

## **LEVOTHYROXINE: FACTORS AFFECTING ITS INTESTINAL ABSORPTION AND METABOLISM**

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### **ABSTRACT**

Thyroxine is the first hormone replacement therapy, first initiated more than a century ago. Its absorption after ingestion is largely in jejunum and ileum. The absorption is affected by many pharmacological agents and herbal remedies. Apart from the above many medical conditions can also cause delayed or malabsorption of thyroxine. Here we enlist the conditions that affect thyroxine absorption and metabolism.

### **INTRODUCTION**

Hypothyroidism is the first endocrine disorder treated with replacement of deficient hormone. Thyroid hormone replacement is available as Levothyroxine (T4), Liothyroxine (T3), Liotrix (1:4 combinations of T3 and T4) and Thyroxine USP (Porcine Thyroid extract).

Levothyroxine (T4) is the ideal choice in replacement therapy as it mimics physiological secretion and peripheral T3 conversion is also near physiological. Usual replacement dose is 1.6mcg-1.8mcg/kg/day. Ideally it is ingested on empty stomach as gastric acidity facilitates its absorption which takes place in jejunum and ileum. 60-80% reaches systemic circulation within 3 hours of ingestion. Patients with small bowel resection or jejunoileal bypass surgery demonstrated increased requirement of thyroxine to attain euthyroid status.

One of the common clinical questions in thyroid clinics is difficulty in attaining euthyroid status despite increasing requirement of thyroid supplement. The typical biochemical picture is high TSH and low T4, T3 levels. If we can rule out non-compliance, then the approach to the problem would be look for factors that prevent thyroxine absorption and or that which increase its metabolism. It can be broadly divided into dietary factors, drug interactions and malabsorption syndromes.

**DIETARY FACTORS**

Food

Dietary Fibre

Espresso Coffee

Herbal Remedies

The timing of food intake affects the absorption of thyroxine. It has been demonstrated that fasting state facilitates thyroxine absorption presumably due to presence of gastric acidity<sup>1</sup>. Dietary fibre causes reduction in bioavailability by adsorption of thyroxine and thus decreasing the absorption. In vitro studies have shown that wheat bran can prevent thyroxine absorption<sup>2</sup>.

It was clearly shown that separating breakfast and thyroxine ingestion by 60 minutes resulted in adequate suppression of TSH<sup>3</sup>.

A recent addition to the list is espresso coffee which is capable of interfering with T4 absorption, and thus affects its bioavailability<sup>4</sup>.

Lemon balm is an herbal remedy often used as antianxiety, sedative and calming effects. It is used as herbal tea and oil. It has anti TSH effect and also prevents intestinal thyroxine absorption<sup>5</sup>.

**DRUGS INTERFERING WITH THYROXINE ABSORPTION**

Proton pump inhibitors

Ferrous sulphate

Calcium carbonate

Phosphate binders

Aluminium containing antacids

Sucralfate

Raloxifene

Orlistat

Cholestyramine

Colesevelam

### *Proton pump inhibitors(PPI)*

PPI's can affect thyroxine absorption as they decrease the acidity. However the data available suggest that the patients treated with proton pump inhibitors for up to 6month showed reduction in thyroxine absorption<sup>6</sup>.

### *Aluminium containing antacids*

Aluminium forms complex with levothyroxine and limits its intestinal absorption. TSH levels significantly increased in thyroxine replaced hypothyroid patients, when concurrent aluminium containing antacids were used. This effect was promptly reversed on stopping the antacids. In vitro studies have demonstrated that small quantity of aluminium salt adsorbs levothyroxine.

### *Sucralfate*

Sucralfate can interfere with intraluminal transport of thyroid hormones. When healthy volunteers were given Levothyroxine with sucralfate concurrently, peak absorption was reduced significantly. When the two drugs were ingested with 8 hr interval in between each other, the peak hormone absorption and time to peak were not significantly different to control<sup>7</sup>.

However similar results were not reproduced when studies were done in primary hypothyroid patients. The reduction in serum FT4 was slight, but TSH elevation was not significant<sup>8</sup>.

The evidence is conflicting whether it prevents intestinal absorption of levothyroxine. A treating physician has to take a practical approach if encountered with the problem.

### *Ferrous sulphate*

Studies have shown that simultaneous ingestion of ferrous sulphate and levothyroxine resulted in elevation of TSH levels<sup>9</sup>. In vitro experiments have demonstrated binding of  $Fe^{3+}$  to levothyroxine molecules forming an insoluble complex and causing malabsorption when ingested together.

### *Calcium carbonate and phosphate binders*

Calcium carbonate is a commonly used in practice. In vivo and in vitro studies have shown that calcium carbonate can adsorb levothyroxine in acidic environment and thus reduce the bioavailability<sup>10</sup>.

Similarly other phosphate binders like sevelamer hydrochloride and lanthanum carbonate interferes with levothyroxine absorption and reduces bioavailability<sup>11</sup>. Cholestyramine and colestevam, a bile acid sequestrants, adsorbs levothyroxine and reduces the bioavailability<sup>12</sup>.

There are case reports of SERM's and orlistat interfering with levothyroxine absorption.

## **DRUGS INCREASING THE METABOLISM OF THYROXINE.**

Antiepileptics like carbamazepine, phenytoin and phenobarbitol which induce hepatic enzyme uridine diphosphateglucuronosyltransferases (UGT) cause increased metabolism of thyroxine and contribute to lowering the plasma levels<sup>13</sup>.

Rifampicin increases hepatic T<sub>4</sub> metabolism and biliary excretion of iodothyronine conjugates. Rifampicin causing frank hypothyroidism in euthyroid hoshimoto's thyroiditis has been reported<sup>14</sup>.

Newer biologic agents like kinase inhibitors, Imatinib, Motesanib, Sunitinib have been reported to induce hypothyroidism but data is still inconclusive<sup>15,16</sup>.

## **MALABSORPTION DISORDERS**

Coeliac disease is frequently associated with other autoimmune conditions. Levothyroxine requirement is significantly high in untreated coeliac disease. Hypothyroidism can be initial manifestation of celiac disease. Small bowel resection, jejunoileal bypass surgery and inflammatory bowel disease cause malabsorption of levothyroxine<sup>17</sup>.

Gastric acidity is very important for intestinal absorption of levothyroxine. H. pylori infection causes increased urease production which neutralises gastric acidity and chronic atrophic gastritis where gastric PH is low, levothyroxine absorption is impaired<sup>6</sup>.

## **MANAGEMENT**

It is not uncommon to encounter a clinical scenario where a hypothyroid patient on replacement dose is referred with high TSH and low T4 despite being on adequate replacement dose.

The approach here would be tricky as compliance issues are to be dealt and non compliance with levothyroxine dose is a common cause of this biochemical abnormality. If we can rule out non compliance by doing a thyroxine absorption test, then we should consider and rule out dietary habits, drug interactions, herbal remedies and malabsorption disorders contributing to the biochemical picture. Many a times patients will need increased dose of levothyroxine to overcome the offending factor.

## KEY POINTS

Ideal dose is 1.6mcgm/kg/day

Maintain at least 60minutes between the drug and meals

Consider interactions when used with other drugs before altering the dose

Assess compliance in all patients with subtherapeutic FT4 levels despite being on adequate dose.

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