Medications	**Mechanism of elevated L-thyroxine requirement**
Phenytoin	Displacement of T4 from TBG binding, elevated hepatic T4 clearance
Carbamazepine	Displacement of T4 from TBG binding, elevated hepatic T4 clearance
Rifampicin	Displacement of T4 from TBG binding, elevated hepatic T4 clearance
Dexamethasone	Inhibition of 5'-deiodinases
Propranolol	Inhibition of 5'-deiodinases
Cytokines	Inhibition of 5'-deiodinases
Amiodarone	Inhibition of conversion
Proton-pump inhibitors	Diminished absorption, T4 soluble only in acid solution
H_2-blockers	Diminished absorption, T4 soluble only in acid solution
Antacids	Diminished absorption, T4 soluble only in acid solution
Cholestyramine	Direct inhibition of intestinal absorption
Ferrous sulfate	Direct inhibition of intestinal absorption
Estrogens	Elevated TBG

*1 The T4 requirement may be elevated by as much as 30%;
*2 TBG, thyroid-binding globulin

Substitution of T4, T3, or iodide

In the following paragraphs, we will consider the various standard postoperative situations one by one and describe the mode of replacement therapy that is recommended for each in the relevant guidelines (2, 7, 13–17).

After surgery for a diffuse or nodular goiter

- Hypothyroidism immediately after surgery, or residual volume less than 6 mL: L-thyroxine (1 µg/kgBW) combined with iodide (100 to 150 µg/day in otherwise healthy adults, or 200 µg in pregnant women). Follow-up measurement of TSH every four weeks (target value for TSH: 1–2 mU/L).
- Euthyroid state after surgery and residual volume greater than 6 mL: iodide (100 to 150 µg/day in otherwise healthy adults, or 200 µg in pregnant women). Follow-up measurement of TSH every four to six weeks (target value for TSH: 1–2 mU/L).

Note: The 6 mL threshold for the amount of residual tissue is a clinical rule of thumb. Other important considerations include functionality (pattern on ultrasound examination), age, and body weight.

After surgery for an autoimmune disease of the thyroid gland (Graves' disease, Hashimoto's thyroiditis)

L-thyroxine replacement without iodide. Follow-up measurement of TSH every four to six weeks (target value for TSH: 1–2 mU/L).

After total thyroidectomy for benign disease, medullary thyroid carcinoma, or anaplastic thyroid carcinoma

L-thyroxine replacement without iodide. Follow-up measurement of TSH every four to six weeks (target value for TSH: 1–2 mU/L).

After total thyroidectomy for papillary or follicular thyroid carcinoma (2, 13–16)

- If ablative radio-iodine treatment is planned shortly after surgery, no hormone replacement (endogenous TSH stimulaton is desired).
- If ablative radio-iodine treatment is planned at a later time after surgery, T3 replacement (e.g., with Thybon™, 20 µg t.i.d.) until radio-iodine treatment is

performed (the shorter half-life of T3 shortens the phase of endogenous TSH stimulation).

The TSH target range after surgery for well-differentiated thyroid carcinoma

The appropriate target range for TSH (13) depends on the patient's risk class, the time elapsed from the onset of the disease to its diagnosis, and the presence or absence of persistent disease. A summary of appropriate TSH target ranges, modified in accordance with the ATA and ETA guidelines, is given in *Box 1* (2, 13–16).

BOX 1

Target ranges for the serum TSH concentration

- **ATA/ETA guidelines for well-differentiated thyroid carcinoma**
  - Persistent disease:
    TSH suppression to <0.1 mU/L
  - Curative but high-risk situation:
    TSH suppression to 0.1–0.5 mU/L for 5 years (3–5 years according to one set of guidelines, 5–10 years according to the other)
  - Curative and low-risk situation:
    Hormone replacement therapy with TSH in low normal range, 0.3–1 mU/L
  - Curative and very-low-risk situation:
    No TSH suppression. Hormone replacement therapy with TSH in normal range, 1–2 mU/L
  - Occult papillary microcarcinoma (pT1a, pNO, pMO):
    No TSH suppression. Hormone replacement therapy with TSH in normal range, 1–2 mU/L

Very low risk:	unifocal, T1 (<1 cm), NO, MO, tumor does not extend beyond capsule
Low risk:	T1 (>1 cm), NO, MO, or T2, NO, MO, or multifocal T1, NO, MO
High risk:	any T3,any T4, any T with N1, or any M1

The question of L-thyroxine allergy or intolerance

Allergy to the naturally occurring human hormone L-thyroxine does not exist. Antibodies against T4 have been described in rare cases of autoimmune disease (e29), but these antibodies are not sought as a routine diagnostic measure. They do not cause any clinical manifestations but might potentially interfere with diagnostic testing or with regulatory circuits, or necessitate a higher dose of hormone replacement. Various components of the L-thyroxine preparations aside from the hormone itself can, however, give rise to allergy or intolerance; when this occurs, switching to another preparation may help. The switch can be performed systematically, guided by a knowledge of the substances other than L-thyroxine that are present in the different preparations, as these vary widely from one preparation to another. Helpful information of this type is provided in *Box 2,* which is based on the information for physicians provided with each preparation (*Rote Liste* ["Red List," a German guide to medications], 2009). Rarely, further diagnostic testing will be needed, with the aid of specialists in allergology and dermatology. In general, when medication intolerance is suspected, the first step is to separate L-thyroxine from iodide supplementation by withholding the latter temporarily for diagnostic purposes, as iodide, which is present in many combined preparations, is much more likely to be poorly tolerated than L-thyroxine. Another diagnostic possibility is lactose intolerance, a history of which should be sought from the patient. This can cause meteorism, flatulence, and abdominal cramps.

Postoperative hypoparathyroidism

Frequency and risk factors

This review is limited to postoperative hypoparathyroidism (18, 19) after surgery on the neck (including neck dissection), thyroid glands, and parathyroid glands. Postoperative hypoparathyroidism is defined as a level of parathormone secretion that is inadequate to sustain normocalcemia six months after surgery. It is found after 0.5% to 6.6% of total thyroidectomies, although centers with extensive experience in endocrine surgery report somewhat lower rates of 0.9% to 1.6% (e30–e33). Transient hypoparathyroidism is much more common after surgery for thyroid carcinoma (e34); its frequency depends on the timing of lymph node dissection in the central compartment (initial dissection versus dissection at reoperation: 23.6% vs. 41.8%). Other factors affecting the rate of postoperative hypoparathyroidism (e33) include the surgeon's experience, the extent of surgery, lymph node dissection, surgery for tumor, retrosternal goiter, Graves' disease, reoperation, parathyroidectomy for primary hyperparathyroidism (hungry bone syndrome), pre-existing vitamin D deficiency, and failure to identify all four parathyroid glands at surgery.

Diagnostic evaluation

If some time has elapsed since surgery, the following laboratory values should be determined: serum calcium and albumin (correction of the calcium level with Payne's formula in case of hypoalbuminuria), ionized calcium, magnesium, creatinine, phosphate, parathormone, and 25-OH-cholecalciferol. On the other hand, if symptomatic hypocalcemia arises shortly after surgery, the differential diagnosis is usually a simple matter.

Payne's formula for correcting the serum calcium concentration (e35): corrected concentration (mmol/L) = measured concentration (mmol/L) – (0.025 × albumin [g/L]) + 1.

Treatment

The goals of treatment (18–20) are elimination of the symptoms and signs of hypoparathyroidism (paresthesiae, muscle cramps, convulsions, stridor, cognitive impairment, abnormal QT interval on ECG), a serum calcium level in the low normal range (2.0 to 2.1 mmol/L), a calcium × phosphate product below

BOX 2

Auxiliary table for switching L-thyroxine preparations (among those available in Germany)

- **Berlthyrox**
  - Calcium hydrogen phosphate
  - Cellulose
  - Carboxymethyl starch
  - Dextrin
  - Long-chain partial glycerides
- **Euthyrox**
  - Corn starch
  - Croscarmellose
  - Gelatin
  - Lactose
  - Magnesium stearate
- **L-Thyroxin Henning**
  - Corn starch
  - Cellulose
  - Silicon dioxide
  - Ricinus oil
  - Sodium carbonate
  - Sodium thiosulfate
- **L-Thyroxin beta and Hexal**
  - Cellulose
  - Magnesium oxide
  - Carboxymethyl starch
  - Magnesium stearate
  - Mannitol
- **Thevier, L-Thyroxin AL, CT, ratiopharm**
  - Cellulose
  - Magnesium stearate
  - Silicon dioxide
  - Talcum
  - Corn starch
- **L-Thyroxin drops (Henning)**
  - Propylene glycol
  - Glycerol
  - Sodium thiosulfate

TABLE 4

Properties of vitamin D derivatives that are suitable for the treatment of hypoparathyroidism

Vitamin D derivative	Example	Dosage	On/off kinetics	Remarks
1α-hydroxy-cholecalciferol	EinsAlpha™	0.5–3 µg	1–2d/ 5–7d	Rapid conversion to 1,25-dihydroxy-cholecalciferol
1,25-dihydroxy-cholecalciferol	Rocaltrol™	0.25–1 µg	1–2d/ 2–3d	Most active metabolite, treatment of choice, best kinetics
Dihydrotachysterol	A.T.10™ Perlen	0.5–1.5 mg	4–7d/ 7–21d	Synthetic vitamin D analogue, activated in the liver, no renal activation needed

5 $mmol^2/L^2$ to prevent calcium phosphate precipitation in the eye/lens, kidneys, and basal ganglia, and reduction of hypercalciuria to less than 300 mg of calcium in a 24-hour urine sample to prevent nephrotoxicity and kidney stones. Once the desired levels have been reached, the serum calcium, phosphate, and creatinine concentrations and the urinary calcium concentration should be rechecked every six months, and an annual ophthalmological examination is recommended for the early detection of cataracts (18). The principles of treatment (18, 19) include oral calcium supplementation (or, in an emergency, intravenous administration of calcium) as well as the oral administration of vitamin D derivatives. Other medications that can be given for special indications include phosphate binders (for refractory hyperphosphatemia) and thiazide diuretics (for refractory hypercalciuria).

Calcium supplementation

The main agents used for oral calcium supplementation (18) are two calcium salts: calcium carbonate and calcium citrate (20–22). The dose is 500 to 1500 mg of elemental calcium daily. Calcium carbonate is most effectively absorbed when the gastric juice has an acidic pH; calcium citrate is thus preferable in the setting of achlorhydria or acid-suppressing therapy. For emergency intravenous treatment (18), a 10% solution of calcium gluconate is available (10 mL of the 10%

solution contains 2.25 mmol of calcium, or 90 mg of calcium ions). In patients with hypoparathyroidism, intravenously administered calcium is effective for only two to three hours (continuous infusion: 1 to 3 mg of calcium gluconate per kilogram of body weight per hour in 5% glucose solution, or else 10 ampoules of 10% calcium gluconate in 500 mL of 5% glucose given over 12 hours through a mechanized infusion pump).

Treatment with vitamin D preparations

Vitamin D preparations are the mainstay of treatment for postoperative hypoparathyroidism (18) and are usually a necessary accompaniment to calcium supplementation. The optimal dose varies markedly among individuals, and it is also important to choose correctly among the various vitamin D preparations that are available (23, e36).

Ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) are commercially available in the USA and Germany, respectively, yet they are not recommended for treatment because their long half-lives increase the risk of intoxication, and also because of their unfavorable on/off kinetics (10–14 days and 14–75 days, respectively) (18). Nor does treatment with these two preparations make any sense from the pathophysiological point of view, because native vitamin D_3 (cholecaliferol, which is given to treat osteoporosis) is activated by a double hydroxylation, first in the liver at position 25 and then again, in a parathormone-dependent process, in the kidney at position 1. It thus cannot be converted to an active form when hypoparathyroidism is the underlying problem.

Three preparations are appropriate for use and are available in Germany: 1α-hydroxy-cholecalciferol (alpha-calcidiol), 1,25-dihydroxy-cholecalciferol (calcitriol), and the synthetic vitamin D analogue dihydrotachysterol. The main features of these three preparations are summarized in *Table 4* (18, 20, 24, e36). Calcitriol (24) is the most commonly used preparation (18, 20); it is the most active vitamin D metabolite (23), has the best on/off kinetics (half-life 4 to 6 hours), is easy to dose, and needs no endogenous activation by hydroxylation (which is important in the setting of parathormone deficiency and impaired hepatic or renal function). Some patients may respond variably to different preparations. An important complication is overdose, i.e., vitamin D intoxication with consequent hypercalcemia. Some patients will need to have their serum calcium concentration checked every day in the early postoperative period.

Reduction of refractory hypercalciuria

If the patient has refractory hypercalciuria (as is mainly seen in pre-existing renal insufficiency or nephrolithiasis), hydrochlorothiazide can be given at a high dose (25 to 10 mg daily).

Reduction of refractory hyperphosphatemia

To treat this problem (18, e36), the patient is first put on a low-phosphate diet: nutritional consultation is obtained, and the patient is advised to restrict consumption of foods and drinks that contain large amounts of phosphate, including cola drinks, eggs, dairy products, meat, and canned foods. If this does not achieve the desired effect, phosphate binders can be given, e.g., aluminum hydroxide (up to 600 mg t.i.d.) or sevelamer (800 mg 1 to 5 times daily).

KEY MESSAGES

- The method of choice for hormone replacement in postoperative hypothyroidism is to give L-thyroxine in a dosage adjusted for the patient's body weight. Evidence from controlled trials does not support the routine use of combination therapy with both L-thyroxine and liothyronine (T3), although this may be useful in individual cases.
- When L-thyroxine replacement therapy is given after surgery for non-malignant thyroid disease, the target range for the serum TSH concentration is 1 to 2 mIU/L. After any change in the L-thyroxine dose or the clinical circumstances, rechecking the TSH level in 4 to 6 weeks is recommended.
- The nature of the underlying thyroid disease and the presence or absence of functional residual thyroid tissue determine whether iodide supplementation should be given in addition to L-thyroxine replacement therapy.
- When L-thyroxine replacement therapy is given postoperatively after the resection of a well-differentiated thyroid carcinoma, there are separately defined TSH target ranges for each risk level and tumor stage.
- In hormone replacement therapy for postoperative hypoparathyroidism, the choice of the vitamin D_3 derivative that is to be given is guided by pathophysiological considerations (mechanisms of hydroxylation at positions 1 and 25 of the native vitamin D_3 molecule) and by pharmacokinetics. The appropriate calcium salt to use is selected in the light of the patient's accompanying medications and gastric pH.

Future prospects

Hormone replacement with recombinant parathormone has not yet been approved for the treatment of hypoparathyroidism. Initial, small-scale randomized trials (25) have shown that the subcutaneous administration of parathormone (PTH [1–34]) once or twice daily is effective and an option for the treatment of refractory hypercalciuria.

Conflict of Interest Statement
The author states that he has no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

Manuscript submitted on 10 February 2010, revised version accepted on 7 April 2010.

Translated from the original German by Ethan Taub, M.D.

REFERENCES

1. Verhaert N, Vander Poorten V, Delaere P, Bex M, Debruyne F: Levothyroxine replacement therapy after thyroid surgery. B-Ent 2006; 2: 129–33.
2. Gärtner R, Reincke M: Substitution von Schilddrüsenhormonen. Der Internist 2008; 49: 538–44.
3. Schäffler A: Funktionsdiagnostik in Endokrinologie, Diabetologie und Stoffwechsel. Heidelberg: Springer-Verlag 2009; 36.
4. Wiersinga WM: Thyroid hormone replacement therapy. Horm Res 2001; 56(Suppl 1): 74–81.
5. Roberts CG, Ladenson PW: Hypothyroidism. Lancet 2004; 363: 793–803.
6. Devdhar M, Ousman YH, Burman KD: Hypothyroidism. Endocrinol Metab Clin North Am 2007; 36: 595–615.
7. Blackwell J: Evaluation and treatment of hyperthyroidism and hypothyroidism. J Am Acad Nurse Pract 2004; 16: 422–5.
8. Mann K, Dralle H, Gärtner R: Schilddrüse. In: Deutsche Gesellschaft für Endokrinologie (ed.). Rationale Therapie in der Endokrinologie. Stuttgart, New York: Thieme 1997; 70–7.
9. Escobar-Morreale HF, Botella-Carretero JI, Gomez-Bueno M, Galan JM, Barrios V, Sancho J: Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyroxine alone. Ann Intern Med 2005; 142: 412–24.
10. Escobar-Morreale HF, Botella-Carretero JI, Escobar del Rey F, Morreale de Escobar G: REVIEW: Treatment of hypothyroidism with combinations of levothyroxine plus liothyronine. J Clin Endocrinol Metab 2005; 90: 4946–54.
11. Panicker V, Saravanan P, Vaidya B, et al.: Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patients. J Clin Endocrinol Metab 2009; 94: 1623–9.
12. Carrozza V, Csako G, Yanovski JA, et al.: Levothyroxine replacement therapy in central hypothyroidism: a practice report. Pharmacotherapy 1999; 19: 349–55.
13. Biondi B, Filetti S, Schlumberger M: Thyroid-hormone therapy and thyroid cancer: a reassessment. Nat Clin Pract Endocrinol Metab 2005; 1: 32–40.
14. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W: European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006; 154: 787–803.
15. Cooper DS, Doherty GM, Haugen BR, et al.: Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006; 16: 109–42.
16. Dietlein M, Luster M, Reiners C: Differenziertes Schilddrüsenkarzinom: Risiko-adaptierte Behandlung und Nachsorge. Thieme-Refresher Onkologie 2008; R1–R24.
17. Schlumberger M, Berg G, Cohen O, et al.: Follow-up of low-risk patients with differentiated thyroid carcinoma: a European perspective. Eur J Endocrinol 2004; 150: 105–12.
18. Shoback D: Clinical practice. Hypoparathyroidism. N Engl J Med 2008; 359: 391–403.
19. Testini M, Gurrado A, Lissidini G, Nacchiero M: Hypoparathyroidism after total thyroidectomy. Minerva Chir 2007; 62: 409–15.
20. Rude RK: Hypocalcemia and hypoparathyroidism. Curr Ther Endocrinol Metab 1997; 6: 546–51.
21. Cooper MS, Gittoes NJ: Diagnosis and management of hypocalcaemia. BMJ 2008; 336: 1298–302.
22. Lebowitz MR, Moses AM: Hypocalcemia. Semin Nephrol 1992; 12: 146– 58.
23. Brown AJ: Therapeutic uses of vitamin D analogues. Am J Kidney Dis 2001; 38(Suppl 5): 3–19.
24. Okano K, Furukawa Y, Morii H, Fujita T: Comparative efficacy of various vitamin D metabolites in the treatment of various types of hypoparathyroidism. J Clin Endocrinol Metab 1982; 55: 238–43.
25. Winer KK, Ko CW, Reynolds JC, et al.: Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1–34) versus calcitriol and calcium. J Clin Endocrinol Metab 2003; 88: 4214–20.

Corresponding author
Prof. Dr. med. Andreas Schäffler
Klinik und Poliklinik für Innere Medizin I
Universität Regensburg
93042 Regensburg, Germany
andreas.schaeffler@klinik.uni-regensburg.de

For eReferences please refer to:
www.aerzteblatt-international.de/ref4710

REVIEW ARTICLE

Hormone Replacement After Thyroid and Parathyroid Surgery

by Andreas Schäffler

eReferences

e1. Seiberling KA, Dutra JC, Bajaramovic S: Hypothyroidism following hemithyroidectomy for benign nontoxic thyroid disease. Ear Nose Throat J 2007; 86: 295–9.

e2. Vaiman M, Nagibin A, Hagag P, Kessler A, Gavriel H: Hypothyroidism following partial thyroidectomy. Otolaryngol Head Neck Surg 2008; 138: 98–100.

e3. Wormald R, Sheahan P, Rowley S, Rizkalla H, Toner M, Timon C: Hemithyroidectomy for benign thyroid disease: who needs follow-up for hypothyroidism? Clin Otolaryngol 2008; 33: 587–91.

e4. Su SY, Grodski S, Serpell JW: Hypothyroidism following hemithyroidectomy: a retrospective review. Ann Surg 2009; 250: 991–4.

e5. Schäffler A: Funktionsdiagnostik in Endokrinologie, Diabetologie und Stoffwechsel. Heidelberg: Springer-Verlag 2009; 121.

e6. Liwanpo L, Hershman JM: Conditions and drugs interfering with thyroxine absorption. Best Pract Res Clin Endocrinol Metab 2009; 23: 781–92.

e7. Benvenga S, Bartolone L, Pappalardo MA, et al.: Altered intestinal absorption of L-thyroxine caused by coffee. Thyroid 2008; 18: 293–301.

e8. Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR: Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med 2004; 351: 241–9.

e9. Cunningham JJ, Barzel US: Lean body mass is a predictor of the daily requirement for thyroid hormone in older men and women. J Am Geriatr Soc 1984; 32: 204–7.

e10. Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ Jr.: Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. N Engl J Med 1999; 340: 424–9.

e11. Smith RN, Taylor SA, Massey JC: Controlled clinical trial of combined triiodothyronine and thyroxine in the treatment of hypothyroidism. Br Med J 1970; 4: 145–8.

e12. Walsh JP, Shiels L, Lim EM, et al.: Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism. J Clin Endocrinol Metab 2003; 88: 4543–50.

e13. Clyde PW, Harari AE, Getka EJ, Shakir KM: Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism: a randomized controlled trial. Jama 2003; 290: 2952–8.

e14. Sawka AM, Gerstein HC, Marriott MJ, MacQueen GM, Joffe RT: Does a combination regimen of thyroxine (T4) and 3,5,3'-triiodothyronine improve depressive symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial. J Clin Endocrinol Metab 2003; 88: 4551–5.

e15. Siegmund W, Spieker K, Weike AI, et al.: Replacement therapy with levothyroxine plus triiodothyronine (bioavailable molar ratio 14 : 1) is not superior to thyroxine alone to improve well-being and cognitive performance in hypothyroidism. Clin Endocrinol (Oxf) 2004; 60: 750–7.

e16. Hennemann G, Docter R, Visser TJ, Postema PT, Krenning EP: Thyroxine plus low-dose, slow-release triiodothyronine replacement in hypothyroidism: proof of principle. Thyroid 2004; 14: 271–5.

e17. Bunevicius R, Jakubonien N, Jurkevicius R, Cernicat J, Lasas L, Prange AJ Jr.: Thyroxine vs thyroxine plus triiodothyronine in treatment of hypothyroidism after thyroidectomy for Graves' disease. Endocrine 2002; 18: 129–33.

e18. Ma C, Xie J, Huang X, et al.: Thyroxine alone or thyroxine plus triiodothyronine replacement therapy for hypothyroidism. Nucl Med Commun 2009; 30: 586–93.

e19. Dayan CM, Panicker V: Novel insights into thyroid hormones from the study of common genetic variation. Nat Rev Endocrinol 2009; 5: 211–8.

e20. Peeters RP, van der Deure WM, Visser TJ: Genetic variation in thyroid hormone pathway genes; polymorphisms in the TSH receptor and the iodothyronine deiodinases. Eur J Endocrinol 2006; 155: 655–62.

e21. Refetoff S, Dumitrescu AM: Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. Best Pract Res Clin Endocrinol Metab 2007; 21:277–305.

e22. Inada M, Nishikawa M: Thyroid hormone metabolism. Nippon Naibunpi Gakkai Zasshi 1993; 69: 9–15.

e23. Kaplan MM: The role of thyroid hormone deiodination in the regulation of hypothalamo-pituitary function. Neuroendocrinology 1984; 38: 254–60.

e24. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR: Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev 2002; 23: 38–89.

e25. Lechan RM, Fekete C: Role of thyroid hormone deiodination in the hypothalamus. Thyroid 2005; 15: 883–97.

e26. Joint statement on the U.S. Food and Drug Administration's decision regarding bioequivalence of levothyroxine sodium. Thyroid 2004; 14: 486.

e27. Bolton S: Bioequivalence studies for levothyroxine. Aaps J 2005; 7: E47–53.

e28. Dong BJ, Hauck WW, Gambertoglio JG, et al.: Bioequivalence of generic and brand-name levothyroxine products in the treatment of hypothyroidism. Jama 1997; 277: 1205–13.

e29. Teuber J, Helmke K, Maser E, Grebe S, Federlin K: Determination of thyroid hormone antibodies and their clinical relevance (author's transl). Immun Infekt 1981; 9: 12–9.

e30. Thomusch O, Machens A, Sekulla C, Ukkat J, Brauckhoff M, Dralle H: The impact of surgical technique on postoperative hypoparathyroidism in bilateral thyroid surgery: a multivariate analysis of 5846 consecutive patients. Surgery 2003; 133: 180–5.

e31. Zarnegar R, Brunaud L, Clark OH: Prevention, evaluation, and management of complications following thyroidectomy for thyroid carcinoma. Endocrinol Metab Clin North Am 2003; 32: 483–502.

e32. Page C, Strunski V: Parathyroid risk in total thyroidectomy for bilateral, benign, multinodular goitre: report of 351 surgical cases. J Laryngol Otol 2007; 121: 237–41.

e33. Asari R, Passler C, Kaczirek K, Scheuba C, Niederle B: Hypoparathyroidism after total thyroidectomy: a prospective study. Arch Surg 2008; 143: 132–7; discussion 38.

e34. Shen WT, Ogawa L, Ruan D, et al.: Central neck lymph node dissection for papillary thyroid cancer: comparison of complication and recurrence rates in 295 initial dissections and reoperations. Arch Surg; 145: 272–5.

e35. Payne RB, Carver ME, Morgan DB: Interpretation of serum total calcium: effects of adjustment for albumin concentration on frequency of abnormal values and on detection of change in the individual. J Clin Pathol 1979; 32: 56–60.

e36. Godlewska P, Kaniewski M, Stachlewska-Nasfeter E, Bisz D, Lyczek J: Parathyroid hypofunction after total thyroidectomy for differentiated thyroid carcinoma–perspectives after long term observation and treatment. Wiad Lek 2001; 54(Suppl 1): 398–404.