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...
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 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.

The pharmacokinetics of thyroid hormones

A proper understanding of the pharmacokinetics of thyroid hormones 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 in postoperative hypothyroidism, one should know the patient’s physiological requirement for L-thyroxine. This depends on a number of factors, 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 T4. In such cases, too, hormone replacement therapy must be monitored by fT4 measurement.

<p>| TABLE 1 |
| Interpreting typical constellations of peripheral thyroid hormones and TSH |</p>
<table>
<thead>
<tr>
<th>fT3</th>
<th>fT4</th>
<th>TSH</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Euthyroidism</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Overt hyperthyroidism</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Overt hypothyroidism</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>High</td>
<td>Latent hypothyroidism</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Low</td>
<td>Latent hyperthyroidism</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Normal/ Low</td>
<td>hypothalamic/pituitary hypothyroidism or non-thyroidal illness syndrome (NTIS)</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Thyrotropin-secreting tumor or resistance to thyroid hormone</td>
</tr>
</tbody>
</table>

<p>| TABLE 2 |
| The physiological L-thyroxine requirement: rules of thumb for replacement in primary hypothyroidism |</p>
<table>
<thead>
<tr>
<th>Age</th>
<th>T4 requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>10–15 µg/kg BW</td>
</tr>
<tr>
<td>Children, 8-12 months</td>
<td>8–10 µg/kg BW</td>
</tr>
<tr>
<td>Children, 2-10 years</td>
<td>4–6 µg/kg BW</td>
</tr>
<tr>
<td>Adolescents</td>
<td>2–3 µg/kg BW</td>
</tr>
<tr>
<td>Adults</td>
<td>1.5 µg/kg BW</td>
</tr>
<tr>
<td>Elderly persons</td>
<td>1–1.2 µg/kg BW</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>1.8–2 µg/kg BW</td>
</tr>
</tbody>
</table>
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 stimulation 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

### TABLE 3

<table>
<thead>
<tr>
<th>Diseases/conditions</th>
<th>Mechanism of elevated L-thyroxine requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malabsorption</td>
<td>Diminished absorption</td>
</tr>
<tr>
<td>Short bowel syndrome</td>
<td>Diminished absorption</td>
</tr>
<tr>
<td>Sprue</td>
<td>Diminished absorption</td>
</tr>
<tr>
<td>Chronic atrophic gastritis*1</td>
<td>Elevated gastric pH, diminished solubility</td>
</tr>
<tr>
<td>Helicobacter pylori infection*1</td>
<td>Increased formation of NH₃</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Elevated TBG,*2 gestational deiodization, elevated renal iodine clearance</td>
</tr>
</tbody>
</table>

**Mechanisms of elevated L-thyroxine requirement**

- Displacement of T4 from TBG binding, elevated hepatic T4 clearance
- Displacement of T4 from TBG binding, elevated hepatic T4 clearance
- Inhibition of S′-deiodinases
- Inhibition of conversion
- Inhibition of 5′-deiodinases
- Diminished absorption, T4 soluble only in acid solution
- Diminished absorption, T4 soluble only in acid solution
- Direct inhibition of intestinal absorption
- Elevated TBG

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

**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):** correct 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...
5 mmol/L² 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 D₂) and cholecalciferol (vitamin D₃) 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 D₃ (cholecalciferol, 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 hypercalcemia
If the patient has refractory hypercalcemia (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).

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 hypercalcemia.

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


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

Deutsches Ärzteblatt International | Dtsch Arztebl Int 2010; 107(47): 827–34
Hormone Replacement After Thyroid and Parathyroid Surgery
by Andreas Schäffler

eReferences


