should be actively investigated *(37)*. Multinodular goiter should be ruled out as the cause especially in areas of iodide deficiency *(213)*. Medication history should be thoroughly reviewed (including over-the-counter preparations, some of which contain T3). If a goiter is absent and the medication history negative, a serum TSH should be rechecked together with TPOAb measurements after 4 to 6 weeks. If the TSH is still low and TPOAb is positive, the possibility of autoimmune thyroid dysfunction should be considered. Treatment of low TSH should be made on a case-by-case basis.

(c) L-T4 Replacement Therapy

It is now well documented that hypothyroid patients have serum FT4 values in the upper third of the reference interval when the L-T4 replacement dose is titered to bring the serum TSH into the therapeutic target range (0.5-2.0 mIU/L) *(219,220)*.

Levothyroxine (L-T4) and not dessiccated thyroid, is the preferred long-term replacement medication for hypothyroidism.

A euthyroid state is usually achieved in adults with a L-T4 dose averaging 1.6 µg/kg body weight/day. Children require higher doses (up to 4.0µg/kg bw/day) and older individuals require lower doses (1.0 µg/kg bw/day) *(221,222)*. The initial dose and the optimal time needed to establish the full replacement dose should be individualized relative to age, weight and cardiac status. The requirements for an increase in thyroxine during pregnancy [Section-2 A3] and in post-menopausal women just starting hormone replacement therapy *(223)* may also be increased.

A serum TSH result between 0.5 and 2.0 mIU/L is generally considered the therapeutic target for a standard L-T4 replacement dose for primary hypothyroidism.

A serum FT4 concentration in the upper third of the reference interval is the therapeutic target for L-T4 replacement therapy when patients have central hypothyroidism due to pituitary and/or hypothalamic dysfunction.

A typical schedule for gradually titrating to a full replacement dose involves giving L-T4 in 25 µg increments each 6 –8 weeks until the full replacement dose is achieved (serum TSH 0.5-2.0 mIU/L). As shown in figure 2, TSH is slow to re-equilibrate to a new thyroxine level. Patients with chronic, severe hypothyroidism may develop pituitary thyrotroph hyperplasia which can mimic a pituitary adenoma, but which resolves after several months of L-T4 replacement therapy *(224)*. Patients taking Rifampin and anticonvulsants that influence the metabolism of L-T4 may also need an increase in their dose of L-T4 to maintain the TSH within the therapeutic target range.

Both free T4 and TSH should be used for monitoring hypothyroid patients suspected of intermittent or non-compliance with their L-T4 therapy. The paradoxical association of a high FT4 + high TSH is often an indication that compliance may be an issue. Specifically, acute ingestion of missed L-T4 doses before a clinic visit will raise the FT4 but fail to normalize the serum TSH because of the “lag effect” (Figure 2). In essence, the serum TSH is analogous to the hemoglobin A1c as a long-term free T4 sensor! At least 6 weeks is needed before retesting TSH following a change in the dose of L-T4 or brand of thyroid medication. Annual TSH testing of patients receiving a stable dose of L-T4 is recommended. The optimal time for TSH testing is not influenced by the time of day the L-T4 dose is ingested *(133)*. However, the daily dose should be withheld when FT4 is used as the therapeutic endpoint, since serum FT4 is significantly increased (~13%) above baseline for 9 hours after ingesting the last dose *(225)*.

Ideally L-T4 should be taken before eating; at the same time of day and at least 4 hours apart from any other medications or vitamins. Many medications can influence T4 absorption/metabolism (especially Cholestyramine, Ferrous Sulfate, Soy Protein, Sucralfate, antacids containing Aluminum Hydroxide, anticonvulsants or Rifampin) *(4,226)*.

(d) L-T4 Suppression Therapy

L-T4 administration designed to suppress serum TSH levels to subnormal values is typically reserved for patients with well-differentiated thyroid carcinoma for which thyrotropin is considered a trophic factor *(227)*. The efficacy of L-T4 suppression therapy has been determined from uncontrolled retrospective studies that have yielded conflicting results *(228,229)*.

It is important to individualize the degree of TSH suppression by weighing patient factors such as age, clinical status including cardiac factors and DTC recurrence risk against the potentially deleterious effects of iatrogenic mild (subclinical) hyperthyroidism on the heart and bone *(36)*. Many physicians use a serum TSH target of 0.05-0.1 mIU/L for low-risk patients and a TSH of <0.01 mIU/L for high-risk patients. Some physicians reduce the L-T4 dose to give low-normal TSH values when patients have undetectable serum thyroglobulin (Tg) levels and no recurrences 5-10 years after thyroidectomy. Suppression therapy for non-endemic goiters is generally considered ineffective *(230)*. Furthermore, patients with nodular goiters often already have suppressed TSH concentrations as a result of thyroid gland autonomy *(213)*.

Guideline 23. Levothyroxine (L-T4) Replacement Therapy for Primary Hypothyroidism

- L-T4, not desiccated thyroid, is the preferred medication for long-term replacement therapy for hypothyroidism.
- A euthyroid state is usually achieved with an average L-T4 dose of 1.6 µg/kg body weight/day. The initial dose and time to achieve full replacement should be individualized relative to age, weight and cardiac status. An initial L-T4 dose is normally 50-100 µg daily. Serum TSH measurement after six weeks will indicate the need for dose adjustment by 25-50 µg increments.
- Children require higher doses of L-T4, up to 4.0µg/kg bw/day, due to rapid metabolism. Serum TSH and FT4 values should be assessed using age-specific and method-specific reference ranges (Table 3).
- A serum TSH level between 0.5 and 2.0 mIU/L is generally considered the optimal therapeutic target for the L-T4 replacement dose for primary hypothyroidism.
- TSH is slow to re-equilibrate to a new thyroxine status (Guideline 2). Six to 8 weeks is needed before retesting TSH after changing the L-T4 dose or brand of thyroid medication.
- Intermittent or non-compliance with levothyroxine (L-T4) replacement therapy will result in discordant serum TSH and FT4 values (high TSH/high FT4) because of a persistently unstable thyroid state (Guideline 2). Both TSH and FT4 should be used for monitoring such patients.
- Thyroxine requirements decline with age. Older individuals may require less than 1.0 µg/kg bw/day and may need to be titrated slowly. Some physicians prefer to gradually titrate such patients. An initial dose of 25 µg is recommended for patients with evidence of ischemic heart disease followed by dose increments of 25 µg every 3-4 weeks until the full replacement dose is achieved. Some believe that a higher target TSH (0.5-3.0 mIU/L) value may be appropriate for the elderly patient.
- In severe hypothyroidism an initial L-T4 loading dose is the most rapid means for restoring a therapeutic FT4 level because the excess of unoccupied binding sites may blunt the FT4 response to treatment.
- Thyroxine requirements increase during pregnancy. Thyroid status should be checked with TSH + FT4 during each trimester of pregnancy. The L-T4 dose should be increased (usually by 50 µg/day) to maintain a serum TSH between 0.5 and 2.0 mIU/L and a serum FT4 in the upper third of the normal reference interval.
- Post-menopausal women starting hormone replacement therapy may need an increase in their L-T4 dose to keep the serum TSH within the therapeutic target.
- TSH testing of patients receiving a stable L-T4 dose is recommended on an annual basis. The ideal time for TSH testing is not influenced by the time of day the L-T4 dose is ingested.
- Ideally L-T4 should be taken before eating, at the same time of day, and at least 4 hours apart from any other medications or vitamins. Bedtime dosing should be 2 hours after the last meal.
- Patients beginning chronic therapy with cholestyramine, ferrous sulfate, calcium carbonate, soy protein, sucralfate and antacids containing aluminum hydroxide that influence L-T4 absorption may require a larger L-T4 dose to maintain TSH within the therapeutic target range.
- Patients taking Rifampin and anticonvulsants that influence the metabolism of L-T4 may also need an increased L-T4 dose to maintain the TSH within the therapeutic target range.

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