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Are Nodular Goiter Patients Previously Treated with L-Thyroxine have Unfavorable Outcomes after Surgery Compared to Patients without Medical Treatment?

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Research Article

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Abstract

This systematic review aimed to analyze the literature on PubMed Database regarding studies which compare the patient's post-thyroidectomy outcomes, between those who were treated with L-Thyroxine prior to surgery and those who underwent to thyroidectomy without hormonal suppressive therapy. 500 articles were screened, 11 articles were selected, which were related to the outcomes of interests. Among all these articles with outcome interests, no article is appropriate to the research question of our investigation. The outcomes of surgical treatment of nodular goiter patients, depending on using L-Thyroxine treatment in anamnesis, are very interesting and could bring light to some issues of endocrinology. There is need for further research on this topic to generate relevant evidence on use of L-Thyroxine.

Keywords: Goiter; Nodule; L-Thyroxine; Surgery; Outcomes

Introduction

Benign thyroid nodules are one of the most common pathologies among the population and the incidence is significantly higher in the areas with iodine deficit. Different sources report a wide range of thyroid nodules prevalence from 10% up to 69% [1]. Levothyroxine treatment is widely used for diminishing nodule and gland sizes [2]. However, in the American Thyroid Association Guidelines Task Force on Thyroid Nodules, hormonal suppression therapy with L-Thyroxine for benign thyroid nodules in patients who live in iodine-sufficient areas is not recommended [3].

A variety of treatment procedures has been suggested for the treatment of nodular disease of the thyroid gland [4]. Due to the fact that the malignancy rate is about 5% among benign thyroid nodules, all patients treated with minimally invasive procedures need serious follow-up with regularly fine-needle aspiration biopsies [5]. So, traditional surgical procedures like total or subtotal thyroidectomies are the dominant treatment method in patients with nodular goiter.

The recent literature review shows the controversial outcomes about the effectiveness of hormonal suppressive therapy with L-thyroxine in the treatment of nodular goiter. Patients with insufficient results after hormonal suppressive therapy have to undergo surgeries [2]. Moreover, L-Thyroxine has an adverse negative effect on bone mineral density [6] and increases the rate of cardiac arrhythmias in patients who are treated for a long time [7].

The aim of this study was systematically analyzing of literature on PubMed Database regarding studies which compare the patient's post-thyroidectomy outcomes, between those who were treated with L-Thyroxine prior to surgery and those who underwent to thyroidectomy without

hormonal suppressive therapy.

Methods

Study Design: Systematic review

Eligibility Criteria

Key questions are commonly formulated according to the "PICO" method, the details of which are presented below.

Population: Adult patients with benign thyroid nodules.

Intervention/Exposure: L-Thyroxin or hormonal suppressive therapy

Comparator/Control: Non-treated patients with L-Thyroxin

Outcome: Unfavorable outcomes (hepatocytes dysfunction, lipid profile changes with a high risk of cardiovascular diseases, worsened quality of life)

Search Strategy: We searched published articles on the PubMed database without language restrictions. We used the below restrictions while searching for the articles,

- Inclusion Criteria: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, Systematic Review
- Exclusion Criteria: Books and Documents, case reports.
- Time Frame: Data published from 2012 till 2022 years.

We searched for articles based on PICO format.

#1 Selection of Articles Related to Study Population: To select all the articles related to thyroid nodules, we used the below search strategy.

Thyroid, nodule [MeSH] OR Thyroid nodules [MeSH] OR Goiter, Nodular [MeSH] OR Nodular Goiter [tiab] OR Nodular Goiters [tiab]

#2 Selection of Article Related to Exposure: To select all the articles related to hormonal therapy with L-thyroxine, we used the below search strategy

L thyroxine [MeSH] OR Thyroxine [MeSH] OR Thyroxin [tiab] OR Thyroid Hormone [tiab] OR L-thyroxine [tiab] OR Tetraiodothyronine [tiab] OR Levothyroxine [tiab] OR Levothroid [tiab] OR Levoxine [tiab] OR Levoxyl [tiab] OR Lévothyrox [tiab] OR Novothyral [tiab] OR Novothyrox [tiab] OR Oroxine [tiab] OR Levothroid [tiab] OR Levoxine [tiab] OR Levoxyl [tiab] OR Lévothyrox [tiab] OR Novothyral [tiab] OR Novothyrox [tiab] OR Oroxine [tiab] OR levothyroxine sodium [tiab] OR Euthyrox [MeSH] OR L-Thyrox* [tiab] OR Levothyroxine [MeSH] OR Levothyrox*[tiab] OR L-Thyrox*[tiab] OR Levo-T [tiab] OR Eutirox [tiab]

#3 Selection of Articles Related to Thyroidectomy:

Thyroidectomy [MeSH] OR thyroidectomies [MeSH)

#4 Selection of articles related to outcomes of surgery:

Treatment outcome [MeSH] OR treatment outcome* [tiab] OR Patient-Relevant Outcome OR Outcomes, Patient-Relevant [tiab] OR Clinical Effectiveness [MeSH] OR Treatment Effectiveness [tiab] OR Outcome, Rehabilitation [MeSH] OR Treatment Efficacy [tiab] OR Clinical Efficacy [MeSH] OR recurrence [MeSH] OR recurrence*[tiab] OR relapse*[tiab] or Quality of life [tiab]

Final search strategy: We combined all the above to create a composite search strategy

#1 AND #2 AND #3 AND #4

Results

Screening of Articles

The initial search results obtained the 524 articles. During the screening process 24 articles were excluded. Exclusion reasons were case reports and articles without an abstract.

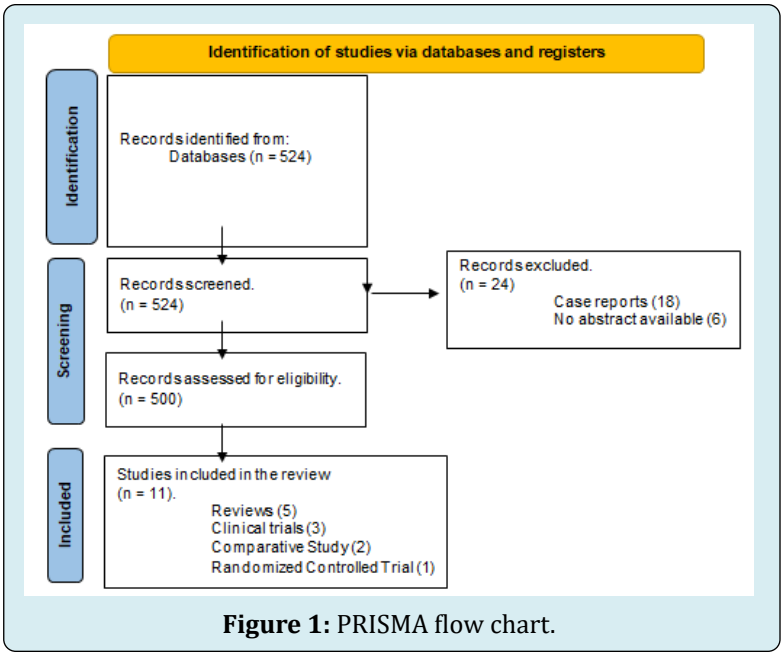

Figure 1: PRISMA flow chart.

500 articles were systematized in Excel sheet. The selection of articles regarding publishing date and article types were shown in Tables 1 & 2 accordingly.

11 articles were selected, which were related to the outcomes of interests. Table 3 shows the characteristics of related articles.

Years	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Total n=500	13	55	55	55	48	51	45	63	51	62	2

Table 1: Selection results for publishing date.

Types	Number
Clinical trial	107
Comparative Study	15
Meta-Analysis	42
Observational Study	6
Retrospective Study	19
Prospective study	2
Randomized Controlled Trial	72
Review	228
Systematic Review and Meta-analysis	3

Table 2: Selection for articles type.

Source	Country	Article type	Outcomes
Sjölin G, et al. [8]	Sweden	Clinical Trial	This study discusses the long-term total outcome of antithyroid drug or J131 or surgical treatment modality regarding how many require levothyroxine supplementation, the need for thyroid ablation, or the individual patient's estimation of their recovery.
Tiedje V, et al. [9]	Germany	Review	This review talks about the treatment of differentiated thyroid cancer. Continued TSH suppressive levothyroxine therapy is only recommended in high-risk patients.
Brun VH, et al. [10]	Norway, Sweden.	Randomized Controlled Trial	This study is about the levothyroxine (LT4) replacement therapy dosage adjustment with a decision aid tool (DAT) that models LT4 pharmacometrics and enables patient-tailored dosage after total thyroidectomy.
Gambale C, et al. [11]	Italy	Review	The review talks about the treatment of differentiated thyroid cancer (DTC). L-T4 therapy should be personalized according to the type of surgery, the age of patients, and their comorbidities.
Buehler LA, et al. [12]	USA	Comparative Study	This study aimed to assess hormonal outcomes and thyroid hormone (TH) replacement after hemithyroidectomy (HT).
Antonelli A, et al. [13]	Italy, USA	Review	In the twelve papers that constitute this Research Topic, various innovative aspects related to therapy of hypothyroidism with L-T4 are reviewed and discussed and provide a stimulating overview of the present state of our knowledge
Gluvic Z, et al. [7]	Serbia, The United Kingdom, Saudi Arabia	Review	This review summarizes the relevant available data related to LT4 suppressive treatment and the associated risk of cardiac arrhythmia.
Leenhardt L, et al. [14]	France	Comparative Study	This study demonstrates the noninferiority of rhTSH vs thyroid hormone withdrawal (THW) in preparation for RAI regarding disease status at the first evaluation in the real-life setting in patients with N1 DTC.
Shin YW, et al. [15]	South Korea, USA	Clinical trial	The study examined whether thyroid hormone withdrawal affects resting state functional connectivity and the mood or QoL of the patients with thyroid hormone withdrawal status.
Moon JH, et al. [16]	South Korea,	Clinical trial	The association between serum thyroid hormone concentration and cognitive function was investigated.
Medas F, et al. [17]	Italy	Review	This review compared pathological features and surgical outcomes of hyperthyroid versus euthyroid patients.

Table 3: Characteristics of 11 included articles on L-Thyroxine treatment in patients with thyroid diseases.

Among all these articles with outcome interests, no article is appropriate to the research question of our investigation. Most articles present the outcomes of the L-Thyroxine therapy after surgery. However, the main aim of our study was the compare the outcomes of the L-Thyroxine therapy before thyroidectomy.

Discussion

Nodular goiter is the most common disease of the thyroid gland with a prevalence of 5-7%, increasing up to 70% among the population of endemic zones [18]. Ultrasound investigation, fine needle biopsy, hormonal analysis of blood, radioisotope scintigraphy, and computer tomography are the main methods in the diagnosis of thyroid nodules [5]. Fine needle biopsy of small nodules detected by USM reveals tumor cells or undifferentiated cytological structures in up to 12% of cases [19]. Among patients with negative needle biopsy results, malignant transformation is recorded in 10-20%. After surgeries regarding suspicious nodules, thyroid cancer is identified in 8.5% - 10% of pathomorphological evaluation of the removed gland tissue [20].

Depending on the size of the nodule and the results of fine-needle aspiration biopsy, there are 4 main approaches to the treatment of nodular disease: clinical observation, hormonal suppressive treatment with L-Thyroxin, treatment with Radioactive J131 and surgical procedure [1]. Hormonal suppressive treatment with L-Thyroxine recommended in small-sized nodules. However, the effectiveness of hormonal treatment with L-Thyroxin in reducing the size of nodes and glands is controversial. In addition, L-Thyroxine, has adverse effects on cardiac function and changes bone mineral composition [21-23]. Moreover, levothyroxine therapy for a long time, has a risk of losing time in cases of tumor transformation of nodules [24].

Long-term levothyroxine treatment costs a lot of money and loaded the health resources. L-Thyroxine therapy in most cases shows not effective outcomes regarding the decreasing nodule size, and most patients must be undergone to surgical procedures, which causes a violation of the patients' quality of life [25].

Liver is responsible for the metabolism of the thyroid hormones and long-term levothyroxine intake negatively influences the hepatocytes. This may result in the insufficient outcomes of the replacement hormone therapy after surgery and lead to increased dosage [26,27].

We tried to compare the literature dedicated to the outcomes of the patients with nodular goiter, who previously treated with levothyroxine for a long time and those who underwent to thyroidectomy without hormonal suppressive therapy. Unfortunately, there was no article with outcomes of studies regarding our research question.

Conclusion

Thyroid nodules smaller than 1 cm were treated with L-Thyroxine, with so-called hormonal suppressive treatment. The effectiveness of hormonal suppressive treatment is disputed in publications. Among some effects on decreasing the nodule size, L-Thyroxine has adverse effects such as a negative influence on the bone mineral density and an increase in the cardiovascular diseases risk.

Patients, with nodular goiter, should be differentiated regarding the use of hormonal suppressive therapy. The outcomes of surgical treatment of nodular goiter patients, depending on using L-Thyroxine treatment in anamnesis, are very interesting and could bring light to some issues of endocrinology. Unfortunately, literature research in PubMed and analyses of all screened articles shows that, there aren't any articles in the context of the impact of L-Thyroxine therapy on surgical management outcomes. There is need for further research on this topic to generate relevant evidence on use of L-Thyroxine.

Conflict of Interest

Authors declare no conflict of interest.

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