

after a period of blocking the thyroid, as the gland has become loaded of iodine substrate for hormone synthesis [32].

However, in the investigation by Takata et al. a combination of iodide solution was used together with methimazole for up to 8 weeks [33]. Iodide was discontinued when patients showed normal free T4. Eleven patients (25%) escaped from the Wolff-Chaikoff effect, and 3 derived no benefit at all. Moreover, in another study including patients with mild GD who received primary treatment with LS (50–100 mg daily), control of hyperthyroidism after 12 months was comparable with that seen in patients receiving low-dose methimazole treatment [34]. How often and how early escape occurs is not clear, but in an observational study from Japan long-term treatment with LS alone or in combination with antithyroid drugs has been used, with 29/44 (66%) being well-controlled on 100 mg LS daily alone for 7 years [35]. In another study of 21 patients with hyperthyroidism given iodide daily, hormone levels started to increase again after 3 weeks in some, but others remained euthyroid even after 6 weeks [36]. Reactivation of thyrotoxicosis could to some extent be explained by a stimulation of the immune system as elevation of TSH receptor antibodies has been noted in euthyroid patients preoperatively with 60 mg iodide twice daily for 10 days [37]. However, in long-term treatment with iodide these antibodies has been reported to decline [35].

## Vascular effects

Plummer observed a 75% decrease in mortality associated with thyroidectomy when LS was introduced [1]. At that time metabolic rate decreased as well as symptoms. As a complement to effect on T4 and T3 reductions vascular effects has been of interest and already in 1925 intrathyroid blood vessel compression was described after LS therapy [38]. Reduced blood flow has since then been described as an effect of LS in GD patients with different methods. In 9 subjects with GD uptake of thallium was decreased with a third after 10 days of LS (0.5 ml tds) [39], and the authors speculated that this could be a result of decreased perfusion, as the amount of colloid had increased. A reduction in vascularity measured with <sup>99m</sup>Tc-pertechnetate after LS has also been shown [40]. In a number of investigations of euthyroid individuals with GD LS has reported to decrease

(VBF) and with 50% of microvessels [40]. If other angiogenic mediators also are involved is unknown. Furthermore, microvessel density, calculated with ultrasound, displayed decreased blood flow after 10 days of 10 drops iodide (74.7 vs. 54.4, mL/min), decreased blood loss (128.6 vs. 108.7 mL) and less expression of CD34 measured with immunohistochemistry [42]. On the other hand, another study demonstrated no difference in blood loss or time of surgical procedure comparing 13 patients on iodide vs. 24 on antithyroid drugs [47].

## Treatment with LS

LS tastes bitter and is also corrosive, and this should be disguised by taking it with a sweet drink such as apple juice. The applied doses come from experience rather than by prospective randomized controlled trials (Table 2). Historically Plummer used 80–320 mg iodide daily and this was established as a pre-treatment before thyroidectomy in GD [1]. However, the efficacy of much smaller doses has also been investigated in the late 1920s to 1960, also in long-term treatment. Thomson et al. found that 6 mg daily iodine induced euthyroidism in most patients [48], and as low doses as 1 mg has also been effective [49]. Reports on escape and the development of antithyroid drugs and radioactive therapy then discouraged physicians from this route of treatment.

Takata et al. demonstrated that normalisation of free T4 was more rapid with a combination of LS and antithyroid drugs, than methimazole alone, however, remission did not differ during a 4–5 year follow-up [33]. In another Japanese study the combination also resulted in a higher proportion of normalized thyroid hormones at 30 and 60 days compared to antithyroid drugs alone [50]. In both these investigations iodide was stopped when free T4 had normalized. In the ATA guidelines 5–7 drops thrice daily of LS or 1–2 drops of SSKI (50–100 mg iodide) 10 days before thyroidectomy is recommended. SSKI contain 1 g of potassium iodide per ml. An iodide dose of 5 drops LS thrice daily is equivalent to 100.5 mg iodide daily [4]. Yilmaz et al. used twice as high dose in their study [43]. Other doses of iodide have also been applied such as 150 or 375 mg daily [36, 51], all with good effect in reducing free T4 and free T3. Lower doses as 50 mg KI have also been applied (equivalent to 38.2 mg of iodide) [50]. In long-term treatment 10–400 mg

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12 drops  
4x/day  
= 30 mg  
x 4  
= 120  
mg/day

7  
years  
at  
100  
mg  
daily!