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**Study of The Efficacy of Sublingual Route  
Administration of Levothyroxine Na Tablets VS  
Oral Route In Cases With Refractory Primary  
Hypothyroidism**

***Thesis***

***Submitted for partial Fulfillment of master degree in Endocrinology***

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

لسبحانك لا علم لنا  
إلا ما علمتنا إنك أنت  
العليم العظيم

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## **List of Abbreviations**

|       |                                     |
|-------|-------------------------------------|
| APCA  | : Anti parietal cell Ab             |
| CD    | : Celiac disease                    |
| ELISA | : Enzyme-linked immunosorbent assay |
| LI    | : Lactose intolerance               |
| L-T4  | : Levothyroxine                     |
| PPIs  | : Proton-pump inhibitors            |
| T3    | : Triiodothyronine                  |
| T4    | : Thyroxine                         |
| TPO   | : Thyroid peroxidase antibody       |
| TSH   | : Thyroid stimulating hormone       |

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# INTRODUCTION

Hypothyroidism is a common disorder, with a prevalence of approximately 5% and incidence of approximately 250/ 100,000 per year in the adult population, but both prevalence and incidence keep raising. (*Madariaga et al., 2014*)

Levothyroxine (LT4) is the recommended hormone for replacement therapy in both overt and subclinical hypothyroidism (*Jonklaas et al., 2014*)

There is a frequently encountered subset of hypothyroid patients (20%-28%) who are refractory to standard thyroid hormone replacement treatment and require unexpectedly high doses of levothyroxine (*Taylor et al., 2014*)

In addition to clinical situations where hypothyroid patients are non-compliant, therapeutic failure may be due to impaired absorption of the administered drug. Dietary fiber and coffee interfere with L-T4 absorption. Malabsorption is also reported in disorders such as *Helicobacter pylori* infection, atrophic gastritis, inflammatory bowel disease,

celiac disease (CD), and lactose intolerance (LI) (*Vaisman et al., 2009*)

Many commonly used drugs such as ferrous sulphate, sucralfate, raloxifene, proton-pump inhibitors (PPIs), bile acid sequestrants, calcium carbonate, phosphate binders, and aluminum-containing antacids have also been shown to interfere with L-T4 absorption. (*Vita et al., 2014*)

The common approach to managing patients with unusual thyroxine needs is to escalate the dose of levothyroxine until targeted TSH levels are achieved. This approach can increase the risk for prolonged exposure to supratherapeutic doses of levothyroxine which increase the chances of adverse outcomes. Such as increased bone loss, cardiovascular, and other more serious medical conditions Moreover,

Repeated adjustments of levothyroxine can also escalate the costs of treatment, as frequent office visits and lab tests are required to determine and maintain the desired dose. These can also reduce patient compliance and satisfaction with hypothyroid treatment. (*Flynn et al., 2010*)

For that reason, an alternative method of levothyroxine administration that are less susceptible to intolerance issues, or, in some cases, to malabsorption should be considered. This may avoid unnecessary thyroid medication adjustments and their consequences for both patients and clinicians.

## **AIM OF THE WORK**

Levothyroxine (L-T4) is the standard therapy of hypothyroidism. Our purpose was to compare the efficacy of the L-T4 sublingual tablet administration to standard oral L-T4 tablet in hypothyroid patients with refractory hypothyroidism.

## *Chapter (1)*

# **HYPOTHYROIDISM**

### **Background:**

Hypothyroidism is a common condition of thyroid hormone deficiency, which is readily diagnosed and managed. The definition of hypothyroidism is based on statistical reference ranges of the relevant biochemical parameters and is increasingly a matter of debate. **(Chaker et al., 2017)**

Hypothyroidism refers to the common pathological condition of thyroid hormone deficiency. If untreated, it can lead to serious adverse health effects and ultimately death. **(Chaker et al., 2017)**

The definition of hypothyroidism is predominantly biochemical. Overt or clinical primary hypothyroidism is defined as thyroid stimulating hormone (TSH) concentrations above the reference range and free thyroxine concentrations below the reference range. Mild or subclinical hypothyroidism, which is commonly regarded as a sign of early thyroid failure, is defined by TSH concentrations above

the reference range and free thyroxine concentrations within the normal range. **(Razvi et al., 2019)**

Subclinical hypothyroidism represents a state with increased values of thyroid stimulating hormone (TSH) and normal values of thyroxine (T4) and triiodothyronine (T3). The disorder is asymptomatic, and the diagnosis is made based on the results of laboratory findings when the level of TSH reaches values above 4.0 mU/l. **(Cojić and Cvejanov.2017)**

### **Epidemiology:**

#### **➤ Prevalence and risk factors:**

The prevalence of overt hypothyroidism in the general population varies between 0.3% and 3.7% in the USA and between 0.2% and 5.3% in Europe, depending on the definition used. **(Asvold et al., 2013)**

Hypothyroidism occurs more frequently in women, in older people (>65 years), and in white individuals, although data on ethnic differences are scarce. **(McLeod et al., 2017)**

Hypothyroidism is more common in patients with autoimmune diseases, such as type 1 diabetes, autoimmune

gastric atrophy, and coeliac disease, and can occur as part of multiple autoimmune endocrinopathies. Individuals with Downs' syndrome or Turners' syndrome have an increased risk of hypothyroidism. By contrast, tobacco smoking and moderate alcohol intake are associated with a reduced risk of hypothyroidism. **(Krzewska and Ben.2016)**

Iodine insufficiency is a common cause of hypothyroidism, External radiotherapy of the head and neck, as well as whole body irradiation may cause damage to the thyroid and lead to hypothyroidism, also drugs as amiodarone, lithium, Interferon and tyrosine kinase inhibitor Sunitinib, an anticancer agent, has been shown to cause hypothyroidism **(Kostoglou- and Ntalles.2010 Athanassiou)**

➤ **Genetic epidemiology:**

The heritability of TSH and free thyroxine concentrations in serum is estimated to be 65% and 23–65%, respectively. **(Barbesino.2019)**

Monogenetic disorders leading to congenital hypothyroidism are rare and include TSH resistance (due to an inactivating mutation in the TSH receptor), thyroid dysgenesis, and thyroid dyshormonogenesis. **(Sanjay.2019)**