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EDITORIAL

Thyroxine treatment: absorption, malabsorption, and novel therapeutic approaches

Marco Centanni

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Although levothyroxine sodium is highly prescribed worldwide, the exact daily dosage, mode of assumption, and refractoriness to treatment are as yet matter of debate. Growing evidence highlighted that undertreatment with T4 has detrimental effects on several tissues and functions. This is even more proper during pregnancy, when an inadequate treatment may increase the likelihood of obstetric complications and may affect the neuropsychological performance during childhood [1]. In adult patients, subclinical hypothyroidism has been reported to be involved in impaired lipid metabolism and atherosclerosis as well as in cardiovascular disorders [2]. The need for an individually tailored dose potently emerges from these findings. Thyroxine treatment should no longer be prescribed according to the commercially available dose size, but rather related to the patient's weight and age [3]. Two major issues are indeed crucial to obtain an optimal daily dose for a specific patient: an unbiased serum TSH value and an efficient absorption process of thyroxine. The assumption that serum TSH would be a reliable marker of pharmacologic euthyroidism in all tissues has been challenged since its value may be affected by a number of drugs, cosmetics, and pathophysiological conditions [4, 5]. Even the upper limit of normal serum TSH ($<$ or $>$ 2.5 mU/l) has been questioned [5]. However, it still remains the best available marker, since the direct measurement of thyroxine absorption is not an easy task. Assuming an unbiased serum TSH value in each patient, the absorption process of T4 becomes key for a successful treatment. The daily dose required to obtain the desired TSH value/therapeutic effect is, in fact, not simply a mirror of the ingested dose of thyroxine. One of the major determinants on pharmacological thyroid homeostasis is, thus the incomplete absorption of oral thyroxine (60–80 % of the administered dose) which takes place at the intestinal level. Indeed, the absorbed dose of T4 may be considered the resultant of: (a) patient compliance; (b) some physiological (pregnancy, weight) and/or paraphysiological (behavioral, nutritional) or pharmacological conditions of increased or decreased T4 need; and (c) the presence of diseases which cause malabsorption of T4 (see [6] for review). Repeated failure to reach therapeutic target in response to an "adjusted" dose is a fairly common and frustrating experience. Larger doses of thyroxine are required to attain the desired serum TSH concentrations, leading to expensive and often inappropriate hormonal monitoring. Once attributed to pseudomalabsorption, the increased need for thyroxine may be also explained by an impaired absorption of levothyroxine. Recently, the modality of drug ingestion gained attention. There is now evidence that at least 1 h delay between T4 tablet ingestion and breakfast warrant the best therapeutic achievement [7]. According to Benvenga et al. [8], even the common use of coffee close to the T4 tablet ingestion results in an altered T4 absorption. According to these authors, coffee physically interacts with T4 tablets and retains thyroxine within the intestinal lumen thus making it less available for absorption [8]. This mechanism closely resembles the one suggested for the reduced absorption of thyroxine in patients with celiac sprue [9]. In these patients, the amount of active hormone available for the absorption may be

M. Centanni
Chief of Endocrinology Unit, Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy

M. Centanni (✉)
Dipartimento di Medicina Sperimentale, Policlinico Umberto I, Viale Regina Elena 324, 00161 Rome, Italy
e-mail: marco.centanni@uniroma1.it

reduced by partially undigested substances, sequestering thyroxine in the intestinal lumen [9]. In this issue of the Journal, Vita et al. [10] seem to have overcome the problem of coffee interference using a soft gel capsules preparation containing T4 dissolved in glycerin. They presented evidence that, unlike tablet formulation of T4, absorption of soft gel capsules is unaffected by the concurrent assumption of coffee. If the soft gel capsules are able to bypass the sequestering mechanism of T4 within the intestinal lumen, then they may be of potential benefit also in celiac patients. Absorption of T4 may be similarly improved in patients with lactose intolerance and other chronic inflammatory, disorders in which intestinal malabsorption of T4 may also occur.

Whatever would be the involved mechanism, these findings and the growing evidence of thyroxine malabsorption may lead to reconsider the whole picture of thyroxine treatments. Further important characteristic of this novel formulation is an improved pH-dependent dissolution profile, as compared to tablets [11]. The increased need for thyroxine in patients with impaired gastric acid secretion has been described since 2006 [12] and a novel role for the stomach in the subsequent intestinal T4 tablet absorption was also highlighted. If a preparation of oral T4 better dissolves in less acidic environment, then the absorption process may be improved in those patients with impaired gastric acid secretion. Indeed, the gastric acid producing machinery is partially or totally damaged in patients with gastric atrophy and/or with Helicobacter pylori infection (in which is also challenged by NH3 production) and is blocked in those treated with proton pump inhibitors (PPI). The huge number of patients with impaired acid secretion and potential T4 malabsorption (30 % of patients in Western Countries have H. pylori infection and PPI are among the most prescribed drugs) may benefit from this novel thyroxine preparation. On this ground, a further step, beside the tablets and the soft gel capsules, may be the therapeutic option represented by the oral liquid preparation of T4.

In vivo studies confirming that the use of more soluble T4 preparations correspond to a more effective treatment in patients with gastrointestinal disorders are still awaited. Indeed, the findings of Vita and coll., published in this issue, indicate the need for different T4 preparations available to meet the habits and the therapeutic needs of different class of patients.

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