PROTOCOL OF A THESIS FOR PARTIAL FULFILMENT OF MASTER DEGREE IN ENDOCRINOLOGY

Title of the Protocol: The impact of Mediterranean Diet on patients with Hashimoto Thyroiditis

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What is already known on this subject? And what does this study add?
Hashimoto's thyroiditis (HT) is an autoimmune disease affecting the thyroid gland, and is one of the most common causes of hypothyroidism. Eating habits may affect the risk of several inflammatory and immune diseases as HT. The current knowledge of the diet in HT is insufficient **(Mikulska et al., 2022)**. The Mediterranean diet (MD) is an anti-inflammatory diet characterized by frequent consumption of olive oil, unrefined cereals, fresh or dried fruit and vegetables, moderate amounts of fish, dairy and meat, and many condiments and spices. It is rich in nutrients and bio actives which have the potential to offer anti-inflammatory aspect **(Forsyth et al., 2018)**. This study aims to assess MD as a dietary intervention in HT patients.

1. INTRODUCTION/ REVIEW

Hashimoto's thyroiditis (HT) is the most frequent autoimmune thyroid disorder. It is the leading cause of hypothyroidism in the iodine-sufficient areas of the world. Pathogenesis of the disease is thought to be a combination of genetic susceptibility and environmental factors that lead to the loss of immunological tolerance, with a consequent autoimmune attack to the thyroid tissue and appearance of the disease**(Ragusa et al., 2019).** There is growing evidence of the existence of a thyroid–gut axis that controls many autoimmune disorders, and patients frequently report changes in their quality of life and thyroid function as a result of dietary modifications **(Danailova et al., 2022).**

The pathologic features of lymphocytic infiltration, especially of T cells, and follicular destruction are the histological hallmark of autoimmune thyroiditis (AIT), that lead to gradual atrophy and fibrosis. An important role in the immune-pathogenesis of AITDs is due to inflammatory chemokines and cytokines **(Ragusa et al., 2019).** HT is associated with various thyroid functional states ranging from euthyroid, subclinical to overt hypothyroidism. The most common lab findings demonstrate elevated thyroid-stimulating hormone (TSH) and low

thyroxine (T4) levels, coupled with increased antithyroid peroxidase (anti-TPO) antibodies **(Caturegli et al., 2014).**

Weight gain is frequently the first symptom of hypothyroidism. Research has shown that even when HT patients achieve an euthyroid state, 82% of women treated still have excess body weight, and 35% of them suffer from obesity **(Danailova et al., 2022).** Additionally, euthyroid individuals with HT continue to suffer from symptoms, such as chronic fatigue, dry skin, hair loss, chronic irritability, and nervousness, impairing quality of life **(Ott et al., 2011).**

There is mounting evidence for the existence of a robust thyroid–gut axis. It is reflected by a significant influence of the intrinsic bacterial microflora in the gut on the immune system reactivity and the thyroid function. Dysbiosis may significantly impair the immune system and compromise inflammatory control, causing autoimmune illnesses such as autoimmune thyroid diseases **(Knezevic et al., 2020).** Dysbiosis can also directly affect thyroid hormone levels due to bacterial deiodinase activity and TSH inhibition **(Golan et al., 2013).**

The premise behind an anti-inflammatory diet as MD is that oxidative stress may be a significant risk factor in the pathogenesis and progression of HT and the development of complications. Therefore, appropriate lifestyle changes should be implemented, including diet and body weight normalization to reduce oxidative stress in these patients. Some vitamins, such as vitamin A, E, or C, and minerals, including Se, which are found in fresh and raw foods, exhibit antioxidant properties. Frequent consumption of these foods reinforces antioxidant defense mechanisms **(Bjørklund & Chirumbolo, 2017).**

For most HT patients, the hormone-replacement therapy with levothyroxine is indispensable. Nevertheless, an appropriate dietary regimen and ecological lifestyle can complement the standard treatment and favor remission of HT by improving the function of the thyroid gland, as well as by regulating the levels of TSH, T3, T4, anti-TPO antibodies. There is still no specific diet recommended for patients with HT, but an anti-inflammatory diet may help HT patients to reduce the need for medicines, slow down the course of the disease, and avoid relapses **(Ihnatowicz et al., 2020).**

Mediterranean diet (MD) is one of the most common anti-inflammatory diets. It is characterized by a large consumption of fruit, vegetables, legumes, nuts, fish, complex carbohydrates, and extra virgin olive oil (EVOO), and a low intake of processed meats, red meats, and sweets. The MD pattern provides a small amount of saturated fatty acid and a high quantity of antioxidants and fiber derived from fruits, vegetables, and EVOO **(Bellastella et al., 2022).** It is conceivable that adoption of this dietary pattern could be protective against HT, counteracting the deleterious effects of oxidative stress and exerting anti-inflammatory and immunomodulatory actions, most likely by affecting cytokine production and gut microbiota composition **(Ruggeri et al., 2021).**

Goitrogens refer to a group of micronutrients that can cause enlargement of the thyroid gland. It includes two main categories which are cruciferous vegetables and soy products. Goitrogens have been shown to inhibit thyroid hormones synthesis in several ways, mostly by inhibiting iodine utilization. Those micronutrients have to be taken in consideration specially in those with thyroid diseases or who are iodine deficient **(Babiker et al., 2020)**.

2. AIM/ OBJECTIVES

This study aims to assess the impact of Mediterranean diet on patients with Hashimoto thyroiditis using the following outcomes:

Primary outcomes: Anti-TPO antibodies, Anti-Thyroglobulin antibodies, TSH, T3, T4

Secondary outcomes: BMI, Lipid profile, Symptoms of hypothyroidism

3. METHODOLOGY:

Patients and Methods/ Subjects and Methods/ Material and Methods

- All participants will be subjected to an interview questionnaire including data pertaining name, age, sex, occupation, past medical history, 24 hours dietary recall, general clinical examination, anthropometric measures of weight, height, BMI, and biochemical Investigations including Lipid profile (Cholesterol/HDL ratio, triglycerides), HbA1C, TSH, free T3, free T4, Anti-TPO, Anti-Thyroglobulin.
- **Type of Study:** single-arm open label clinical trial
- **Study Setting:** Outpatient clinics of Ain Shams University hospitals, Cairo, Egypt.
- **Study Population:** this study will be conducted on patients with HT
- ***Inclusion Criteria:***

    1. - Female and male patients with HT diagnosed by a combination of clinical features of hypothyroidism and presence of anti-thyroid antibodies.
    2. - Age from 20 to 50 years old

- ***Exclusion Criteria:***

    1. -Pregnant or lactating females
    2. -Age below 20 years and above 50 years
    3. -presence of any other medical disorder

-Pre-intervention Baseline assessment:

1. Anti-TPO
2. Anti-Thyroglobulin
3. TSH, free T3, free T4
4. BMI (measured in kg/m^2)
5. Lipid profile (Total Cholesterol, HDL, LDL, Triglycerides)
6. HBA1C, Fasting Blood Sugar, 2 hours Post Prandial
7. CBC
8. ESR

9. Levothyroxine dose needed to reach euthyroid state

- **Intervention:**

The Mediterranean diet MD provides close to 30% energy from total fat (19% from MUFA, 5% from PUFA, 9% from SFA), 15% from protein and 55% energy from carbohydrate (Davis et al., 2015).

The daily caloric requirements of each individual will be set according to the age, and physical activity of the patient as per the tables in the Dietary Guidelines of the Americans, published by the United States Department of Agriculture (USDA, 2015-2020).

Reducing dietary goitrogens will be put into consideration when making meal plans.

At first there will be group sessions of 5-7 patients for 2-3 hours where Mediterranean diet and exchange lists will be explained. Then there will be a one to one (doctor to patient) 1 hour session where the 90 days program will be tailored individually to meet the nutritional requirements, food preferences and socioeconomic status of each patient. The patients will be given handouts displaying the caloric content of foods and the different exchange lists.

For the first four weeks of the program, there will be weekly 2 hour sessions. The first hour will be a group meeting where they can gain support from each other and common concerns can be clarified. Then a 1 hour one to one session will be held.

Adherence of participating cases to the diet regimen will be assessed through the recording in their handouts. Any complaint will be recorded and dealt with and any necessary modifications made.

Pre-intervention clinical and laboratory assessment done at 0 months, will be repeated at 3 months

- **Study intervention period:** 3 months
- **Outcome:**

measurement of:

1. Anti-TPO

2. Anti-Thyroglobulin
3. TSH, Free T3, Free T4
4. BMI
5. Lipid profile (Total Cholesterol, HDL, LDL, Triglycerides)
6. Levothyroxine dose needed to reach euthyroid state
7. CBC (to check for adverse events as anemia)
8. ESR

- **Sample Size:** Using the G power program for sample size calculation, setting power at 80% alpha error at 5%, reviewing results from previous studies (Danailova et al, 2022, and Bellastella et al, 2022) showed that HT patients showed a high intake of animal proteins, saturated fats, and refined sugar-in other words, the prototype of the so-called Western-type diet, in contrast with the Mediterranean one. Also, intake of the Mediterranean diet is associated with improving symptoms, assuming an effect size difference =0.5 regarding AB levels before and after dietary intervention and after a 10% adjustment for dropout rate, a sample size of at least 40 patients will be needed.
- **Sampling Method:** Convenience sampling such as that all male and female patients with HT will be invited to join the Mediterranean Diet regimen. Those who agree to participate and provide a written informed consent will be enrolled in the study.
- **Adverse events:** Possible adverse events in terms of anemia or disturbance of lipid profile will be assessed at 3 months and the patient withdrawn from the study if they occur.
- **Ethical Considerations:** A written informed consent will be obtained from each patient before enrolment in this study.

Statistical Analysis: Data will be collected and entered into the software and edited for errors Data were expressed as median and interquartile range. Analytical statistics were done using the Wilcoxon rank test and Spearman correlation test. The Wilcoxon rank test was used to compare parameters expressed in median and IQR pre- and post-intervention. The Spearman

correlation test was used to measure the direction and strength of association between different study parameters. The P-value was used to measure the level of significance, where P > 0.05: non-significant (NS), P < 0.05: significant (S), and P < 0.01: highly significant (HS).

- **software to be used:** SPSS (Statistical Package for Social Sciences) version 20 will be the statistics software to be used. Citation of SPSS: IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

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