KULA, Paula, HABER, Mateusz, CZACHOR, Adrianna, KUCY, Natalia, KOTULA, Alicja, GRELEWICZ, Olga, SERVAAS, Elwira, JUŚKIEWICZ, Adam and SIEMIĄTKOWSKI, Robert. How to Choose the Best Treatment Strategy for Graves' disease – Cooperation Between Doctor and Patient. Quality in Sport. 2024;26:54944. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.26.54944
https://apcz.umk.pl/QS/article/view/54944

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 05.09.2024. Revised: 19.09.2024. Accepted: 12.10.2024. Published: 14.10.2024.

How to Choose the Best Treatment Strategy for Graves' disease – Cooperation Between Doctor and Patient

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ABSTRACT

Graves' disease (GD) is an autoimmune thyroid disease characterized by hyperthyroidism, enlarged thyroid gland, and ophthalmopathy. It is the most common cause of hyperthyroidism, especially in middle-aged women. The pathological mechanism involves the production of antibodies against the TSH receptor (TRAbs), which leads to uncontrolled stimulation of the thyroid gland and excessive production of thyroid hormones.

This study examined optimal treatment strategies for Graves' disease, emphasizing the critical role of physician-patient collaboration. The paper discusses the clinical aspects of Graves' disease, focusing on the recurrent nature of the disease with periods of exacerbations and remissions. Additionally, attention is drawn to the commonly associated disease: orbitopathy, which may lead to permanent damage to the orbital tissues, eye movement disorders, deterioration of visual acuity, and even blindness.

The paper presents current therapeutic approaches, including pharmacotherapy, radioactive iodine treatment and surgical interventions. It emphasizes the importance of personalized treatment plans and the need for regular monitoring to minimize the risk of complications. This study emphasizes active patient involvement in treatment decisions to determine the most effective treatment strategy for Graves' disease, improving patient outcomes and quality of life.

Key words: Graves’ disease, hyperthyroidism, treatment, thyroidectomy, radioiodine, antithyroid drugs

INTRODUCTION

Graves' disease (GD) is an autoimmune disorder that impacts the thyroid gland. It is characterized by the excessive production of thyroid hormones, caused by the uncontrolled stimulation of the thyroid gland by TSH receptor antibodies in the bloodstream [22,35]. It is the leading cause of hyperthyroidism and thyrotoxicosis. This condition can lead to a

spectrum of symptoms including weight loss, tachycardia, heat intolerance, and ophthalmopathy, which significantly impact the quality of life. Therefore, it is very important for all healthcare professionals to delve deeper into the pathophysiology of the disease, diagnostic techniques, treatment methods and relapse prevention strategies. This makes it possible to provide patients with Graves' disease with the best and most accurate care [34,36].
The management of Graves' disease is challenging due to the chronic nature of the disease, the variability in patient response to treatment, and the potential for significant side effects associated with therapeutic interventions. It requires a careful balance between therapeutic efficacy and the minimization of adverse effects, making patient engagement and tailored treatment strategies imperative. The primary treatment options for Graves' disease include antithyroid drugs (ATDs), radioactive iodine therapy (RAI), and thyroidectomy. Each treatment modality presents distinct benefits and risks, necessitating a tailored approach based on individual patient characteristics and preferences. The decision-making process for selecting the most appropriate treatment for Graves' disease is complex and should ideally involve a collaborative approach between the physician and the patient [7].

Aim of the Study

The aim of this study is to present various forms of treatment for Graves' disease and to identify the most effective strategies. Our goal is to underscore the importance of a collaborative approach between doctors and patients in the decision-making process, thereby ensuring that treatment plans are tailored to meet individual patient needs and preferences.

Materials and Methods

For this review, we conducted searches across multiple databases, including PubMed, Elsevier, Medline, and Google Scholar, to identify scientific literature with the most recent knowledge on the pathophysiology, clinical presentation, diagnostic methods, and treatment strategies for Graves' disease. We used keywords such as 'Graves' disease', 'hyperthyroidism', 'thyroidectomy', 'radioiodine' and 'antithyroid drugs'. Only articles written in English were considered. The selected studies were carefully reviewed for their relevance to the topic of this review.

CURRENT STATE OF KNOWLEDGE

Pathophysiology

Graves' disease (GD) is an autoimmune disease that primarily affects the thyroid gland, leading to hyperfunction of the organ and, consequently, hyperthyroidism. The pathophysiology of GD is complex and involves both genetic predisposition and environmental factors. The key element of this disease is the production of immunoglobulins - autoantibodies that mimic the action of thyroid-stimulating hormone (TSH) and bind to the TSH receptor on thyroid cells, causing uncontrolled activation of these receptors. This leads to excessive synthesis and release of thyroid hormones such as thyroxine (T4) and triiodothyronine (T3). Thyroid hormones affect many organ systems, and their excess manifests itself with characteristic clinical symptoms [7,22,23].

TSH receptors are also present in orbital tissues, especially fibroblasts and adipocytes. They are equally activated by autoantibodies directed against the TSH receptor (TRAbs), which leads to the development of autoimmune inflammation also in the eye sockets [23,40].

The precise mechanisms triggering the autoimmune response in GD are not fully understood, but it is believed that genetic predispositions and environmental factors play crucial roles in its pathophysiology. Genetic predispositions, such as polymorphisms in the human leukocyte antigen (HLA) region, account for up to 80% of the risk of developing the disease. The remaining 20% is associated with environmental factors, including smoking, sex hormones, pregnancy, stress, infections, and iodine intake. Environmental factors disrupt mechanisms responsible for immunological tolerance, which, in genetically predisposed individuals, may contribute to the onset of GD [7,24,38,39].

Clinical presentation

Graves' disease is a systemic autoimmune disease characterized by a wide spectrum of symptoms. Depending on the development of the disease, the symptoms may vary in severity. In the initial phase, we usually observe subclinical hyperthyroidism - this means that symptoms may not yet be present or may be mild. However, in the next stage of the disease, the symptoms gradually worsen or new ones appear, which means that an overt form of the disease has developed [23].

The most troublesome symptoms are those resulting from excessive thyroid stimulation. One of the more characteristic symptoms is goiter - enlargement of the thyroid gland, which may be visible and palpable during a physical examination. The blood vessels around the enlarged

organ may dilate, resulting in increased blood flow and an audible vascular murmur. Increased production of thyroid hormones leads to accelerated metabolism, which is often manifested by weight loss (despite excessive appetite), heat intolerance and excessive sweating. These hormones affect many organ systems, such as the cardiovascular system, central nervous system, and reproductive system. Heart palpitations, tachycardia at rest, as well as anxiety, irritability, insomnia and hand tremors may often occur. Other symptoms that patients may complain about include frequent bowel movements or diarrhea. Women may complain of menstrual disorders, such as irregular or absent periods, as well as reduced libido, which results from the influence of thyroid hormones on the body's hormonal balance [3,23]. The impact of the disease on the entire body may lead to a general feeling of fatigue and weakened muscle strength. This is an important aspect because it significantly affects the quality of life of patients [2,22].

Graves' disease is also associated with extrathyroidal symptoms, including orbital disease (Graves' ophthalmopathy), skin changes (thyroid dermopathy), and rarely abnormalities of fingertips and nails (thyroid acroachia) [7,27].

Ophthalmopathy manifests itself by inflammation and swelling of the tissues of the orbit and eyelids, proptosis, redness of the conjunctiva and dysfunction of the eye muscles, which may lead to limited eye movement. When corneal ulceration arises due to eyelid regurgitation or optic neuropathy, the potential risk of vision loss must be considered [8,12].

Thyroid dermopathy, also known as pretibial edema, is another characteristic feature of Graves' disease, although it occurs much less frequently. Myxedema of the shins without involvement of the feet and characteristic skin lesions resembling an orange peel are observed - discoloration and thickening of the lesion or plaques, which are asymmetric and convex [3].

Thyroid acropachy is the rarest manifestation of Graves' disease. It involves the thickening and rounding of the distal phalanges due to swelling of the soft tissues in the hands and feet, typically resulting in the clubbing of fingers and toes [3].

It should be noted that in the elderly population, the disease may present atypically, often without specific clinical symptoms. It can manifest as a thyrocardiac syndrome, characterized

by atrial fibrillation, exacerbation of heart failure, and coronary artery disease, or as an apathetic syndrome, which includes severe depression and weight loss [2].

Graves' disease is characterized by a recurrent course with periods of exacerbation and remission. Even in cases of untreated hyperthyroidism due to Graves' disease, the natural course of the condition may lead to spontaneous remission. However, before reaching this stage, patients are at risk of serious, life-threatening complications such as thyroid storm, stroke, and myocardial infarction. Graves' orbitopathy follows a similar course, with potential remission over time. Nevertheless, the risk of permanent damage to the orbital tissues remains, which can lead to impaired eye movement, decreased visual acuity, and, in extreme cases, even blindness [7,22,34].

Management

Graves' disease (GD) is a chronic condition that significantly impacts patients' quality of life. If left untreated, it leads to severe cardiovascular and psycho-cognitive complications, resulting in considerable morbidity and mortality [10]. The treatment of Graves' disease aims to achieve and maintain a state of euthyroidism in the body, thereby preventing disease relapse. This approach alleviates existing hyperthyroidism symptoms and prevents potential complications such as the progression of ophthalmopathy or dermopathy [9].

For patients with GD, treatment requires a comprehensive and individualized approach that considers various factors, including the severity of the disease, potential side effects of treatments, and patient preferences. Currently, the primary treatment modalities are antithyroid medications, radioactive iodine therapy, and surgical intervention—thyroidectomy [30,20].

Antithyroid drugs

In the pharmacological treatment of Graves' disease, antithyroid drugs (ATDs)—also known as thioamides, which include methimazole (MMI) and propylthiouracil (PTU)—are utilized. Their primary mechanism of action is the inhibition of thyroid hormone (T3, T4) synthesis by blocking thyroid peroxidase (TPO), a key enzyme in this process [7]. These drugs do not affect the secretion of hormones that have already been synthesized; therefore, normalization

of circulating hormone levels typically occurs within a few weeks of starting treatment [33]. Additionally, ATDs are thought to exert an immunosuppressive effect on the thyroid, leading to a reduction in TRAb antibody levels, although these levels persist significantly longer than thyroid hormone levels [9,30]. PTU also possesses the ability to peripherally block the conversion of thyroxine (T4) to the more active triiodothyronine (T3) [1].

ATDs can be administered using two different methods: the titration method or the block-and-replace method [7,45]. The titration method involves using a variable initial dose, usually 15–40 mg of methimazole daily, which is gradually reduced to the lowest dose that maintains euthyroidism. In contrast, the block-and-replace method involves administering a standard dose of the ATD, such as 20–30 mg of methimazole daily, along with a replacement dose of levothyroxine to prevent hypothyroidism. This method appears to be more effective in reducing the autoimmune activity of the disease, potentially leading to a longer duration of remission. However, a drawback of this approach is the need to take a higher number of tablets daily, raising concerns about patient adherence to the prescribed regimen. Regular monitoring of thyroid hormone levels is essential to adjust drug dosages and assess the response to therapy. Initially, these checks should be conducted every 4-8 weeks until euthyroidism is achieved, after which a decision on further management should be made [7].

ATDs often constitute the first line of treatment for Graves' disease due to their safety and accessibility [4,20]. Their use allows for the achievement of euthyroidism in a relatively short period and alleviates the symptoms of hyperthyroidism in a non-invasive and reversible manner [29]. However, the main drawback of ATDs is the high recurrence rate of the disease after discontinuation of therapy [20,41]. Relapse can be very burdensome for patients, due to the recurrent symptoms of hyperthyroidism and the potential emergence of complications [30].

The treatment with antithyroid drugs (ATDs) is generally well tolerated by patients, with adverse effects rarely reported; however, this does not mean they should be disregarded [18]. More common and usually mild side effects include itching, skin rashes, joint pain, muscle aches, and nausea [9,29,30,35]. The side effects of methimazole (MMI) are dose-dependent and are more frequently observed in the initial phase of therapy [43,44]. In contrast, the adverse effects of propylthiouracil (PTU) are less clearly dose-related. Most adverse effects resolve spontaneously or can be alleviated by reducing the drug dosage or using an antihistamine [18].

A serious adverse effect is agranulocytosis, a life-threatening condition characterized by a drastic reduction in the number of granulocytes in the blood to less than 500/ml [30]. Agranulocytosis is rare, but its occurrence necessitates the immediate discontinuation of treatment and the initiation of intensive therapy. It typically appears within the first three months of therapy, and its incidence is not dependent on the type of drug used (MMI or PTU). Before initiating ATD treatment, the granulocyte count should be measured—a result of less than 500/ml is a contraindication for starting therapy. However, it is generally considered that routine monitoring of granulocyte counts during treatment is unnecessary since agranulocytosis occurs suddenly [7]. It is crucial that patients are aware of the potential risk and seek immediate medical attention if concerning symptoms such as fever, sore throat, or dysuric symptoms in women occur, to discontinue treatment [18].

Another serious, albeit even rarer, adverse effect primarily associated with PTU treatment is hepatotoxicity, which typically appears after three months of therapy [30,35]. This allergic hepatitis can lead to massive organ damage. In such cases, PTU treatment should be immediately discontinued. Hepatic dysfunction is accompanied by increased aminotransferase activity. Before starting ATD treatment, liver function parameters should be measured—an aminotransferase level greater than five times the upper limit of normal is a contraindication for treatment [7]. However, similar to the assessment of agranulocytosis, routine liver function tests are not recommended. In patients with hyperthyroidism not undergoing treatment, asymptomatic elevations in aminotransferase levels are common. These levels may slightly increase after starting PTU treatment but typically normalize during therapy and do not always predict further increases [18].

The primary challenge in ATD therapy is the high risk of relapse after discontinuation, which presents a significant challenge for clinicians [29,41,42]. Scientific studies indicate that the standard treatment regimen of ATDs for 12-18 months restores euthyroidism with approximately a 50% risk of relapse after drug cessation [5]. However, some studies suggest that long-term treatment may lead to a higher remission rate and a lower risk of relapse while also being safe for the patient [5,20]. There are reports that the relapse rate after ATD therapy may be associated with various factors. Thyroid volume, serum TRAb concentration, smoking, postpartum period, severe biochemical hyperthyroidism, and Graves' ophthalmopathy may significantly influence the increased risk of relapse, while the association with age, sex, and family history remains uncertain [5,29]. However, none of these variables are sufficiently

sensitive or specific to allow for accurate risk stratification on their own [5,7,18]. Nonetheless, analyzing an individual patient's risk of relapse could be helpful in optimizing the duration of treatment rather than assuming a predetermined long-term period [20].

Antithyroid drugs (ATDs) constitute an effective therapeutic option, enabling conservative treatment without the need for thyroid tissue removal. They are characterized by a high safety profile, allowing their use in both children and pregnant women. These drugs can be used for extended periods, and their therapy can lead to remission, while simultaneously avoiding the risk of developing hypothyroidism and other complications associated with more invasive treatment methods [9]. However, one of the main limitations of ATD use is the high relapse rate, which remains independent of the type of drug used or the treatment regimen [7,13].

β-blockers

β-blockers (β-adrenergic receptor antagonists) play a crucial role in the early stages of treating Graves' disease, particularly in reducing symptoms caused by excessive sympathetic nervous system activity. These symptoms include increased sweating, anxiety, muscle tremors, palpitations, and tachycardia [7]. Drugs such as propranolol are particularly effective in quickly reducing these symptoms due to their ability to inhibit β-adrenergic receptors and, at higher doses, inhibit the peripheral conversion of thyroxine (T4) to triiodothyronine (T3). It is important to note that β-blockers do not directly affect the synthesis or release of thyroid hormones and, therefore, should not be used as monotherapy. They are a key component of adjunctive therapy, providing rapid symptom relief and improving the quality of life for patients. Monitoring blood pressure and being aware of potential side effects, such as bradycardia or exacerbation of asthma symptoms, are essential for the safe use of β-blockers [9].

Radioactive iodine therapy

Radioactive iodine therapy (RAI) is another commonly used treatment method for Graves' disease. The thyroid gland has a unique ability to absorb iodine from the bloodstream, which is exploited in this therapy. It involves the oral administration of radioactive iodine-131 (131I) to the patient. This iodine is taken up by the follicular cells of the thyroid, resulting in the accumulation of the isotope in the gland [9,18]. Iodine-131 emits beta radiation, which

damages thyroid cells, causing an early inflammatory response, follicular cell necrosis, and closure of blood vessels. These processes lead to a reduction in thyroid size and inhibition of T3 and T4 hormone secretion, ultimately resulting in hypothyroidism.

Due to the selective uptake of 131I by the thyroid, this method is highly effective and precisely targeted, thereby minimizing the impact on other tissues. Besides its safety, the main advantage of this method is its effectiveness, with an approximate success rate of 80% [9]. Since the therapy results in the irreversible destruction of thyroid tissue, it can lead to euthyroidism or even hypothyroidism, which is the primary adverse effect of this treatment. It is considered optimal to administer the smallest effective dose of 131I that would restore euthyroidism while avoiding hypothyroidism. Unfortunately, determining the ideal dose is challenging due to various factors. Moreover, several studies suggest that calculated 131I doses do not offer significant benefits (in terms of cure rate or prevention of hypothyroidism) compared to fixed doses [11,19,32]. Therefore, the most common dosing regimen is the fixed-dose regimen [16]. Additionally, it appears that the development of hypothyroidism is inevitable and will occur regardless of the administered 131I dose. Therefore, it is important to inform the patient about the likely outcomes and the need for subsequent lifelong levothyroxine replacement therapy. In some cases, transient thyroiditis may occur, manifesting as swelling and neck pain. There are also concerns about an increased risk of thyroid cancer or other malignancies; however, the evidence is inconclusive.

Treatment with 131I may exacerbate preexisting ophthalmopathy due to the release of autoantigens during thyroiditis induced by the therapy. Patients may also experience a lower quality of life compared to those who underwent ATD therapy or surgical thyroidectomy [30,36]. Hence, it is essential to individually assess the patient's situation and thoroughly discuss potential benefits and risks before initiating a particular treatment method. Collaboration between the doctor and the patient is crucial to ensure effective therapy, adherence to recommendations, regular monitoring of thyroid function, and reporting of any new symptoms. Radioactive iodine therapy is indicated for patients who have contraindications to ATD therapy, those who have experienced a relapse after ATD treatment, and patients who are not suitable candidates for surgery [28]. RAI is contraindicated in pregnant women, women planning pregnancy within the next six months, breastfeeding mothers, patients with thyroid cancer or its suspicion, patients who do not comply with radiological safety guidelines, and patients with moderate to severe thyroid-associated orbitopathy (TAO) [9,22,36].

Surgical intervention

Surgical treatment is one of the options for managing Graves' disease (GD). It is relatively rarely used and involves two surgical methods: total thyroidectomy, which entails the complete removal of the gland and necessitates lifelong thyroid hormone supplementation [30]; and partial thyroidectomy, which involves leaving a small portion of the gland, thereby increasing the risk of disease recurrence. Therefore, the preferred and more commonly used surgical option is total thyroidectomy [9,21].

Surgical intervention in GD is a definitive treatment method. It leads to rapid control of hyperthyroidism and limits exposure to radioactivity, which may additionally prevent the progression of Graves' ophthalmopathy (GO). Surgeons with extensive experience in thyroid operations report that the complication rate after thyroidectomy in patients with Graves' disease is less than 3% [17,37]. Nevertheless, the possibility of complications must be considered. The most concerning complications include permanent damage to the recurrent laryngeal nerve and hypoparathyroidism, which can occur in up to 5-10% of patients [25,31]. Other, rarer complications include transient hypocalcemia, postoperative bleeding, wound infections, and scarring. Hypothyroidism, however, is generally regarded as a predictable outcome of the surgery rather than a complication and occurs in the majority of patients [18,30].

Surgery is primarily recommended in situations where other treatments (ATD or RAI) are insufficient and the disease recurs, or when they are contraindicated, such as in pregnant women or patients with GO [14,15]. Other indications for surgical treatment of GD include large goiters causing compressive symptoms, suspected or confirmed thyroid cancer, concurrent hyperparathyroidism, high levels of TRAb antibodies, and patient preference [6,26,30]. Surgical treatment should also be considered in cases where the patient poorly adheres to medical recommendations or has limited access to healthcare [9,18].

Surgical treatment of GD is safe and effective, especially for patients who cannot utilize other therapeutic methods. Although it requires lifelong thyroid hormone supplementation and may involve surgical complications, it minimizes the risk of disease recurrence and eliminates potential complications associated with hyperthyroidism. Therefore, the decision to opt for

this treatment method should be made individually, taking into account the clinical profile, patient preferences, and access to healthcare.

Summary

In summary, the treatment of Graves' disease requires careful consideration of available therapeutic methods and active collaboration between the patient and the physician. There are three main treatment options: antithyroid drugs (ATDs), radioactive iodine therapy (RAI), and surgical interventions, each with its unique advantages and disadvantages. ATDs offer the possibility of preserving thyroid function but are associated with a high risk of relapse. RAI therapy and surgical removal of the thyroid lead to permanent hypothyroidism, necessitating lifelong hormone supplementation, but they offer a low recurrence rate [9,18,35]. Choosing the appropriate therapy is a complex process that requires consideration of both short- and long-term treatment effects, potential side effects, and patient preferences. It is crucial for the physician to thoroughly discuss all available options, their benefits and drawbacks, and to jointly decide on the optimal treatment path. The patient must be aware of the risks, benefits, and logistics associated with each treatment method to make informed decisions [7,13]. Through clear communication and understanding of the patient's values and preferences, the best therapeutic outcomes can be achieved. In some cases, the patient's health condition may require temporary ATD treatment to achieve euthyroidism before making a long-term therapeutic decision. Collaboration and patient involvement in the decision-making process are essential to ensure effective treatment and improve the quality of life for individuals with Graves' disease [10,20,35].

CONCLUSION

Choosing the best treatment strategy for Graves' disease is a multifaceted process that hinges on a thorough understanding of the available therapeutic options and a collaborative approach between the doctor and the patient. Each treatment modality—antithyroid drugs (ATDs), radioactive iodine therapy (RAI), and surgical intervention—offers distinct benefits and

potential drawbacks. The key to optimal management lies in tailoring the treatment plan to the individual needs and preferences of the patient.

Antithyroid drugs offer a non-invasive option that can preserve thyroid function, although they are associated with a higher risk of disease relapse. Radioactive iodine therapy and thyroidectomy provide more definitive solutions with lower recurrence rates but necessitate lifelong hormone replacement therapy due to induced hypothyroidism. The selection of the appropriate treatment must consider both clinical aspects and the patient's lifestyle, values, and expectations.

The selection of the appropriate treatment strategy must involve an active and open dialogue between the patient and the healthcare provider. This collaborative process should include a detailed discussion of the short- and long-term consequences of each treatment option, taking into account the patient's medical history, lifestyle, values, and preferences. Patients should be empowered to participate in decision-making by providing them with comprehensive information about the benefits and risks associated with each treatment method. This partnership builds trust, enhances patient satisfaction, and leads to more personalized and effective care.

Given the complexity and variability of Graves' disease, an individualized approach to treatment is essential. Factors such as the severity of the disease, the presence of comorbid conditions, the patient's age, and their personal preferences must be considered. For example, young patients or those planning pregnancy may prioritize preserving thyroid function and avoiding radiation therapy, while older patients or those with significant comorbidities may prefer a more definitive solution, such as surgery or RAI.

Effective management of Graves' disease extends beyond the initial treatment decision. Regular monitoring of thyroid function, adjusting therapy as needed, and ongoing patient education are critical components of long-term care. Patients should be encouraged to promptly report any new or worsening symptoms and to attend follow-up appointments. Providing psychological support and addressing quality of life issues, such as the impact of the disease and its treatment on daily activities, can further improve patient outcomes.

In conclusion, the successful treatment of Graves' disease depends not only on the efficacy of medical interventions but also on the strength of the doctor-patient relationship. A

personalized approach, grounded in mutual respect and open dialogue, can significantly enhance treatment outcomes and improve the overall quality of life for patients with Graves' disease. By prioritizing patient engagement and individualized care, healthcare providers can ensure that each patient receives the most appropriate and effective treatment tailored to their unique situation.

AUTHORS CONTRIBUTION:

Conceptualization: Paula Kula, Mateusz Haber, methodology: Alicja Kotula; software: Adam Juśkiewicz; check: Olga Grelewicz, Natalia Kucy, Elwira Servaas; formal analysis: Elwira Servaas; investigation: Olga Grelewicz; resources: Adrianna Czachor; data curation: Alicja Kotula; writing - rough preparation: Paula Kula; writing - review and editing: Natalia Kucy; visualization: Adam Juśkiewicz, Robert Siemiątkowski; supervision: Adrianna Czachor, Robert Siemiątkowski; project administration: Mateusz Haber.
All authors have read and agreed with the published version of the manuscript.

Conflict of interest: The authors declare no conflict of interest.

Funding: This review has not received any external funding.

Statement of institutional review committee: not applicable

Informed consent: not applicable

Data availability: not applicable

Acknowledgments: not applicable

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