JISS Journal of Indonesian Social Science

Vol. 6, No. 11, November 2025
E-ISSN:2723 – 6692
P-ISSN:2723– 6595
http://jiss.publikasiindonesia.id/

The Role of Work Stress as Triggering Factor of Graves' Disease

Riovani Nurfahmi Adam*, Teddy Ervano, Andi Alfian
Universitas Yarsi, Indonesia
Email: riofahmi31@gmail.com*, teddyrspr@gmail.com, a.alfian@yarsi.ac.id

KEYWORDS
Graves' disease; occupational stress; HPA axis; hyperthyroidism, autoimmunity

ABSTRACT
Graves' disease is the most common form of autoimmune hyperthyroidism, caused by overstimulation of the thyroid-stimulating hormone receptor by autoantibodies (TRAb). Besides genetic and immunological factors, chronic occupational stress plays a critical role in triggering and worsening the disease. Persistent activation of the hypothalamic-pituitary-adrenal (HPA) axis may lead to immune dysregulation and thyroid autoimmunity. A female Head of Accounting with a high workload experienced weight loss, palpitations, tremor, and insomnia. Lab tests showed elevated T3 and FT4, suppressed TSH, and positive TRAb. Thyroid ultrasound revealed diffuse gland enlargement consistent with toxic diffuse goitre. She was diagnosed with Graves' disease and treated with thiamazole, propranolol, and alprazolam. Her perfectionist work style and chronic stress likely triggered sustained HPA axis activation and autoantibody production. Studies show psychosocial stress increases risk of Graves' disease via complex neuroendocrine-immune pathways. Chronic HPA axis activation alters cortisol and elevates proinflammatory cytokines such as IL-6 and TNF-α, causing loss of immune tolerance to thyroid tissue. This case highlights the need to address psychosocial factors in managing Graves' disease. Comprehensive treatment including medication, stress management, psychosocial support, and workload adjustment is key to remission and improved quality of life.

INTRODUCTION

Graves' disease (GD) was first described by an Irish physician, Robert James Graves, in 1835 (Coco, Gatti, Piantanida, Gallo, & Mortara, 2021; Toro-Tobon & Stan, 2024). Graves' disease is characterized by symptoms such as an enlarged thyroid gland (goiter), palpitations or tachycardia, and exophthalmos (Bartalena, 2018). This disease is part of a broader category of autoimmune thyroid diseases (AITD), which can cause dysfunction of various organs and is characterized by the presence of thyroid-stimulating hormone receptor antibodies (TRAb) (Ortarzewska et al., 2023; Vargas-Uricoechea et al., 2023; Vieira et al., 2020; Zhao et al., 2021). Unlike other autoimmune diseases, which generally cause decreased organ function, Graves' disease actually causes an increase in thyroid function (Coco et al., 2021). This elevated thyroid activity can lead to thyrotoxicosis and enlargement of the thyroid gland (1) (Shahid et al., 2018).

Graves' disease is the most common cause of hyperthyroidism, accounting for 60–80 percent of hyperthyroid cases worldwide (Lee & Pearce, 2023; Taylor et al., 2018; Wiersinga, Poppe, & Effraimidis, 2023). Its prevalence varies among populations due to genetic factors and iodine intake (Farebrother, Zimmermann, & Andersson, 2019; Katagiri, Yuan, Kobayashi, & Sasaki, 2017). The disease is more prevalent in women, with a female-to-male incidence ratio of 10:1; clinical

manifestations typically begin between the ages of 20 and 50 years (2) (Jung et al., 2017; Peoples, Medsger Jr, Lucas, Rosario, & Feghali-Bostwick, 2016).

In addition to genetic and immunological factors, environmental factors such as psychosocial stress and workload also contribute to the onset of Graves' disease (Antonelli et al., 2020). A case-control study reported that patients with Graves' experienced more stressful life events—including changes in working conditions and workplace conflicts—in the 12 months preceding disease onset (3) (Hendrickson, 2023). Conversely, thyroid disease also impacts patients' working lives (Nickel et al., 2019). A systematic review showed that individuals with thyroid diseases, including hyperthyroidism, face higher risks of long-term sick leave, reduced work capacity, and increased absenteeism compared to healthy populations (4) (Van Vliet et al., 2021).

This report describes Mrs. M, a 47-year-old woman with a high workload as head of the accounting division, whose hyperthyroidism symptoms appeared and worsened in recent months (Janevik-Ivanovska et al., 2015). The combination of biological predisposition and work stress may be important factors in explaining the onset of Graves' disease in this patient, emphasizing the need to consider psychosocial aspects in the diagnosis and management of hyperthyroidism (Dengler & Bell, 2022). Based on this background, this study aims to analyze the role of work stress as a triggering factor for the occurrence of Graves' Disease through a case study approach and a review of the latest literature. The benefit of this study is to provide a comprehensive understanding of the relationship between psychosocial factors and the pathogenesis of thyroid autoimmune diseases, offering a foundation for developing a holistic approach to Graves' Disease management that addresses not only medical aspects but also stress factors and patients' mental health.

METHOD

Case Reports

The patient is Mrs. M, a 47-year-old woman, Betawi tribe, Muslim, last education Bachelor's degree, works as an office employee and is married. She came to the hospital with the main complaint of losing about 7 kg in the last three weeks, although the frequency of eating actually increased. Patients also complain of fatigue easily, frequent heart palpitations, sweating a lot even in an air-conditioned room, tremors in both hands, and difficulty sleeping at night—usually only 2-3 hours of sleep. These complaints appear every day, getting heavier especially when doing light activities.

Similar symptoms have actually begun to be felt since eight months ago, characterized by mild weight loss, but at that time patients considered it the result of heavy work so they did not seek treatment. From the family history, it is known that the patient's mother suffers from type 2 diabetes mellitus, but there are no other family members with the same complaint. The patient had no history of malignancy or other metabolic diseases, and had never smoked or consumed alcohol.

Vital signs examination showed a pulse of 110 times/minute, blood pressure 116/70 mmHg, breathing rate 18 times/minute, and a temperature of 37 °C. On physical examination, there was a slight tremor in the upper extremities and a slight enlargement in both thyroid

glands, but there was no bruising and no signs of exophthalmus were found. The patient's Wayne Index score was 20, which led to suspected hyperthyroidism.

Laboratory examination showed a total T3 of 5.29 ng/ml (N: 0.58–1.59), FT4 of 3.08 ng/dl (N: 0.70–1.48), an increase in TRAb of 2.4 U/L (N: <1.75), while TSH <0.05 uIU/ml (N: 0.35–4.94). These results are consistent with thyroid hyperfunction. Thyroid ultrasound shows bilateral mild thyrommegaly with effects leading to *diffuse toxic goitre* cq *Graves' disease*. Based on these clinical and supporting findings, the patient was diagnosed with *Graves' disease* and given thiamazole 3 × 10 mg, propranolol 4 × 10 mg, and alprazolam 1 x 0.5 mg.

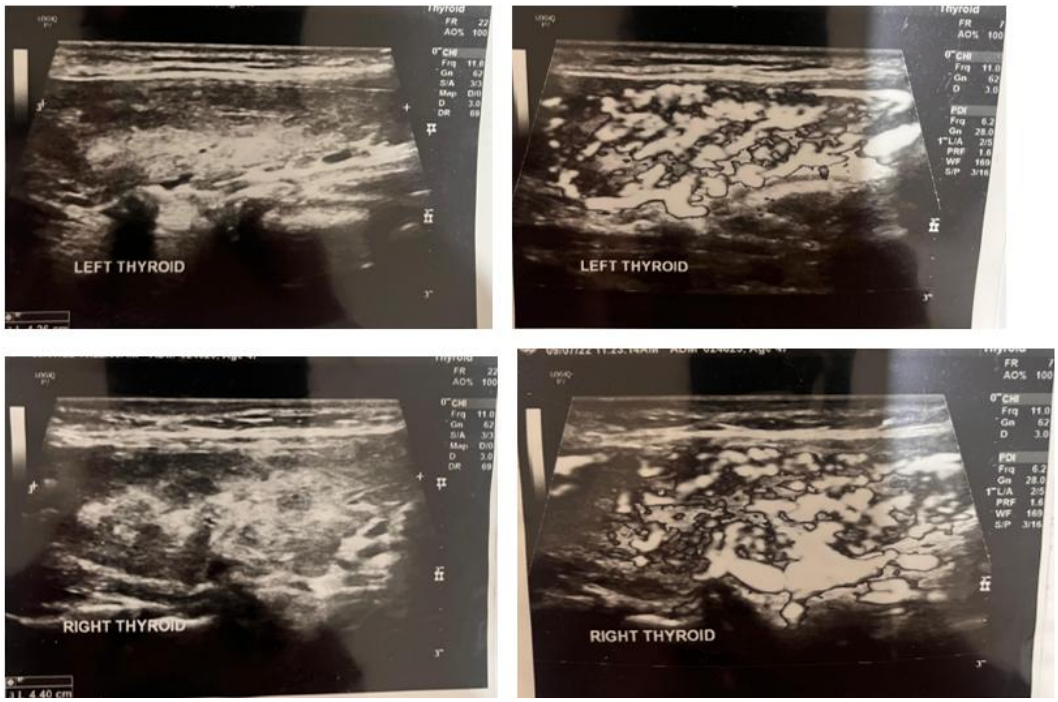

Figure 1. Thyroid Ultrasound
Source: Patient personal documentation, 2024

Outside of medical issues, the patient works as the Head of the Accounting Division at an educational institution. His daily activities are dominated by administrative work, audits, and internal and external meetings. Patients leave for work every morning at around 08.00 and usually go home at 17.00. Patients are known to be perfectionists and do not go home before their work targets are achieved, so they often come home late than their colleagues. Even so, the patient has a happy family life and does not face financial problems.

RESULTS AND DISCUSSION

Mrs. M's case provides a fairly clear picture of how workload can play a role in the emergence and development of Graves' disease. The patient, a 47-year-old woman, came with typical complaints of hyperthyroidism in the form of quite drastic weight loss, palpitations, tremors, heat intolerance, and sleep disturbances. Laboratory results showed very high levels of T3 and FT4, significant TSH decreases, and positive TRAb. Thyroid ultrasound examination showed diffuse enlargement, which, together with clinical findings, corroborated the diagnosis of Graves' disease.

Graves' disease is the most commonly found form of autoimmune hyperthyroidism. The disease arises as a result of the formation of antibodies against TSH receptors (*thyroid stimulating hormone receptor antibody*/TRAb) which mistakenly stimulates these receptors, causing the thyroid gland to hyperplasia and overproducing thyroid hormones (1). This condition causes typical symptoms such as weight loss, heart palpitations, tremors, sweating easily, and diffuse thyroid enlargement. Moreover *graves' disease* It accounts for about 60–80% of all cases of hyperthyroidism, and most commonly affects women aged 20–50 years. This disorder not only impacts the endocrine system, but also affects the emotional state, stamina, as well as the patient's quality of life due to the excessive increase in body metabolism (2).

Physiologically, the function of the thyroid gland is controlled by the hypothalamic–pituitary–thyroid axis (HPT axis) which works through feedback mechanisms. The hypothalamus will release *thyrotropin releasing hormone* (TRH) which then stimulates the anterior pituitary to expel *thyroid stimulating hormone* (TSH). Furthermore, TSH stimulates the thyroid gland to produce two main hormones, namely thyroxine (T_4) and triiodotironin (T_3). These two hormones will provide negative feedback to the pituitary and hypothalamus to maintain a balance of thyroid hormone production (5).

In addition to being regulated by these feedback mechanisms, the secretion of thyroid hormones also follows a diurnal pattern or circadian rhythm controlled by the suprachiasmatic nucleus in the hypothalamus. Under normal conditions, TSH levels peak at night until early morning (around 23:00–03:00), then decrease during the day to evening. This rhythm helps maintain the stability of the body's metabolism throughout the day. Meanwhile, T_4 and T_3 levels tend to be more stable due to their longer half-life, although they can still fluctuate slightly as TSH levels change (5,6).

Graves' disease is the most common form of autoimmune hyperthyroidism, in which antibodies to TSH receptors (*thyroid stimulating hormone receptor antibody* or TRAb) overstimulates the thyroid gland so that the production of thyroid hormones increases. In addition to genetic factors, psychological stress—including stress due to workload—has been shown to play a role in triggering the onset of this disease (7). The proposed mechanism involves activation of the hypothalamic–pituitary–adrenal axis (HPA axis) and the sympathetic nervous system due to chronic stress, which then disrupts the immune balance and triggers the formation of autoantibodies.

In long-lasting stressful situations, such as high workloads and constant psychological stress, activation of the HPA axis will lead to increased release of cortisol and catecholamines. Repeated excess cortisol can suppress the secretion of TRH and TSH, as well as affect the activity of the deiodinase enzyme that plays a role in the conversion of T_4 to active T_3 (8). Prolonged activation of HPA can also disrupt the immune system, increase levels of pro-inflammatory cytokines such as IL-6 and TNF-α, as well as decrease regulatory T cell function that is important for maintaining tolerance to thyroid tissue (7).

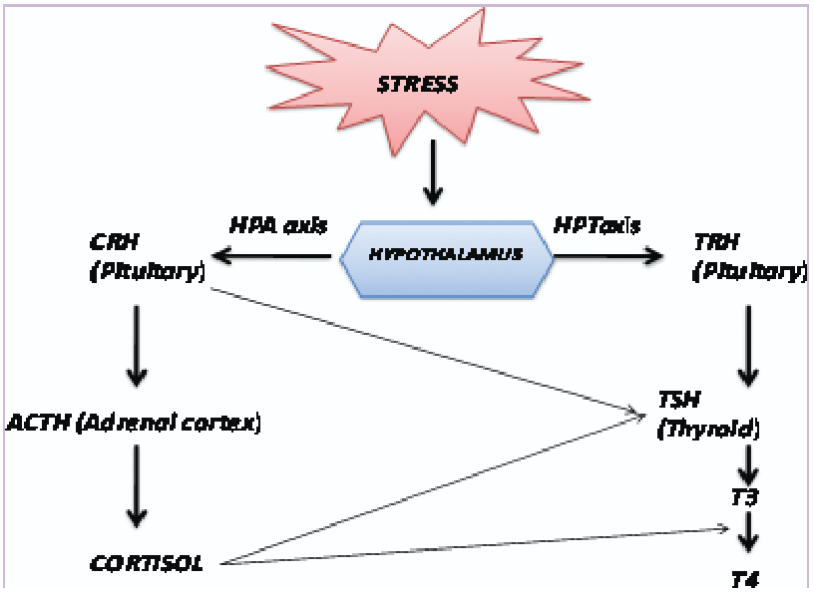

Figure 2. Effects of stress on the HPA and HPT axes
Source: Mukkadan et al., (2015)

Some studies suggest that severe psychosocial stress can trigger the onset or worsen of Graves' disease. A meta-analysis found that individuals who experience chronic stress have a higher risk of developing this disease than the general population (7). In Mrs. M's case, a perfectionist personality, long working hours, and persistent sleep disorders can be considered a form of chronic stress that triggers the activation of the mechanism. These factors are thought to strengthen the autoimmune response and accelerate the onset of symptoms of hyperthyroidism suffered by patients.

Table 1. Summary of the results of meta-analysis and meta-regression of the relationship between stress and Graves' disease

Analysis	Number of studies (k)	Nile (d/b)	95% CI	p value	Information
Comparison of SLEs between GD and control patients	9	d : 1.81	0.43 – 3.19	0.01	Stress is significantly associated with the onset of GD
Influence of female proportions	9	b : 0.22	0.07 – 0.36	< 0.01	Stronger effects on women
Influence of average age	9	b : -0.62	−0.80 – −0.43	< 0.01	Stronger effects at a young age
The effect of stress on the outcome of antithyroid therapy	4	d : 0.32	−0.06 – 0.70	0.09	Insignificant to the success of therapy

Source: Wang et al., (2023)

Based on the table above, the results of a meta-analysis of 13 studies with a total of 2,892 participants showed that stressful life events (*stressful life events/SLEs*) has a significant association with an increased risk of occurrence *Graves' disease*. Value *effect size* A considerable amount (D = 1.81; P = 0.01) confirms that stress is one of the environmental factors that play an important role in triggering the onset of this disease.

Further analysis through meta-regression showed that the relationship between stress and the occurrence of *Graves' disease* tend to be stronger in women ($\beta = 0.22$; $p < 0.01$) as well as in younger age groups ($\beta = –0.62$; $p < 0.01$). These findings indicate that young women have a higher susceptibility to the effects of chronic stress, especially in triggering autoimmune reactions in the thyroid gland.

Interestingly, stress did not show a significant influence on the success of antithyroid therapy ($d = 0.32$; $p = 0.09$). This suggests that stress plays a role more as an early trigger for the onset of disease, rather than as a factor that directly determines response to treatment.

These results are in line with the condition of the patients in this report, where prolonged work stress, high responsibility burden, and chronic sleep disorders are thought to contribute to the activation of the hypothalamic–pituitary–adrenal (HPA) axis and changes in the immune system that then trigger the formation of antibodies against TSH receptors (TRAb). Thus, the results of this meta-analysis reinforce the suspicion that chronic work stress may be an important triggering factor in the process of occurrence *Graves' disease*, especially in women of productive age.

Mrs. M's position as a Division Head with great responsibility, long working hours, and strict targets is a stressor that can worsen the condition. Patients leave for work every morning at around 08.00 and usually go home at 17.00. According to the International Labour Organization (10), the ideal working hours are 8 hours per day or 40 hours per week for five working days in one week. However, patients often exceed these work time limits due to high job demands and responsibilities. This is in line with several epidemiological studies showing that chronic work stress increases the risk of Graves' disease (3,7). Interestingly, a recent case study reported that some patients were able to experience improvement simply by reducing emotional stress, without antithyroid medication (14). These findings emphasize that stress is not only a trigger, but also affects the course of the disease.

Some studies show that high-pressure jobs and large responsibilities have a higher risk of thyroid disorders. Jobs with high responsibilities and work pressure are known to have a greater risk of thyroid dysfunction. Exposure to chronic work stress, long working hours, and heavy mental load are closely related to an increased incidence of thyroid dysfunction, including hyperthyroidism (4). Meanwhile, most patients *Graves' disease* reported the occurrence of work conflicts, changes in workload, and workplace stress in one year prior to the onset of disease symptoms (3).

From these findings, it can be concluded that chronic work stress in positions with great responsibility can be an important trigger for the onset of Graves' disease. This is in line with the case of patients in this report, where high workload and psychological stress are strongly suspected to play a role in triggering the onset of the disease.

Furthermore, *Graves' disease* impact on the quality of work. Various reviews report that thyroid disorders can decrease concentration, increase fatigue, and reduce productivity (4). Mrs. M herself often feels tired quickly and has difficulty sleeping, a condition that certainly affects physical and mental resilience in her work. In addition, this disease is often accompanied by psychiatric complaints such as anxiety and cognitive impairment (12), which have the risk of interfering with decision-making in strategically positioned patients.

In general, the impact *Graves' disease* extends to the employment aspect. Studies reported an increase in attendance, reduced effective working hours, and the risk of disability

in patients with thyroid disorders (13). Mrs. M, who is at the peak of her career, faces a major challenge to maintain her performance without adequate medical and psychosocial support. The latest data even shows an increase in the number of incidents *Graves' disease* During the pandemic, it signifies a significant role of environmental factors and external stresses (11).

With this background, the management of Mrs. M needs to be carried out comprehensively. Antithyroid drugs remain the main therapy, but the success of treatment is also highly dependent on stress management, family support, and a conducive work environment. Education on the importance of maintaining a balance between work demands and rest needs must be emphasized so that the risk of recurrence is reduced and the patient's quality of life is maintained. This case confirms the need for a multidisciplinary approach that not only highlights the medical, but also psychological and occupational health aspects in the treatment of Graves' disease.

CONCLUSION

Research indicates a significant association between occupational stress and the onset of Graves' disease, with one study estimating that individuals exposed to occupational stress are approximately 8.6 times more likely to develop the condition. Chronic stress may activate the hypothalamic–pituitary–adrenal axis, impair immune regulation, and trigger autoantibody production that leads to hyperthyroidism. Case reports and observational studies also suggest that stress relief can induce remission in some patients with stress-induced Graves' disease, highlighting the complex role of psychological factors in disease progression. Despite these findings, current literature remains limited, and further research is needed to clarify the precise mechanisms by which occupational stress influences autoimmune thyroid pathology, and to determine effective interventions that incorporate stress management alongside medical treatment. Future studies could explore the long-term benefits of integrated multidisciplinary approaches, including psychosocial support, stress reduction techniques, and occupational health strategies, to prevent disease onset, improve clinical outcomes, and enhance patients' quality of life.

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