“CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY

BUCHAREST

DOCTORAL SCHOOL

GENERAL MEDICINE

ABSTRACT OF THE DOCTORAL THESIS

Ph.D COORDINATOR:

PROF. UNIV. DR. BADIU CORIN

Ph.D STUDENT:

STANCU ANA-MARIA

2024

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BLOCK-REPLACE THERAPY IN AUTOIMMUNE THYROID DISEASE

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- Hormone and Metabolic Research, year 2024, ahead of print, accepted on April 2nd, 2024, ISSN: 0018-5043, IF 2 (2023): **Stancu AM,** Pop O, Purice M, Badiu C. Lipid Profile Evolution in Graves' Disease Treated with Titration Regimen of Anti-Thyroid Drugs Versus Block and Replace Regimen. Horm Metab Res. 2024 Apr 2. doi: 10.1055/a-2281-0911. Epub ahead of print. PMID: 38565183. (Chapter 6)
- Endokrynologia Polska, year 2024, Volume 75, number 3, pages 317-327, ISSN: 0423-104X/ e-ISSN:2299-8306, IF 2 (2023): **Stancu AM,** Badiu C. Block-and-replace regimen versus titration of antithyroid drugs: a recent meta-analysis. *Endokrynol Pol*. 2024;0(0). DOI: 10.5603/ep.99555 (Chapter 7)

Introduction

Autoimmune thyroid disease (AITD) includes a broad spectrum of clinical manifestations that can range from hypothyroid to hyperthyroid. This autoimmune spectrum contains Hashimoto's thyroiditis (HT) at one end and Graves' disease (GD) at the opposite end. In GD the main manifestation is an excess of thyroid hormones, while chronic autoimmune thyroiditis (CAT) is characterized by the development of hypothyroidism over time. Spontaneous immunological shifts between the two conditions, although rare, are increasingly accepted.

GD remains a major cause of hyperthyroidism in areas with adequate iodine intake. It can affect individuals of any age, with the highest prevalence in the third decade of life. Women are more commonly diagnosed with GD than men.

Drug therapy is the first line of treatment for hyperthyroidism due to GD. The medication used is antithyroid drugs (ATD), the most commonly used being carbimazole (CBZ), with its active metabolite methimazole (MMI), and propylthiouracil (PTU). Administration can be done by dose titration or using a block-replace regimen, where a high dose of antithyroid drug is maintained, supplemented with levothyroxine (LT4). The duration of drug therapy, regardless of the regimen used, varies between 12-18 months. The risk of relapse is also similar in both regimens.

Although initially described by Hashizume in 1991, block-replace therapy is still considered controversial. The research aims to analyze the indications of block-replace therapy in autoimmune thyroid disease, the evolution of thyroid and lipid profiles under treatment with antithyroid drug and levothyroxine, and the impact of therapy on Graves' ophthalmopathy and thyroid volume.

Working Hypothesis and General Objectives

The use of block-replace therapy in the management of patients with autoimmune thyroid disease is controversial. The general working hypothesis involved analyzing the biochemical and hormonal profile in adult patients with newly diagnosed or relapsed GD with or without Graves' ophthalmopathy (GO), who are on antithyroid medication ± levothyroxine.

The aim of this study is to investigate the indications and impact of drug treatment in autoimmune hyperthyroidism. To this end, the evolution of thyroid and lipid profiles before the initiation of block-replace therapy and during therapy was monitored. The data were obtained to optimize drug therapy in patients with newly diagnosed or relapsed primary hyperthyroidism caused by Basedow Graves' disease (BGD).

Research Objectives:

1. **Main Objectives:**

a) The time required to normalize thyroid function under block-replace therapy or dose titration of antithyroid drug in patients with primary hyperthyroidism due to Basedow Graves' disease.

b) Identification of predictive factors that hinder thyroid function balance in patients with autoimmune hyperthyroidism under block-replace therapy or dose titration of antithyroid drugs.

c) The percentage of adverse reactions during the block-replace regimen depending on the administered medication dose.

Secondary Objectives:

a) Study the morphological evolution of the thyroid gland under block-replace therapy.

b) Evaluate the vitamin D status in patients diagnosed with BGD.

c) Assess the lipid profile of patients with hyperthyroidism due to BGD before and after the initiation of therapy.

d) Investigate the impact of synthetic antithyroid medication ± levothyroxine therapy on Graves' ophthalmopathy.

Study 1 – "Effects of block-replace regimen in patients with autoimmune hypothyroidism converted to Graves' disease" investigates the impact of block-replace therapy on the thyroid and lipid profiles in two patients with autoimmune thyroid disease. The main objective was to balance thyroid function in the medium term (3-6 months) using block-replace therapy in two cases of autoimmune conversion from hypothyroidism to clinically manifest hyperthyroidism. The evolution of antibody titers: TRAb and anti-thyroid peroxidase (anti-TPO) antibodies were

also monitored before and during block-replace therapy. Neither patient developed adverse reactions to antithyroid drug and levothyroxine therapy, with doses used within therapeutic limits and according to European and American Endocrine Guidelines. Secondary objectives included morphological description of the thyroid gland via cervical ultrasound of the two patients included in the study, determining serum cholesterol levels, LDL-cholesterol, HDL-cholesterol, and triglycerides before and during drug therapy, and ophthalmological examination by a specialist.

Study 2 – "Lipid profile evolution in Graves' disease treated with titration regimen of anti-thyroid drugs versus block and replace regimen" hypothesizes the changes in the lipid profile with thyroid function balance through drug treatment in a titration regimen of antithyroid drugs versus block-replace therapy. The main objective was to balance thyroid function through 18 months of ATD administration in a dose titration regimen or using block-replace therapy. Adverse reactions to medication and doses used were noted during therapy. The secondary objective was to compare lipid profile changes during drug therapy for Graves' disease compared to the time of diagnosis when antithyroid drug was used in a dose titration regimen versus block-replace therapy.

Study 3 – "Block-replace regimen versus titration of anti-thyroid drugs: a recent meta-analysis" hypothesizes researching differences in the literature between block-replace therapy used for treating autoimmune hyperthyroidism and conventional dose titration therapy of antithyroid drugs. The main objective was to compare the incidence of clinically developed hypothyroidism over 18 months of block-replace therapy versus dose titration of antithyroid drugs. The secondary objective was to compare the number of thyroid function tests and the incidence of Graves' ophthalmopathy between two groups of patients with Basedow Graves' disease treated with a dose titration regimen of antithyroid versus block-replace regimen.

Study 4 – "Thyroid and lipid profile values in patients with versus without Graves' ophthalmopathy" hypothesizes determining differences between the thyroid and lipid profiles in patients with Graves' disease without ophthalmopathy compared to those with Graves' ophthalmopathy. For each subgroup, the vitamin D level and prevalence of smokers were additionally studied.

Study 5 – "Thyroid volume in Graves' disease under block-replace therapy versus titration regimen" hypothesizes evaluating the impact of block-replace therapy versus ATD titration

regimen on thyroid volume over 18 months. The main objective was to determine thyroid volume before and after drug treatment using cervical ultrasound in patients treated with ATD titration versus block-replace regimen. The secondary objective was to compare the number of thyroid function tests and adverse reactions to medication in the two groups of patients with Graves' disease.

General Research Methodology

Study 1 – "Effects of block-replace regimen in patients with autoimmune hypothyroidism converted to Graves' disease", **Study 2** – "Lipid profile evolution in Graves' disease treated with titration regimen of antithyroid drugs versus block-replace regimen", **Study 4** – "Thyroid and lipid profile values in patients with versus without Graves' ophthalmopathy," and **Study 5** – "Thyroid volume in Basedow Graves' disease under block-replace therapy versus antithyroid drug titration" include patients hospitalized in the "C.I. Parhon" National Institute of Endocrinology, Endocrinology IV department, Bucharest. Study 1 presents two cases of spontaneous autoimmune conversion from clinically manifest hypothyroidism to clinically manifest hyperthyroidism, followed over a minimum period of 6 months. Study 2 includes a group of 149 patients consecutively admitted to the Endocrinology IV department, being an observational, prospective study with a duration of 18 months. Study 4 is conducted on a group of 151 patients with Basedow Graves' disease, divided based on the presence or absence of Graves' ophthalmopathy. Differences between the two subgroups are monitored regarding thyroid profile, lipid profile, vitamin D levels, and smoking prevalence. Study 5 includes 128 patients with Basedow Graves' disease under medication, with serial thyroid ultrasounds performed.

The studies were approved by the Ethics Committee of the Scientific Council of the "C.I. Parhon" National Institute of Endocrinology, Bucharest, no. 12/10.09.2021 (Appendix 1). The research methodology adhered to the provisions of the Declaration of Helsinki regarding ethical principles in human medical research. Each patient signed an informed consent before entering the research study (Appendix 2).

Study Design

- **Study 1** is a case series involving two clinical cases monitored over a period of 6 months.
- **Study 2** is an observational, prospective study with a duration of 18 months.
- **Study 4** is an observational, cross-sectional study.
- **Study 5** is also an observational, prospective study, but with a maximum duration of 6 months.

Working Method

Study 1 and **Study 2** aim to monitor the thyroid and lipid profiles of patients with Basedow Graves' disease undergoing ATD therapy in either dose titration or block-replace regimen. The research protocol includes study visits represented by consecutive hospitalizations of patients at the "C.I. Parhon" National Institute of Endocrinology, Endocrinology IV department, Bucharest, Romania. The duration of these studies is 6 months (Study 1 and Study 5) and 18 months (Study 2).

Study 4 provides additional data on patients with Graves' ophthalmopathy, while **Study 5** presents the changes in thyroid morphology due to drug therapy. The common inclusion and exclusion criteria for the studies are described below, with each study adding specific criteria detailed in the chapters dedicated to each study.

General Inclusion Criteria for the Studies:

- Age over 18 years
- Patients diagnosed with Basedow Graves' disease under medication

Exclusion Criteria for the Studies:

- Patients with Basedow Graves' disease who have undergone total thyroidectomy or radioiodine therapy
- Minor patients
- Pregnant patients with Basedow Graves' disease

For each patient meeting the inclusion criteria, the following information was obtained:

1. Informed consent in accordance with ethical standards (Declaration of Helsinki 1964)

2. Date of admission, discharge, duration and number of hospitalizations, patient's medical history
3. Demographic information: sex, age, place of origin, smoking status, alcohol consumption
4. Information about the studied pathology: newly diagnosed or relapsed cases
5. Associated comorbidities
6. Clinical parameters:
    - Reasons for hospitalization
    - Vital signs: blood pressure (BP), heart rate (HR), oxygen saturation (SaO2), body mass index (BMI, kg/m²)
7. Biological parameters:
    - Biochemical measurements (complete blood count, blood glucose, transaminases, lipid profile, creatinine), hormonal and immunological measurements (TSH, fT_4, T_3, TRAb, anti-TPO antibodies, 25 (OH) vitamin D)
8. Paraclinical investigation parameters:
    - Thyroid ultrasound: thyroid lobe dimensions, echostructure, and vascularization
9. Specialist examinations – ophthalmology, cardiology (as needed)
10. Medication at admission and discharge
11. Adverse reactions to drug therapy
12. Treatment compliance, duration of therapy, medication regimen followed, therapeutic recommendations

The data from the study visit were obtained from the anamnesis, clinical observation sheets, and the hospital's electronic database. All these data were entered into a statistical program for processing.

Laboratory Investigations

Patient monitoring was performed by measuring thyroid hormones: TSH (reference range: 0.5-4.5 mUI/L), fT_4 (9-19 pmol/L), T_3 (80-200 ng/ml), and antibody titers TRAb (reference range < 1.75 UI/mL), anti-TPO antibodies (<5.61 UI/mL). Additionally, each hospitalization included a minimum protocol: complete blood count: leukocytes (4,000-10,000/uL), hemoglobin (12-15.5 g/dl), platelets (150,000-400,000/uL), blood glucose (70-100

mg/dl), AST (5-34 U/L), ALT (0-55 U/L), total cholesterol (<200 mg/dl), HDL-cholesterol (40-60 mg/dl), LDL-cholesterol (60-160 mg/dl), triglycerides (0-149 mg/dl), and creatinine (0.5-1 mg/dl).

Each blood sample was collected from venous blood in the morning, fasting, before the administration of antithyroid medication ± levothyroxine. All blood samples were centrifuged. The determination of TSH, fT_4, and TRAb was performed using electro-chemiluminescence, while spectrophotometry was used for lipid profile determination.

Statistical Analysis

The database was created in Microsoft Excel, and the statistical processing was performed using MiniTab Statistical Software 20. Descriptive analysis was used for automatic calculation of means, medians, minimums, and maximums. To compare means between two groups, the t-Student test was applied. A p-value < 0.05 was considered statistically significant.

Study 3 – "Block-Replace Regimen versus Titration of Antithyroid Drugs: A Recent Meta-Analysis". The objective of this literature research study is to compare the incidence of clinical hypothyroidism and the development of Graves' ophthalmopathy (OG) in patients with Basedow Graves' disease treated for 18 months with antithyroid drugs (ATD) using a dose titration regimen versus block-replace therapy.

Study Design

As indicated by the title, this study is a meta-analysis conducted in August 2023, including articles published up to July 31, 2023.

Working Method

Studies were identified using two electronic databases: PubMed (MEDLINE) and the Cochrane Library (CENTRAL). The search terms used were in English: "block replace," "thyroid," and "Graves." Articles considered for analysis were those with full text available and written in English. The search was independently conducted by two authors, and any discrepancies were discussed and resolved.

Inclusion Criteria:

- Prospective or retrospective cohort studies with a duration of 18 months.
- Studies that include newly diagnosed GD patients or relapsed GD patients treated with ATD using either dose titration regimen or block-replace therapy.
- Studies that include patients aged over 18 years.
- Block-replace therapy defined as the concomitant administration of ATD and LT_4.

Exclusion Criteria:

- Studies written in a language other than English or not available in full text.
- Studies including minor patients, pregnant patients, radioiodine-treated patients, or those who have undergone total thyroidectomy.
- Studies where block-replace therapy involved the combination of ATD and T_3.
- Studies that did not investigate the incidence of hypothyroidism or the development of GO during medication therapy in GD patients.

Data extraction (authors' names, year of publication, article titles, etc.) was automatically performed using the Reference Manager software. Adhering to the inclusion and exclusion criteria, two authors independently reviewed the remaining articles. Each author entered information into the database, such as the number of patients included in the studies, patient age, sex, diagnosis, treatment method, incidence of hypothyroidism, and incidence of GO during medical therapy. Missing data were obtained from letters to the editor and by consulting guidelines for the diagnosis and treatment of autoimmune hyperthyroidism.

For each article included in the meta-analysis, the risk of bias was calculated using the Newcastle-Ottawa scale (Appendix 3). This scale assesses three criteria: selection, comparability, and outcomes. A score above seven indicates high study quality.

Statistical Analysis

The statistical analysis was performed using Review Manager 5.4 software. Dichotomous data were expressed as Mantel-Haenszel (M-H) odds ratios (OR) with 95% confidence intervals

(CI) using a random-effects model. Continuous variables were expressed as mean difference or adjusted mean difference. Heterogeneity among the studies was evaluated by visual inspection of the forest plot and calculation of the I^2 statistic. An I^2 value greater than 75% indicates high heterogeneity, while a value less than 25% indicates low heterogeneity. Subgroup analysis was not utilized.

Conclusions and Personal Contributions

Study 1 - Effects of Block-Replace Regimen in Patients with Autoimmune Hypothyroidism Converted to Graves' Disease (Case Series and Literature Review)

The prevalence of conversion from hypothyroidism to hyperthyroidism is estimated at 1.2% of patients[1,2]. This case series presents two adult patients who developed autoimmune hyperthyroidism many years after being diagnosed with clinical hypothyroidism.

Similar to this study, most patients were initially diagnosed with hypothyroidism due to Hashimoto's thyroiditis (HT). Upon discontinuing LT_4 therapy, the patients were diagnosed with Graves' disease (GD) with hyperthyroidism. Furquan et al. reported three similar cases involving middle-aged Asian women[3]. Ahmad et al. described a case with a 27-year interval before the onset of hyperthyroidism[4]. Additionally, Fan et al. presented a case of a 51-year-old female oscillating between clinical hypothyroidism and hyperthyroidism[5]. Takasu et al. documented a case series of eight patients who, after several months or years of levothyroxine treatment, developed persistent hyperthyroid symptoms following cessation of the replacement therapy[6]. Watari et al. reported a similar case, although the patient had a history of hepatitis C and HIV infection[7]. Hyperthyroid patients were treated with antithyroid drugs (ATDs). Bando described the first case of conversion from hypothyroidism to hyperthyroidism associated with thyroid hemiagenesis, treated with methimazole (MMI) and LT_4 [8]. Clifford and Wakil opted for surgical intervention as their patient developed agranulocytosis on a daily dose of 25 mg carbimazole (CBZ)[9]. Gerges et al. recommended radical treatment (radioiodine therapy or thyroidectomy) for two cases of conversion from hypothyroidism to hyperthyroidism[1].

The two cases from the endocrinology department were advised to undergo medication treatment with antithyroid drugs, initially with different regimens—block-replace for the first

case and dose titration for the second case. Eventually, the second case was also recommended the block-replace regimen to achieve euthyroidism and improve Graves' ophthalmopathy (GO).

The mechanism underlying the conversion from hypothyroidism to hyperthyroidism remains unclear. One theory is supported by the activity of thyroid antibodies. Hashimoto's thyroiditis (HT) is characterized by elevated antithyroid peroxidase (anti-TPO) antibodies, leading to thyroid gland destruction and permanent hypothyroidism. In Graves' disease (GD), TSH receptor antibodies can either stimulate or inhibit the thyroid gland[3]. Hyperthyroidism occurs when thyroid-blocking antibodies (TBAb) convert to thyroid-stimulating antibodies (TSAb). This conversion can be spontaneous or triggered by external factors such as infections or a history of cervical irradiation in genetically susceptible patients[1,4]. TBAb converted to TSAb can also be triggered by LT_4 treatment[5]. In this case series, no external triggering factors were identified, but both patients had strongly positive anti-TPO antibodies titers and developed hypothyroidism, necessitating LT_4 treatment. Before developing thyrotoxicosis, Case 1 had been on the same dose of LT_4 for several years. Case 2 became hyperthyroid within months of initiating LT_4 therapy. Despite discontinuing LT_4 treatment, thyroid-stimulating hormone (TSH) remained suppressed, and the patients developed exophthalmos. Both patients had elevated TRAb titers. The limitations of this case report were the inability to determine TSAb and TBAb during the periods of hypothyroidism and hyperthyroidism. The exact cause of conversion between hypothyroidism and hyperthyroidism is unknown, and further studies are needed to elucidate the pathogenesis of this phenomenon.

Study 2 -Lipid Profile Evolution in Graves' Disease Treated with Titration Regimen of Antithyroid Drug versus Block and Replace Regimen

A total of 160 patients with Graves' disease (GD) undergoing treatment with methimazole (MMI) ± levothyroxine (LT_4) were included in the study. Statistical analysis excluded six non-compliant patients and five patients who switched to propylthiouracil (PTU) (one pregnant woman, three patients who developed severe erythema on the thorax and limbs, and one patient who developed cholestasis on 60 mg of MMI per day). The remaining 149 patients were divided into two subgroups (A and B) based on the medication regimen used: dose titration of antithyroid drugs (ATDs) and block-replace therapy.

Both subgroups had similar values of TSH suppression and increased fT_4 levels at diagnosis. Patients treated with the ATD dose titration regimen had a higher mean TRAb value at diagnosis compared to those in the block-replace therapy group. This can be explained by the fact that more patients with relapsed GD were included in subgroup B and had previously received ATD therapy. Both subgroups had low total cholesterol levels at GD diagnosis, which increased during hyperthyroidism treatment. The subgroup treated with ATD dose titration initially had lower cholesterol levels than the block-replace therapy subgroup. After starting therapy, subgroup A experienced a significant increase in total cholesterol, LDL-cholesterol, and HDL-cholesterol. In this study, total cholesterol increased by 43.24 mg/dl, LDL-cholesterol by 29.19 mg/dl, and HDL-cholesterol by 10.76 mg/dl in patients treated with MMI alone, with $p < 0.001$. Conversely, the block-replace therapy subgroup had higher cholesterol levels at diagnosis. Despite this, cholesterol levels only increased for total cholesterol and LDL-cholesterol, with a smaller increase than in the ATD dose titration subgroup. The block-replace regimen did not affect HDL-cholesterol levels, and the increase in total cholesterol and LDL-cholesterol was 35.24 mg/dl and 26.09 mg/dl, respectively, with $p < 0.001$. The increase in cholesterol levels during therapy was smaller in the block-replace therapy subgroup compared to the dose titration subgroup, even when comparing the cholesterol values of euthyroid patients at diagnosis and during therapy.

In this study, the antithyroid drug (ATD) used was MMI, with no statistically significant differences between the two subgroups regarding the average daily dose of the drug. Minor adverse reactions were described. Only 1.87% (3/160) of patients experienced rashes at a dose of 40 mg/day of MMI, and 0.62% (1/160) of patients developed cholestasis at a dose of 60 mg/day of MMI. One patient in the study incorrectly took 100 mg of MMI daily for 2 weeks, fortunately without severe adverse reactions.

Treatment of hyperthyroidism is associated with a significant worsening of the lipid profile. In a systematic review by Kotwal, total cholesterol increased by 44.5 mg/dl (95% CI: 37.99-51.02), LDL-cholesterol by 31.13 mg/dl (95% CI: 24.33-37.39), and HDL-cholesterol by 5.52 mg/dl (95% CI: 1.48-9.56), with no statistically significant difference in triglyceride levels[10]. Sauter et al. observed that only total cholesterol and LDL-cholesterol increased following hyperthyroidism treatment. Patients treated with synthetic antithyroid drugs increased their total cholesterol and LDL-cholesterol by 27% and 39%, respectively, with a p-value < 0.01

in both cases[11]. O'Brien et al. demonstrated that once hyperthyroidism is treated, the total cholesterol/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol ratios increase[12]. Another study showed that adding antioxidant supplements to antithyroid drug treatment in patients with newly diagnosed Graves' disease did not significantly affect total cholesterol or HDL-cholesterol levels[13].

The block-replace regimen is recommended for patients who require fewer thyroid function tests and those who experience fluctuations in thyroid function during medication therapy[14,15]. It may also be considered a first option for patients with newly diagnosed or recurrent hyperthyroidism[15]. Remission rates are similar for patients treated with dose titration versus those on a block-replace regimen for 12-18 months[16]. Numerous risk factors for predicting Graves' disease (GD) relapse, such as smoking, ophthalmopathy, levels of fT_4 and TRAb, increased thyroid volume, and iodine contamination from contrast agents, have been involved in this process[17,18]. The Graves' Recurrent Events after Therapy (GREAT) score, which includes age, fT_4 levels, thyroid-stimulating hormone receptor antibody (TBII) levels, and goiter size, has shown good external validation in assessing the risk of relapse[19]. A GREAT+ score can be used by adding genetic testing[20]. In our study, TBII measurement was not feasible. According to a meta-analysis by X. Jiang et al., polymorphism of the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) gene is associated with the risk of GD relapse in Caucasian patients after discontinuation of antithyroid therapy[21].

Despite high relapse rates, antithyroid drugs (ATDs) are the first-line treatment for GD in Europe. The most commonly used ATD is MMI (79.3%), followed by carbimazole (CBZ) (17.9%) and PTU (2.9%). Typically, the initial dose is 20-30 mg of MMI per day, equivalent to 40 mg of CBZ per day[22]. These drugs have immunosuppressive effects and inhibit the synthesis of T_3 and T_4.[23] In the literature, ATD doses used in the block-replace regimen have been up to 100 mg of CBZ per day[14,24]. As a result, the incidence of adverse reactions was higher than in the dose titration regimen, with an incidence of agranulocytosis at 12%.[24]

By balancing thyroid and lipid profiles, complications of GD, such as exacerbation of ophthalmopathy or severe hypothyroidism, can be avoided. Sabini et al. found a correlation between total cholesterol and LDL-cholesterol levels and the development of ophthalmopathy in patients with newly diagnosed GD (less than 44 months). Total cholesterol and LDL-cholesterol values above 191 mg/dl and 118.4 mg/dl, respectively, were associated with the presence of

ophthalmopathy.[25] Patients with ophthalmopathy also had higher LDL-cholesterol values compared to those without ophthalmopathy (135.3±42.3 mg/dl versus 106.6±23.9 mg/dl)[26]. Therefore, the protective role of statins in patients with ophthalmopathy appears promising[27].

Study 3 – Block and Replace Regimen versus Titration of Antithyroid Drugs: A Recent Meta-Analysis

Incidence of Clinical Hypothyroidism

There was no statistically significant difference between the two ATD regimens regarding the incidence of clinical hypothyroidism during the 18 months of treatment (M-H OR 1.54, 95% CI: 0.75 - 3.16, p=0.24) (Figure 7.2A). Only 8.3% (24/289) of patients treated with block-replace therapy developed clinical hypothyroidism compared to 3.98% (17/427) of patients on dose titration regimens.

Prevalence of Euthyroidism

Patients with Graves' disease (GD) on block-replace therapy were less likely to achieve euthyroidism compared to patients on ATD dose titration regimens (M-H OR 0.55, 95% CI: 0.34-0.88, p=0.01) (Figure 7.2B). In this statistical analysis, all patients who achieved euthyroidism, as well as those with subclinical hypo- or hyperthyroidism, were considered to have achieved control of hyperthyroidism due to GD.

Number of Thyroid Function Tests During Medication Therapy

The number of thyroid function tests during medication therapy was evaluated in one study. Patients treated with block-replace had an average of 3.2±1.2 thyroid function tests per year, while patients on ATD dose titration required 3.4±1.5 tests per year, with an adjusted mean difference of -0.4 (95% CI: -0.7; -0.1), p=0.008.[28]

Incidence of Ophthalmopathy Development During ATD Therapy

Both studies included patients without ophthalmopathy at diagnosis. There was no statistically significant difference in the incidence of ophthalmopathy development during block-

replace therapy compared to ATD dose titration (M-H OR 1.18, 95% CI: 0.20-7.06, p=0.86) (Figure7.2C).

When analyzing only the study that specifically excluded patients with ophthalmopathy at diagnosis, the incidence of ophthalmopathy during block-replace therapy was lower than during dose titration therapy (9.1% vs. 17.8%), though the difference was not statistically significant (M-H OR 0.47, 95% CI: 0.19-1.14, p=0.10) (Figure 7.2D).

This meta-analysis included two observational cohort studies. Participants with GD were either on block-replace therapy or on ATD dose titration. No difference in the incidence of hypothyroidism between the two treatment regimens was observed. Neither study reported the dose of ATDs used. According to a systematic review by Abraham et al., CBZ was used in doses of 30-60 mg/day, with only one study using up to 100 mg/day[24]. Current guidelines recommend an initial dose of CBZ 40 mg/day, MMI 30 mg/day, or PTU 50-150 mg three times a day[15,29].

This study indicated a lower probability of achieving stable thyroid function with block-replace therapy compared to dose titration. This result had low GRADE quality evidence, and further studies are needed. The first reason for the low evidence quality is the inclusion of patients with euthyroidism, hypo-, and subclinical hyperthyroidism in the estimate of stable thyroid function. Secondly, in the retrospective cohort study, there were more patients in the block-replace subgroup with complicated GD at initial evaluation compared to the dose titration subgroup. This is consistent with literature where block-replace therapy is an option for patients with fluctuating thyroid hormones[5]. Lewandowski et al. described an atypical presentation of GD in a 31-year-old patient who presented with an acute myocardial infarction. She achieved hyperthyroidism control through block-replace therapy[30]. Additionally, block-replace therapy may be preferred in patients with limited access to healthcare due to fewer thyroid function tests required during treatment[15,28].

The development of ophthalmopathy during block-replace therapy compared to ATD dose titration was evaluated in one study. The incidence of ophthalmopathy was lower in the block-replace subgroup compared to the dose titration group, though the difference was not statistically significant[28]. No other studies investigating this aspect were found. The second study did not report the proportion of patients with ophthalmopathy at diagnosis. However, more patients with extra-thyroidal manifestations of GD were treated with block-replace therapy. In the block-replace group, 15.5% of patients had ophthalmopathy and 2.8% had dermopathy

compared to 6.3% and 1.4%, respectively, in the dose titration group[31]. The results of both studies have very low evidence quality. Further studies are needed to assess whether block-replace therapy is a protective factor against the development of ophthalmopathy.

No studies were found comparing the effects of using ATDs in different regimens on metabolism.

Study 4 – Thyroid and Lipid Profile Values in Patients with versus Without Graves' Ophthalmopathy

In this study, the proportion of patients with Graves' ophthalmopathy (GO) was higher than values reported in the literature. This may be explained by the study being conducted at a tertiary endocrinology center. However, this is not unusual, as similarly high proportions have been reported in other studies. Additionally, the study included more patients with moderate-severe and severe forms of GO. No statistically significant differences were found between the subgroups with GO (+) and GO (−) in terms of patient age, presence of dyslipidemia, or statin use. On the other hand, the proportion of smokers was higher in the GO (+) subgroup compared to the GO (−) subgroup.

When comparing thyroid hormone levels between the two subgroups, no statistically significant differences were found. However, when comparing the number of patients with fT_4 < 8 pmol/L, the proportion of hypothyroid patients was higher in the GO (+) subgroup. The mean fT_4 was also lower in patients with moderate-severe and severe GO compared to those with mild forms. The TRAb levels were higher in the GO (+) subgroup than in the GO (−) subgroup, but this difference was not statistically significant.

In this study, the proportion of patients treated with antithyroid drugs (ATDs) under a titration regimen was similar to those treated under a block-replace regimen in both subgroups. However, the average dose of LT_4 used in the GO (+) subgroup was statistically significantly higher than that used in the GO (−) subgroup. The dose of MMI was similar in both subgroups.

No statistically significant difference was found in cholesterol levels between patients with GD with or without GO. The duration from the diagnosis of hyperthyroidism to inclusion in the study was greater than 44 months. However, a statistically significant difference was

observed between the mean triglyceride levels of patients with mild GO compared to those with moderate-severe and severe forms.

Additionally, there were more patients with vitamin D deficiency (25(OH) vitamin D < 20 ng/ml) in the GO (+) subgroup compared to the GO (−) subgroup. Further studies are needed to determine the role of vitamin D in the development and progression of GO.

Graves' ophthalmopathy is a sight-threatening condition, affecting approximately 25% of patients with Graves' disease[23,32]. Treatment for GO involves both general measures (local treatment, smoking cessation, maintaining euthyroidism) and specific measures (corticosteroids, orbital radiotherapy, surgery, selenium, rituximab, tocilizumab, teprotumumab, mycophenolate)[32,33]. Recent findings suggest that patients with hyperthyroidism due to Graves' disease who are treated with statins have a lower risk of developing GO. Elevated total cholesterol levels are also correlated with the presence of GO in patients with Graves' disease[34]. Similar results have been found for LDL cholesterol[26]. Other risk factors for the occurrence and progression of GO in patients with Graves' disease include smoking, advanced age, and male sex[35].

Sabini et al. compared cholesterol levels in 133 patients with GO to 117 patients without GO admitted consecutively to a tertiary endocrinology center. No statistically significant difference in cholesterol profiles between patients with GO versus those without GO was found. After statistical correction for symptom duration < 44 months, a correlation between elevated total cholesterol and LDL-cholesterol levels and the presence of GO was observed[25]. Lanzolla et al. highlighted the relationship between cholesterol levels and the presence of GO. Total cholesterol and LDL cholesterol levels were higher in patients with GO compared to those without GO: 211.6 ± 44 mg/dl versus 176 ± 27.2 mg/dl, p=0.0001, and 135.3 ± 41.3 mg/dl versus 106.6 ± 23.9 mg/dl, p=0.0007, respectively[26]. Bartalena et al.'s study on GO prevention showed a higher proportion of smokers in the GO group[36]. According to Naselli et al., thyroid dysfunction and elevated TRAb levels negatively correlate with GO[37]. Prummel et al. demonstrated that thyroid dysfunction correlates with a more severe form of GO[38]. TRAb levels are considered useful in predicting the risk of developing GO in newly diagnosed Graves' disease patients and are included in the PREDIGO score[20].

Block-replace therapy may be beneficial for patients with Graves' disease and GO, with fluctuating thyroid function, or for those requiring fewer hospital visits[14,28]. Duntas suggested

that ATD dose titration could be used as first-line therapy, and block-replace therapy may be a safe alternative option in selected cases of Graves' disease[39]. During the COVID-19 pandemic, block-replace therapy was proposed as a first-line treatment for newly diagnosed or relapsed hyperthyroidism[15].

Vitamin D deficiency has been studied as a risk factor for the development of GO[40].

Management of Graves' ophthalmopathy is complex and involves both general measures, such as maintaining euthyroidism, and specific measures, including glucocorticoid therapy, orbital radiotherapy, surgery, or immunological therapies. Risk factors such as smoking, hypothyroidism, elevated lipid profiles, and vitamin D deficiency can affect disease progression, making the identification and correction of these factors important.

Study 5 – Thyroid Volume in Graves' Disease Under Block-Replace Therapy versus Antithyroid Drug Titration

Regardless of the regimen used—block-replace or antithyroid drug (ATD) titration—the thyroid volume slightly decreased after 6 months of treatment for Graves' disease (GD), though this change did not reach statistical significance.

Patients treated with block-replace therapy had a larger thyroid volume compared to those treated with ATD titration, despite minimal variations in thyroid function. However, the block-replace subgroup had a higher incidence of Graves' disease relapse. Literature data support that patients prone to relapse after 12-18 months of ATD treatment, regardless of the regimen used, are those with large goiters at diagnosis, elevated fT_4 and TRAb levels. These characteristics, along with young age (< 40 years), comprise the Graves' Recurrent Events After Therapy (GREAT) score[19].

The lower doses of ATDs used in the block-replace subgroup and the lower TRAb values compared to the titration regimen subgroup can be explained by the higher percentage of patients who experienced a relapse in the block-replace group. These patients had previously undergone 12-18 months of ATD treatment that reduced TRAb titers but did not normalize them. Razvi et al. concluded in their meta-analysis that block-replace therapy might be reserved for difficult cases where maintaining euthyroidism is not possible with ATD titration alone or in cases of GD

relapse. Additionally, patients with fluctuating thyroid function under ATD or complicated GD may be candidates for block-replace therapy[14].

Thyroid volume calculation was in line with literature data using the ellipsoid formula. Thyroid ultrasound is an operator-dependent paraclinical investigation. The study aimed to minimize this risk by having a single operator perform all thyroid ultrasounds. For thyroid volume calculation, the maximum diameters of each thyroid lobe were used in the formula, with a correction factor of 0.5233 applied.

Literature indicates that untreated GD patients present with goiter, and on ultrasound, the thyroid appears hypoechoic with increased vascularization. According to R. Vita et al., thyroid volume is greater in men compared to women: 37.1 ± 15.7 ml vs. 22.1 ± 12.9 ml, p=0.01. Furthermore, greater thyroid volume correlates with increased gland vascularization. Increased thyroid vascularization is associated with marked hypoechogenicity and elevated fT_4 and TRAb levels.[41]

A study by A. Brancatella found that patients with severe lymphocytic infiltration of the thyroid had a larger thyroid volume compared to those with mild infiltration: 37.8 ml vs. 25.6 ml, p=0.06.[42]

Ultrasonographic measurement of thyroid volume plays a significant role in managing GD cases, being proposed as a predictive factor for disease relapse risk[17]. Thyroid gland with volumes 2.5 times above the upper limit of normal are associated with a higher risk of GD relapse after medical therapy[43].

Vascularization of the thyroid is crucial both in diagnosing GD and managing the disease. The median value of the vascular index in GD patients is significantly higher compared to healthy subjects: 12 (2.3-32.1) vs. 5.04 (1.1-10.8), p<0.001. When a threshold value of 6.3 is established, GD can be diagnosed with a sensitivity of 83.8% and specificity of 70%[44]. After 12-18 months of medical therapy, when TSH and TRAb values are normalized, discontinuation of therapy is recommended[45]. Thyroid vascularization at the end of 12-18 months of ATD treatment can guide therapeutic decisions when TRAb values are unavailable.

Block-replace therapy using modest doses of ATDs (methimazole 30 mg/day or carbimazole 40 mg/day) may be an option for selected cases. Patients with complicated GD, those with difficult access to healthcare, or those unable to undergo repeated thyroid function tests are candidates for block-replace therapy[14,15,28,46].

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