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RESEARCH ARTICLE

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Methimazole Increases Body Weight in Graves' Disease Patients Reaching Euthyroidism

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Abstract:

Graves' disease (GD) is one of the most common autoimmune diseases that cause hyperthyroidism. One of the standard therapies for GD is the antithyroid drug, methimazole (MMI). The goal of GD therapy is to achieve euthyroidism in the patient. Hyperthyroid therapy is often associated with weight gain. This study aimed to determine the effect of MMI administration on weight changes in GD patients who reached euthyroidism. This retrospective cohort study was conducted using the Borneo Wetland Study on Thyroid 2 (BEST-T2) database belonging to the endocrine clinic of the internal medicine department at Ulin Hospital Banjarmasin. We collected data from 58 GD patients. Data were analyzed using the paired t-test with SPSS version 23 software with a confidence level of 95%. The majority of Graves' disease (GD) patients who achieved euthyroid status after receiving methimazole (MMI) were women, with an average age of 40 ± 11.6 years, an initial TSH level of 0.38 (0.004) μIU/ml, and an initial FT4 level of 25.41 (16.51) pmol/l. The duration to reach euthyroid status in GD patients after MMI administration was 16 ± 13.4 months. This study showed a significant change in body weight before MMI treatment (53.69 ± 8.2 kg) compared to after MMI treatment (59.41 ± 8.6 kg) with 5.72 kg weight changes in GD patients who reached euthyroidism at Ulin Hospital Banjarmasin ($p<0.001$). MMI treatment influences weight changes significantly in GD patients reaching euthyroidism.

Keywords: euthyroid; Graves' disease; methimazole; weight changes

Introduction

Graves' disease (GD) is a systemic autoimmune disease characterized by the infiltration of tissues by specific T cells into the tissues expressing thyroid-stimulating hormone (TSH) receptors.[1] The condition of GD leads to hyperthyroidism, which is an increased production of thyroid hormones.[2] The prevalence of GD hyperthyroidism is relatively high compared to other causes, approximately 60–80%.[3] Indonesian basic health research in 2013 reported that the prevalence of hyperthyroidism in Indonesia reached 0.4%, with an incidence rate in South Kalimantan at 0.2%.[4] Epidemiological data on GD in Indonesia is still limited because epidemiological studies focus on hyperthyroidism in general and not specifically on GD.[5]

The goal of GD therapy is to achieve normal thyroid function and prevent recurrent hyperthyroidism.[6] One of the standard therapies for GD is antithyroid drugs (ATD) administered for 12–18 months.[7] The most commonly used class of ATD includes thionamides, namely methimazole (MMI), carbimazole (CBZ), and propylthiouracil (PTU).[8] The MMI is the most commonly used ATD.[9] Initially, MMI can be administered orally at a dose of 10–30 mg per day, depending on the severity.[1] The MMI can achieve euthyroidism within 4–6 weeks.[10]

ATD therapy can improve euthyroidism compared to without therapy. Euthyroidism involves the normalization of thyroid hormone levels during therapy with MMI.[1] Some studies indicate that higher doses of MMI are associated with higher initial euthyroidism.[11] Euthyroidism can be achieved with a therapy duration of 12–18 months, and this duration is considered an upper limit for therapy. Azizi et al state that long-term ATD therapy is associated with higher euthyroidism and lower drug-related complication rates.[12]

Hyperthyroidism is associated with symptoms of weight loss.[13] ATD is often linked to the return of body weight to its initial state. Kyriacou et al state that the use of ATD is associated with a weight gain of 2–4 kg that occurs early after starting therapy and persists for at least one year after therapy.[14] After therapy with MMI, the initial weight increases, stabilizes and gradually decreases during the subsequent period.[15]

Literature discussing the effects of MMI administration on the weight changes of GD patients who achieve euthyroidism is still very limited, while field facts indicate that many patients are treated with MMI. The study on the effects of MMI administration on weight changes in GD patients who achieve euthyroidism has not been widely conducted in Indonesia and has never been done at the Ulin Hospital Banjarmasin.

This study aimed to determine the characteristics of GD patients, especially the duration of achieving euthyroidism after MMI administration and the weight before receiving MMI therapy and after achieving euthyroidism. It also aimed to investigate the effects of MMI administration on weight changes in GD patients who achieve euthyroidism based on gender and age at Ulin Hospital Banjarmasin.

Research Method

This study was conducted with a retrospective cohort design. The GD patient's data were obtained from the thyroid patient database of the endocrine clinic of the internal medicine department at Ulin Hospital Banjarmasin, known as the Borneo Wetland Study on Thyroid 2 (BEST-T 2). The GD patient samples that met the inclusion criteria were collected using a total sampling technique. The normality of the data was tested using the Kolmogorov-Smirnov test. As the data were normally distributed, the hypothesis test used a paired t-test with a 95% confidence level (α

= 0.05). The data were also grouped based on gender (male and female) and age (18–40 years and >40 years) categories for subgroup analysis. Data analysis was conducted using Microsoft Excel 2016 and Statistical Package for Social Sciences (SPSS) version 23.

Results

The ethical clearance letter was issued by the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Universitas Lambung Mangkurat, with the number 356/KEPK-FK ULM/EC/X/2023, and the Research Ethic Committee of Ulin Hospital Banjarmasin with the number 236/XI-Reg-Riset/RSUDU/23, allowing this study to be conducted in October–November 2023. All GD patients recorded in the BEST-T 2 database have reached euthyroidism, totaling 79 data until October 2022. Exclusion criteria were applied, resulting in a sample of 58 GD patients for this study. The study flowchart can be seen in Figure 1.

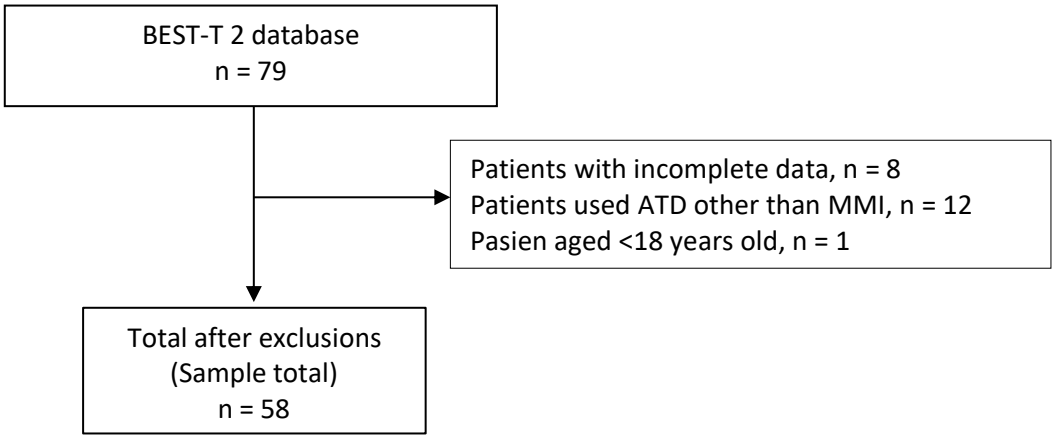

Figure 1. Study flowchart

Table 1. Baseline Characteristics

Characteristics	
Gender n (%)	
- Male	10 (17.2)
- Female	48 (82.8)
Age (years ± SD)	40 ± 11.6
TSH levels (μIU/ml)	
- Before treatment	0.38 + 0.004)
- After treatment	1.74 (1.361)
FT4 levels (pmol/l)	
- Before treatment	25.41 (16.51)
- After treatment	8.39 (10.97)
Time to achieve euthyroidism (months ± SD)	16 (± 13.4)
MMI Dosage (mg)	
- Before treatment	15.31 (± 8.0)
- After treatment	6.72 (± 3.7)
Body Weight (kg)	
- Before treatment	53.69 (± 8.2)
- After treatment	59.41 (± 8.6)
- Weight changes	5.72

Table 1 showed that the majority of GD patients were 48 female. This aligned with the characteristics of patients in the study by Prumnastianti *et al* (2021), which indicated that 72.5% of patients with hyperthyroidism were female.[17] Similar findings were reported in the study by Savitri *et al* in 2016, stating that GD occurs more frequently in females compared to males, at a rate of 70%.[18]

The average age of GD patients in this study was 40 ± 11.6 years. Wardana *et al.* (2019) in their study stated that the highest incidence of GD occurred in the age group of 20–40 years.[19] However, Made *et al.* (2020) in their study indicated that the majority of hyperthyroid cases can occur in the age range of 40–60 years. Nevertheless, both GD and hyperthyroidism can occur at any age.[20]

In this study, GD patients who achieved euthyroidism experienced an increase in TSH levels from 0.38 ± 0.004 μIU/ml to 1.74 ± 1.361 μIU/ml, along with a decrease in free thyroxine (FT4) levels from 25.41 ± 16.51 pmol/l to 8.39 ± 10.97 pmol/l. This indicated that GD patients reaching euthyroidism showed an improvement in thyroid function. The average time to achieve euthyroidism in the subjects of this GD study was 16 ± 13.4 months. This study was consistent with the findings of Azizi et al. in their study in 2022, which stated that GD patients reach euthyroidism within 2–16 months after receiving MMI drug therapy.[21]

The use of MMI in this study was chosen over PTU due to the greater effectiveness and safety of MMI for hyperthyroid patients in terms of reducing FT4 levels and increasing TSH levels.[22] The MMI medication has a smaller impact on liver organ damage compared to PTU.[23] The BEST-T2 database indicated that the number of patients receiving MMI therapy was higher than PTU therapy, making it not feasible to conduct a comparative study.

The average MMI dose in this study was 15.31 ± 8.0 mg, with the final dose when patients reached euthyroidism being 6.72 ± 3.7 mg. This aligned with the guidelines set by the European Thyroid Association[1] and the American Thyroid Association[24], which stated that the initial dose for MMI is typically 10–30 mg per day, depending on the severity of the hyperthyroidism. The daily maintenance dose of MMI can be reduced to 2.5–10 mg.

Table 2. Analysis of MMI effect on weight changes in GD patients reaching euthyroidism at Ulin Hospital Banjarmasin

Group	Body Weight (kg)			p-value
	Before MMI Therapy	After MMI Therapy (Euthyroidism)	Change	
All patients (n = 58)	53.69 (± 8,2)	59.41 (± 8.6)	5.72	<0.001*
Gender				
- Male (n = 10)	54.4 (± 8,8)	62.8 (± 10.5)	8.4	0.009*
- Female (n = 48)	53.54 (± 8,2)	58.71 (± 8.1)	5.17	<0.001*
Age (year)				
- 18-40 (n = 31)	52.94 (± 6,5)	58.5 (± 7.7)	5.56	<0.001*
- >40 (n = 27)	54.56 (± 9,9)	60.46 (± 9.5)	5.91	0.003*

Table 2 showed that the average body weight of GD patients increased from 53.69 ± 8.2 kg to 59.41 ± 8.6 kg. Weight gain was also observed in patient groups based on gender and age. The largest change in weight gain was found in the male patient group, reaching 8.4 kg. The results of the analysis of the effects of MMI administration on the weight change

of GD patients reaching euthyroidism at Ulin Hospital Banjarmasin indicate a significant difference ($p<0.001$).

Discussion

This study's results were in line with previous research by Zakirin *et al.* (2022) at H. Adam Malik Hospital Medan involving pediatric GD patients. In that study, there was a significant difference in patients' body weight between the first and second visits after MMI therapy.[25] These study results support the findings of Moretto *et al.* (2012), which indicated a significant body weight change from hyperthyroidism to euthyroidism ($p<0.001$).[26]

Another study by Karmisholt *et al.* (2020) at Aalborg University Hospital found significant differences in weight changes in hyperthyroid patients after receiving ATD therapy ($p = 0.011$).[27] This study was consistent with the study by Kim *et al.* (2018) at Seoul National University Hospital, which concluded that therapy for Graves' disease patients using ATDs such as MMI could lead to weight gain.[15] Both studies used a prospective cohort approach.

Similar findings were obtained by Widyawigata *et al.* (2019) at Dr. Kariadi Hospital Semarang. The study measured changes in body mass index (BMI) in patients before and after thyroidectomy therapy. In this study, there was a significant increase in the BMI status of hyperthyroid patients during the postoperative period. Additionally, gender influenced the increase in BMI.[28] Another study conducted by Figueroa *et al.* (2008) at the Doctors Weight Loss Center stated that there was a significant relationship between BMI and TSH levels. Furthermore, TSH levels increased with age and BMI.[29]

The MMI medication works by inhibiting thyroid peroxidase (TPO), which hinders the combination of tyrosine and iodide, effectively reducing the biosynthesis of thyroid hormones.[30] During therapy, when thyroid hormone levels return to normal, energy expenditure and basal metabolic rate decrease. This often leads to weight gain in GD patients after receiving MMI therapy.[31] The weight gain may be attributed to an increase in body fat mass.[32] On average, male patients experience greater weight gain compared to female patients. This is due to the storage and accumulation of fat in the visceral area, which is more prevalent in males than females due to hormonal differences.[33]

This study represented the first study to analyze the effects of MMI administration on changes in weight in GD patients who achieve euthyroidism in South Kalimantan. The study also provided insights into the time frame for achieving euthyroidism and the weight before and after reaching euthyroidism in GD patients in the endocrine clinic of the internal medicine department at Ulin Hospital Banjarmasin.

Nevertheless, this study still has several limitations that may impact the clinical outcomes. Firstly, the analysis in this study was conducted bivariate, so it couldn't control for other potential risk factors that might influence the results. Secondly, this study did not investigate the biochemical mechanisms that could lead to changes in the weight of GD patients after receiving MMI therapy. This study indicated a weight gain observed in GD patients after undergoing MMI therapy only. Thirdly, the BEST-T2 database did not include information on the dietary habits and carbohydrate intake of patients, which could be related to weight loss. Fourthly, the recorded weight values in the BEST-T 2 database were the weights of patients diagnosed with GD when they visited the endocrine clinic of the internal medicine department at Ulin Hospital Banjarmasin, so the exact initial weight values before GD diagnosis were not precisely known. Moreover, these recorded weight values are

solely based on the history taken between clinicians and patients, rather than measurements using weight scales. Fifthly, the determination of euthyroid status in the patient database was not based on thyroid hormone receptor antibody (TRAb) but still relied on clinical symptom examinations. However, TRAb tests could confirm the clinical symptom, indicating GD as the cause of hyperthyroidism.[34]

Hopefully, this may contribute to knowledge and provide information to healthcare professionals and patients regarding the effects of MMI administration on weight changes in GD patients reaching euthyroidism. For healthcare professionals, an increase in weight in GD patients may be an indicator that the patient is approaching euthyroidism. Therefore, monitoring the laboratory levels of TSH and FT4 in these patients should be performed to avoid the risk of drug-induced hypothyroidism. This information may also influence healthcare professionals to adjust the dosage of MMI for these patients. For patients, this study can serve as an education that weight gain after receiving therapy is a normal occurrence and should not be a cause for concern.[35,36]

Conclusions

There was a significant weight change in GD patients who achieved euthyroidism after MMI administration at the endocrine clinic of the internal medicine department at Ulin Hospital Banjarmasin. Male patients had more weight gain compared to female patients.

Further studies are needed using multivariate analysis to control several risk factors, ensuring more accurate results. Additionally, investigating pathways is necessary to understand the mechanisms leading to weight gain in GD patients when reaching euthyroid status. Hopefully, the BEST-T2 database may provide more comprehensive information on patient history and physical examination results, as well as supplement data on the patient's initial weight before GD diagnosis and the multiple changes in weight after therapy. Moreover, the diagnosis of GD and determining the time to achieve euthyroid status may use TRAb examinations.

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References

1. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European Thyroid Association guideline for the management of graves' hyperthyroidism. Eur Thyroid J. 2018;7(4):167-86.
2. Glover K, Mishra D, Singh TRR. Epidemiology of ocular manifestations in autoimmune disease. Front Immunol. 2021;12:744396.
3. Subekti I, Pramono LA. Current Diagnosis and management of Graves' disease. Acta Med Indones. 2018:50(2);177-82.
4. Badan Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan RI. Riset kesehatan dasar 2013. Jakarta: Kementerian Kesehatan RI; 2013.
5. Hussain YS, Hookham JC, Allahabadia A, Balasubramanian SP. Epidemiology, management, and outcomes of Graves' disease—real-life data. Endocrine. 2017;56(3):568-78.
6. Bayramoğlu E, Elmaogullarl S, Sagsak E, Aycan Z. Evaluation of long-term follow-up and methimazole therapy outcomes of pediatric Graves' disease: A single-center experience. J of Pediatr Endocrinol Metab. 2019;32(4):341-6.
7. Struja T, Fehlberg H, Kutz A, Guebelin L, Degen C, Mueller B, Schuetz P. Can we predict relapse in Graves' disease? Results from a systematic review and

meta-analysis. Eur J Endocrinol. 2017;176(1):87-97.
8. Yanrike H. Perbedaan Efek terapi inisial methimazole dibandingkan dengan propylthiouracil terhadap kadar free thyroxine pada penyakit Graves. [tesis]. [Padang]: Fakultas Kedokteran, Program Studi Pendidikan Dokter Spesialis-1 Bagian Ilmu Penyakit Dalam, Universitas Andalas; 2019.
9. Liu L, Lu H, Liu Y, Liu C, Xun C. Predicting relapse of Graves' disease following treatment with antithyroid drugs. Exp Ther Med. 2016;11(4):1443-58
10. Klatka M, Grywalska E, Partyka M, Charytanowicz M, Kiszczak-Bochynska E, Rolinski J. Th17 and Treg cells in adolescents with Graves' disease: Impact of treatment with methimazole on these cell subsets. Autoimmunity. 2014;47(3):201-11.
11. Kruljac I, Solter D, Vrkljan AM, Solter M. Remission of Graves' disease is not related to early restoration of euthyroidism with high-dose methimazole therapy. Endocr Res. 2015;40(1):25-8.
12. Azizi F, Amouzegar A, Tohidi M, Hedayati M, Khalili D , Cheraghi L, et al. Increased Remission Rates after Long-Term Methimazole Therapy in Patients with Graves' Disease: Results of a Randomized Clinical Trial. Thyroid. 2019;29(9):1192-200.
13. El Kawkgi OM, Ross DS, Stan MN. Comparison of long-term antithyroid drugs versus radioactive iodine or surgery for Graves' disease: A review of the literature. Clin Endocrinol (Oxf). 2021;95(1):3-12.
14. Kyriacou A, Kyriacou A, Makris KC, Syed AA, Perros P. Weight gain following treatment of hyperthyroidism—A forgotten tale. Clin Obes. 2019;9(5):e12328.
15. Kim MJ, Cho SW, Choi S, Ju DL, Park DJ, Park YJ. Changes in body compositions and basal metabolic rates during treatment of Graves' disease. Int J Endocrinol. 2018:9863050.
16. Dahlan MS. Statistik untuk kedokteran dan kesehatan: Deskriptif, bivariat, dan multivariat dilengkapi aplikasi dengan menggunakan SPPS. Edisi 4. Jakarta: Salemba Medika; 2009
17. Prumnastianti G, Setyo SNHY, Santoso D, Santosa RI. Hubungan gangguan fungsi tiroid terhadap kadar LDL-kolesterol. Jurnal SainHealth. 2021;5(2):6-12.
18. Savitri AD, Sutjahjo A, Baskoro A. Perbandingan Kadar thyroid stimulating hormone receptor antibody (TRAb) pasien penyakit Graves' dengan dan tanpa oftalmopati. Jurnal Kesehatan Soetomo. 2016;3(4):151-6.
19. Wardana RCA, Saraswati MR, Dwipayana IMP, Gotera W. Karakteristik pasien gangguan fungsi tiroid di RSUP Sanglah Tahun 2019. JMU. 2023;12(4):65-70.
20. Made N, Srikandi PR, Suwidnya W, Putri K, Srikandi R. Hipertiroidisme Graves disease: Case report. Jurnal Kedokteran Raflesia. 2020;6(1):2020.
21. Azizi F, Saadat N, Abdi H, Mehran l, Masoumi S, Takyar MA, Amouzegar A. Time to normalization and sustainable normal serum thyrotropin concentrations in patients with hyperthyroidism: Comparison of methimazole and radioactive iodine treatments. Endocr Pract. 2022;28(11):1140-5.
22. Tan S, Chen L, Jin L, Fu X. The efficiency and safety of methimazole and propylthiouracil in hyperthyroidism: A meta-analysis of randomized controlled trials. Medicine (Baltimore). 2021;100(30):e26707.
23. Yu W, Wu Y, Li L, Wang J, OuYang H, et Shen H. Side effects of PTU and MMI in the treatment of hyperthyroidism: A systematic review and meta-analysis. Endocr Pract. 2019;26(2):207-17.
24. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association guidelines for diagnosis and management of

hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26(10):1343-421
25. Zakirin, Sugih AK, Tobing TCL, Wahyuni AS, Lubis IND, Nasution BB. Effects of thiamazole administration on weight changes in children with Graves' disease at H. Adam Malik General Hospital Medan, Indonesia. IJRP.ORG. 2021;92(1);154-9.
26. Moretto RL, Pedro ABP, Leite AC. Avaliação do peso corporal em pacientes com doença de Graves durante o tratamento com metimazol. Arq Bras Endocrinol Metab. 2012;56(6):364-9.
27. Karmisholt J, Carlé A, Andersen S. Body weight changes in hyperthyroidism: Timing and possible explanations during a one year repeated measurement study. Eur Thyroid J. 2021;10(3):208-14.
28. Widyawigata RZG, Prajoko YW, Mahati E, Adrianto AA. Tiroidektomi meningkatkan IMT (indeks massa tubuh) pada pasien hipertiroid di RSUP Dr. Kariadi Semarang. JKD. 2019;8(4):1225-35.
29. Figueroa B, Velez H, Irizarry-Ramirez M. Association of thyroid-stimulating hormone levels and body mass index in overweight Hispanics in Puerto Rico. Ethn Dis. 2008:18(Suppl2);151-4.
30. Xu B, Wu D, Ying H, Zhang Y. A pilot study on the beneficial effects of additional selenium supplementation to methimazole for treating patients with Graves' disease. Turk J Med Sci. 2019:49;715-22.
31. Hayashi A, Takano K, Kawakami Y,Hitomi M, Ohata Y, Suzuki A, et al. Short-term change in resting energy expenditure and body compositions in the therapeutic process for Graves' disease. Intern Med. 2020;59(15):1827-33.
32. Chng CL, Lim AYY, Tan HC, Kovalik JP, Tham KW, Bee YM, et al. Physiological and metabolic changes during the transition from hyperthyroidism to euthyroidism in Graves' disease. Thyroid. 2016;26(10):1422-30
33. Sugiritama IW, Wiyawan IGNS, Arijana IGK, Ratnayanti IGA. Gambaran IMT (indeks massa tubuh) katogori berat badan lebih dan obesitas pada masyarakat Banjar Demulih, Kecamatan Susut, Kabupaten Bangli. Denpasar: Program Studi Pendidikan Dokter Fakultas Kedokteran Universitas Udayana; 2015.
34. Maena MQ. Diagnosing Graves' disease and non-Graves hyperthyroidism using TSH receptor antibody test versus non-TSH receptor antibody test methods of diagnosis. OJEMD;10(2):7-17.
35. Hadi S, Tjahjono HK, Palupi M. Systematic review: Meta sintesis untuk riset perilaku organisasional. Yogyakarta:Viva Victory Abadi; 2020.
36. Hariton E, Locascio JJ. Randomized controlled trials-the gold standard for effectiveness research. BJOG. 2018:125(13);1716.