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An observational study of incidence of metabolic syndrome among patients with controlled Grave's disease

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ABSTRACT

Background: Graves disease is one of the most common autoimmune diseases affecting Indians, accounting for 50–80% of hyperthyroidism cases. The major morbidities associated with Graves' disease are universally acknowledged. Thus, preventing metabolic syndrome could lead to a reduction in the country's disease burden.
Objectives: The objectives of this study are to determine the detection of metabolic syndrome in patients who have achieved clinical and biochemical euthyroid status after treatment, as well as to evaluate the clinical and biochemical parameters that lead to metabolic syndrome in Graves' disease patients.
Materials and methods: This is a prospective observational study of 96 Graves' disease patients in a tertiary care hospital in rural Kolkata. The study participants were chosen using systemic random sampling. The clinical and biochemical parameters of the participants in the study were evaluated. The paired t tests were used. A P value of 0.05 is regarded as significant.
Results: After achieving euthyroid status, 36% of the study population developed metabolic syndrome according to International Diabetes Federation (IDF) criteria.93.5% of those who developed metabolic syndrome had a normal BMI at the time of Graves' disease diagnosis.
Conclusion: Following a healthy lifestyle, which includes healthy eating habits, proper drug compliance, and follow-up, may help to prevent the occurrence of metabolic syndrome. By lowering the risk of developing metabolic syndrome, patients may be able to live a healthier lifestyle by keeping the disease under control.

1. Background

Thyroid dysfunction and metabolic syndrome are the two most frequent endocrine disorders with significant comorbidity.[1] The morbidity and mortality caused by both of the aforementioned disorders have a considerable impact on global healthcare.[2,3] Hypothyroidism leads to significant weight gain, primarily due to oedema, whereas hyperthyroidism leads to weight loss, primarily due to an increased catabolic state affecting muscle and adipose tissues.[4] Globally, Graves' disease is the most frequent cause of hyperthyroidism. It is seen in 20–30 people out of 100,000 people in iodine-rich parts of the world every year. It affects 3% of women and 0.5% of males over the world. The highest incidence occurs between the ages of 30 and 60 years, with a population prevalence of 1–1.5%.[5] It has a predilection towards women with a female to male ratio of 5–10:1.[6] Population studies show that 16.7% of the adult population in India suffers from Graves' disease.[7] In a recent study conducted in eastern India, it has been seen that 43.2% people suffer from metabolic syndrome. The incidence of metabolic syndrome in these patients can cast a dark shadow over the proven benefits of achieving remission. It was seen that 52.2% of females and 34.2% of males had the disorder. Further age standardization showed an overall 33.5% prevalence of the metabolic syndrome, with 42.3% females and 24.9% males had the syndrome.[8] It has a female-to-male ratio of 5–10:1,[6] indicating a preference for females. Graves' disease affects 16.7% of India's adult population, according to population research.[7]

According to a recent study conducted in eastern India, 43.2% of

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people had metabolic syndrome. The high prevalence of metabolic syndrome in these patients may put doubt on the benefits of establishing remission. The condition was seen in 52.2% of females and 34.2% of males. Further age standardisation revealed that the metabolic syndrome was present in 33.5% of the population, with 42.3% of females and 24.9% of males.[8]Given the proclivity of the Indian population to develop metabolic syndrome as a result of various factors such as epigenetics, dietary habits, lifestyle, and other factors, as well as the unrestricted appetite of patients in remission in the absence of an enhanced catabolic state, it is necessary to determine the actual incidence and risks of metabolic syndrome in the said population.

In a questionnaire-based follow-up study of 235 patients in Sweden who had previously been treated for hyperthyroidism, it was discovered that 79% of those who had previously been treated for hyperthyroidism had problematic weight gain.[9] Similarly, a study indicated that 69% of patients gained more weight following treatment than they had lost before to remission of Graves' illness.[10]

In a questionnaire-based follow-up study of 235 patients in Sweden who had previously been treated for hyperthyroidism, it was discovered that 79% of those who had previously been treated for hyperthyroidism had problematic weight gain.[9] Similarly, a study indicated that 69% of patients gained more weight following treatment than they had lost before to remission of Graves' illness.[10] Patients with pre-existing obesity, Graves' illness, previous weight loss, and hypothyroidism development all predicted abnormal weight gain.[11]

Regrettably, the specific process behind this remains unknown. Also, there is a possibility that this is due to long-term neurochemical control of food and weight as a result of hyperthyroidism.[12] Failure to adapt food intake to the decrease in catabolism caused by therapy is a prevalent suggestion. A group of patients receiving carbimazole medication but no dietary counselling gained 16% of their body weight, according to studies. The group that received additional supervision from a dietitian, on the other hand, gained 9.8% (p0.05).[13] Furthermore, a study found that inadequate thyroid management and the need for replacement therapy were the root causes of weight increase[14]

Pharmacotherapy-induced remission in Graves' disease could possibly be a risk factor for the development of the metabolic syndrome, diabetes, hypertension, and dyslipidemia. Patients with Graves' illness who are in remission have been seen to gain uncontrollable quantities of weight. The metabolic syndrome load, on top of the Graves' disease illness burden, could result in considerable disadvantages. There are a few modest observational studies on this subject, with few current investigations in our country. As a result, there is a need to handle this situation. As a result, the current study aims to find out how common the metabolic syndrome is in Graves' disease patients who have achieved clinical and biochemical management.This study also attempted to shed some light on the remission state as a risk factor for diabetes development.

2. Material and methods

A prospective observational study was carried out at a tertiary care hospital in rural Kolkata. Diagnosed cases of clinical Graves' disease who were undergoing or had completed thionamide therapy and became clinically and biochemically euthyroid were chosen from general medicine, endocrine outpatient clinics, and general medicine inpatient wards. In addition, patients with no history of metabolic syndrome prior to the diagnosis of Graves' disease and newly diagnosed cases of Graves' disease who do not have altered serum biochemical parameters pertaining to the metabolic syndrome diagnosis or central obesity are included in the study. The study also includes patients ranging in age from 18 to 60 years.Females who were pregnant or planning to become pregnant during the study period were excluded, as were individuals with uncontrolled/poorly treated Graves' disease, diabetes mellitus, systemic hypertension, or dyslipidemia. From 2016 to 2018, the study lasted two years.Using the formula $Z^2p(1\text{-}p)/e^2$, a sample size of 96 was obtained with a relative precision of 0.2 and a confidence interval of 95%. Systematic random sampling was used to generate the computed samples. At the start of the study and throughout the study, every third patient who met the study's criteria was assessed at the baseline with a complete medical history, clinical signs and symptoms, vital measurements such as waist circumference, height, weight, blood pressure, and biochemical parameters such as lipid profile, thyroid function test, and fasting blood glucose levels 1 month after clinical euthyroid state with stable thionamide dosage or discontinuation of thionamides. Informed consent has been obtained from the participants who were willing to participate in the study and for subsequent publication of research findings.

Following that, the subjects were examined for clinical symptoms and biochemical indicators associated with metabolic syndrome, as defined by the IDF (2006) criteria.[22] Blood samples were taken after an overnight fast (8 h) to measure fasting blood glucose levels, and random samples were used for other tests. The metabolic syndrome is defined by triglyceride levels of $\geq$150 mg/dL (1.7 mmol/L), HDL levels of $<$40 mg/dL (1.03 mmol/L) in males and $<$50 mg/dL (1.29 mmol/L) in females, and fasting blood glucose levels of $\geq$100 mg/dL (5.6 mmol/L). Thyroid function tests were performed in the lab using the equilibrium dialysis method. Blood pressure is measured with a mercury manometer, and a systolic or diastolic BP of $\geq$130 or $\geq$85 mm Hg indicates hypertension.

Non-stretchable tape was used to measure waist circumference halfway between the highest points of the iliac crest and the bottom of the ribcage. Obesity is defined as a measurement of $\geq$90 cm in males and $\geq$80 cm in females. Other than the completion of the study, the occurrence of metabolic syndrome was considered the study's endpoint. The Institutional Ethics Committee approved the study, and it was registered with The Drug Controller General of India under the number ECR/322/Inst/WB/2013. SPSSv22 was used to analyse the data. Quantitative variables are expressed as percentages, and statistically significant differences were assessed using the chi-square test, with a significance level of $p < 0.05$.

3. Results

Only 86 of the 96 patients who were enrolled in the research completed it. There were ten study participants (10.42% of the total sample size) who were not followed up with. [1st Table] The bulk of the 86 participants (51.2%) were between the ages of 18 and 30. Females made up a higher proportion of study participants (76.7%) than males (23.3%). The majority of patients who took part in the study (36.1%) had graves' disease lasting 51–75 months, including 25 females and 6 men. The majority of the study population had a BMI of 14.6–17.5 at the time of diagnosis of condition (32.5%). In the study population, no one had a family history of diabetes.

Amongst the various symptoms of the disease such as weight loss with increased appetite, prominence of eyes, preference for cool temperature, puffiness of lids, blurred or double vision, pain or irritation of eyes, decreasing acuity, dyspnoea, decreased motility, palpitations of the heart, polyuria, menstrual irregularity a, decrease in menstrual flow, or menorrhea this study assessed the prevalence of two main clinical features such goitre and ophthalmopathy (see Table 1).

The prevalence of goitre and ophthalmopathy at the time of diagnosis of Graves' illness is shown in [Table 2]. The prevalence of ophthalmopathy was reported to be 26.74% across all age groups (23 patients). The age group 18–40 years old had the highest prevalence, while the age group 51–60 years old had the lowest. Similarly, the overall prevalence of goitre was found to be 37.20% across all age groups (32 patients). The age group of 41–60 years had the lowest prevalence, while the age group of 18–30 years had the highest.

Correspondingly, gender-wise 23 patients (26.75%) among the study population were found to have ophthalmopathy at the time of diagnosis of graves' disease of which 73.91% were females and 26.08% were

Table 1
Distribution of study variables among the study participants. (n = 86).

S.no	Variable	n (%)
1	**Age**	44 (51.2)
	18–30 years	25 (29.1)
	31–40 years	10 (11.6)
	41–50 years	7 (8.1)
	51–60 years	
2	**Gender**	20 (23.3)
	Male	66 (76.7)
	Female	
3	**Duration of Graves' disease**	12 (13.9)
	12–25 months	28 (32.6)
	26–50 months	31 (36.1)
	51–75 months	15 (17.4)
	76–100 months	
4	**BMI at diagnosis (In Kg/m^2)**	20 (23.3)
	12–14.5	28 (32.5)
	14.6–17.5	11 (12.8)
	17.6–19.5	27 (31.4)
	19.6–22.9	

males respectively. Likewise, 32 patients (37.20%) of the study population were found to have goitre in which 81.2% were females and 18.8% were males.

Among the study population, 14 patients developed both ophthalmopathy and goitre whereas 9 patients had only ophthalmopathy and 18 patients had only goitre. 45 patients were free of both goitre and ophthalmopathy in the current study. Upon calculating the correlation between ophthalmopathy and goitre, a significant correlation was obtained ($p < 0.006092$). Hence, in this study there is a significant correlation between occurrence of goitre and ophthalmopathy in graves' disease patients.

At the time of diagnosis of graves' disease, 23 individuals (26.75%) of the study group were discovered to have ophthalmopathy, with 73.91% of females and 26.08% of males, respectively. Similarly, goitre was discovered in 32 individuals (37.20%) of the study group, with 81.2% of females and 18.8% of males.

14 patients in the research acquired both ophthalmopathy and goitre, while 9 patients only had ophthalmopathy and 18 patients only had goitre. In the current study, 45 individuals were free of both goitre and ophthalmopathy. When the correlation between ophthalmopathy and goitre was calculated, a significant correlation ($p < 0.006092$) was found. As a result, there is a substantial link between the occurrence of goitre and ophthalmopathy in Graves' disease patients in this study.

The distribution of several clinical and biochemical markers among the study population is shown in [Table 3]. Fasting plasma glucose levels ranged from 72 to 96 mg/dL at enrolment to 76–151 mg/dL after euthyroid condition was achieved. At enrolling, serum triglyceride levels ranged from 53 to 140 mg/dL to 60–420 mg/dL when euthyroid condition was achieved. After achieving euthyroid state, blood high density lipoprotein values ranged from 47 to 87 mg/dL at enrolment to 31–80 mg/dL (see Table 4).

The systolic blood pressure (SBP) ranged from 104 to 124 mm Hg at enrolling to 106–190 mm Hg once euthyroid condition was achieved. Diastolic blood pressure (DBP) ranged from 64 to 82 mm Hg at enrolling to 64–110 mm Hg once euthyroid condition was achieved. The waist circumference ranged from 45 to 66 cm at enrolling to 64–99 cm once euthyroid state was achieved. Serum free T4 levels ranged from 1.61 to 4.52 pmol/L at enrolment to 1.03–1.36 pmol/L once euthyroid state was achieved. Because the patients were being treated for Graves' disease, there was a considerable drop in overall serum free T4 levels.

[4th Table] After achieving control (euthyroid state), 31 out of 86 patients (36.05%) developed metabolic syndrome, with 40.90% of females and 20% of males.

4. Discussion

In this observational study of persons with Graves' illness, we discovered that higher BMI levels were linked to a higher risk of metabolic syndrome. As a result, after achieving clinical and biochemical

Table 3
Association of the Clinical and Biochemical parameters between the enrolment phase and euthyroid phase. (n = 86).

Variables	At enrolment into study Mean (SD)	At euthyroid phase Mean (SD)	p-value[a]
Fasting plasma glucose level	85.402 (±6.08)	95.570 (±15.21)	0.0001
Serum triglycerides	96.88 (±18.37)	138.39 (±42.45)	0.0001
Serum HDL	62.547 (±7.32)	49.812 (±10.56)	0.0001
Systolic BP	121.23 (±5.21)	130.91 (±15.99)	0.0001
Diastolic BP	75.30 (±4.28)	80.56 (±10.01)	0.0001
Waist circumference	55.698 (±6.41)	79.337 (±9.09)	0.0001
Serum free T4	3.338 (±0.80)	1.188 (±0.09)	0.0001

[a] Paired *t*-test was used, P value of <0.05 is significant.

Table 4
Incidence of metabolic syndrome among graves' disease participants. (n = 86).

S. no	Variable	Metabolic syndrome present	Metabolic syndrome absent	p- value
1	**Age**	12 (13.9%)	32 (37.2%)	0.073
	18–30 years	12 (13.9%)	13 (15.1%)	
	31–40 years	6 (7%)	4 (4.7%)	
	41–50 years	1 (1.2%)	6 (7%)	
	51–60 years			
2	**Gender**	4 (4.7%)	16 (18.6%)	0.09
	Male	27 (31.3%)	39 (45.4%)	
	Female			
3	**Duration of Graves**	1 (1.2%)	11 (12.8%)	0.096
	12–25 months	9 (10.5%)	19 (22.1%)	
	26–50 months	15 (17.4%)	16 (18.6%)	
	51–75 months	6 (7%)	9 (10.5%)	
	76–100 months			
4	**BMI at diagnosis (In Kg/m^2)**	1 (1.2%)	19 (22.1%)	<0.00001
	12–14.5	1 (1.2%)	17 (19.8%)	
	14.6–17.5	3 (3.5%)	8 (9.3%)	
	17.6–19.5	26 (30.2%)	11 (12.8%)	
	19.6–22.9			

Table 2
Distribution of clinical features for graves' disease at diagnosis. (n = 86).

Variable	Ophthalmopathy present	Ophthalmopathy absent	p-value	Goitre present	Goitre absent	p-value
Age group	8 (34.8%)	36 (57.14%)	0.281	18 (56.25%)	26 (48.1%)	0.607
18–30	8 (34.8%)	17 (27.0%)		10 (31.25%)	15 (27.8%)	
31–40	4 (17.4%)	6 (9.52%)		2 (6.25%)	8 (14.8%)	
41–50	3 (13.0%)	4 (6.34%)		2 (6.25%)	5 (9.3%)	
51–60						
Gender	6 (26.08%)	14 (22.2%)	0.708	6 (18.8%)	14 (25.9%)	0.449
Male	17 (73.91%)	49 (77.8%)		26 (81.2%)	40 (74.1%)	
Female						

euthyroid status, persons who did not see a considerable drop in BMI acquired metabolic syndrome.

Graves' illness usually strikes people between the ages of 40 and 60.[15,16] A Polish research of 735 Graves' disease patients and 1216 healthy controls demonstrated a link between HLA DRB1*03 and Graves' disease diagnosis at a younger age (less than 30 years).[17] The bulk of the individuals with identified Graves' illness were between the ages of 18 and 30, followed by 31–45 years of age, according to the results of the previously cited study.

Graves' disease is 5–10 times more common in females than in males worldwide (F: M = 5–10:1). Our sample population is based on statistics from throughout the world. The short sample size and periodicity may account for the minor disparity. In autoimmune illness, the fundamental cause of sexual dimorphism has yet to be discovered. However, extensive study has looked into how differences in immune response, organ sensitivity, reproductive function, micro chimerism, sex hormones, and the environment affect the prevalence, susceptibility, and severity of autoimmune illness in males and females.[18]

In India, the prevalence of ophthalmopathy in Graves' disease varies by ethnic group. In a 2014 research of 235 individuals, it was discovered that the incidence of Graves' ophthalmopathy was similar in males (28%) and women (27%).[19] Males have a 5% higher incidence of ophthalmopathy in our study, although these figures are nearly identical to those seen in other regional studies. This higher rate of ophthalmopathy in males can be attributed to smoking, as Indian males are more likely to smoke than Indian females. Female smokers are significantly less common. The most important modifiable risk factor for ophthalmopathy is smoking, which influences the condition's rapid progression.[20]

It was also noted how long it took to establish clinical and biochemical control. It lasted anywhere from 13 months to 94 months. The group 51–75 months had the highest number of patients (36.04%). To obtain first control, a therapy of 18–24 months is usually required. The disparity is likely attributable to a variety of factors including pharmacogenetics, non-adherence, severity of disease at onset, and individual iodine status. In India, iodization of salt is used to attain universal iodine coverage. While the vast majority of patients live in places close to the sea, where iodine is abundant. Solomon et al.[21] conducted a case study with 494 persons to look into the association between iodine consumption and Graves' disease remission rates over a 20-year period. They discovered that the change in Graves' disease remission rates was linked to iodine in the diet over the same time period.

Patients, on the other hand, were informed in great detail about the benefits of compliance as well as the potential hazards of non-compliance. Our patients were highly motivated to stick to the therapy in order to overcome non-adherence. This study also found a significant link between clinical and biochemical parameters like fasting blood sugar, SBP, DBP, serum HDL, serum triglycerides, serum free T4, and waist circumference at enrolment and at achieving euthyroid status, which explains why achieving euthyroid status in Graves' disease with pharmacotherapy leads to significant increases in all of the above-mentioned parameters and influences the development of the disease. Despite the fact that each of the parameters deteriorated significantly as a result of Graves' disease treatment, neither the emergence of metabolic syndrome nor the changes in the parameters were shown to be significantly associated to the time it took to achieve euthyroid condition. In this study, women performed worse than men, with 40.90% of women developing metabolic syndrome compared to 39.90% of men (20% of the men developed the metabolic syndrome). Women in our country's social environment have less time to care for themselves, their eating habits, and their therapy compliance. They're also more likely to binge eat (typically to make up for missing meals), which could have been a risk factor for metabolic syndrome development.

5. Conclusion

Between the start and end of the study, all of the metabolic syndrome's individual parameters show significant worsening. As a result, many patients may benefit from lifestyle adjustment counselling in addition to their disease-specific treatment. These patients may benefit greatly from easily accessible, affordable, and appropriate nutritional guidance, as well as regular follow-up. Our research focused on individuals from rural areas who were from lower socioeconomic categories and couldn't afford to eat three square meals a day.

6. Limitations

Ours was a small-scale observational study conducted in a Tertiary Care Center where referred cases account for the great majority of cases. A large number of cases may have been lost in transit, resulting in an inaccurate representation of the population. Other tests, such as thyroid scanning, blood T3 estimation, serum iodine levels, and genetic testing (HLA DRB1*03), were not possible or performed in our hospital. Patients were, however, reinforced in their drug adherence by suitable incentive, and therapeutic adherence was confirmed orally alone. Because this was a hospital-based study, Berkesonian bias could have played a role.

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Declaration of competing interest

None.

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References

1 Waring AC, Rodondi N, Harrison S, Kanaya AM, Simonsick EM, et al. Thyroid function and prevalent and incident metabolic syndrome in older adults: the health, ageing and body composition study. *Clin Endocrinol*. 2012;76:911–918.
2 Alexander CM, Landsman PB, Teutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes*. 2003;52:1210–1214.
3 Cameron AJ, Magliano DJ, Zimmet PZ, et al. The metabolic syndrome as a tool for predicting future diabetes: the AUSDIAB study. *J Intern Med*. 2008;264:177–186.
4 Iwen KA, Schroder E, Brabant G. Thyroid hormones and the metabolic syndrome. *Eur Thyroid J*. 2013;2(2):83–92.
5 Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. European thyroid association guideline for the management of graves' hyperthyroidism. *Eur Thyroid J*. 2018;7:167–186. https://doi.org/10.1159/000490384, 2018.
6 Alan P. Farwell. Graves' Disease. https://rarediseases.org/rare-diseases/graves-disease/.
7 Usha Menon V, Sundaram KR, Unnikrishnan AG, Jayakumar RV, Nair V, Kumar H. High prevalence of undetected thyroid disorders in an iodine sufficient adult south Indian population. *J Indian Med Assoc*. 2009;107:72–76.
8 Prasad DS, Kabir Z, Dash AK, Das BC. Prevalence and risk factors for metabolic syndrome in Asian Indians: a community study from urban Eastern India. *J Cardiovasc Dis Res*. 2012;3(3):204–211.
9 Berg G, Michanek A, Holmberg E, Nystrom E. Clinical outcome of radioiodine treatment of hyperthyroidism: a follow up study. *J Intern Med*. 1996;239:165–171.
10 O'Malley B, Hickey J, Nevens E. Thyroid dysfunction – weight problems and the psyche: the patients' perspective. *J Hum Nutr Diet*. 2000;13:243–248.
11 Dale J, Daykin J, Holder R, Sheppard MC, Franklyn JA. Weight gain following treatment of hyperthyroidism. *Clin Endocrinol*. 2001;55:233–239.
12 Jansson S, Berg G, Lindsted G, Michanek A, Nystrom E. Overweight – a common problem among women treated for hyperthyroidism. *Postgrad Med*. 1993;69:107–111.
13 Alton S, O'Malley BP. Dietary intake in thyrotoxicosis before and after adequate carbimazole therapy; the impact of dietary advice. *Clin Endocrinol*. 1985;23:517–520.
14 Brunova J, Bruna J, Joubert G, Koning M. Weight gain in patients after therapy for hyperthyroidism. *S Afr Med J*. 2003;93:529–531.
15 El-Kaissi S, Frauman AG, Wall JR. *Intern Med J*. 2004 Aug;34(8):482–491.
16 Van Dyk HJ. Orbital Graves' disease. A modification of the "NO SPECS" classification. *Ophthalmology*. 1981;88:479–483.
17 DeGroot LJ, Quintans J. The causes of autoimmune thyroid disease. *Endocr Rev*. 1989;10:537–562.

18 Manji N, Carr-Smith JD, Boelaert K, et al. *J Clin Endocrinol Metab*. 2006 Dec;91(12): 4873–4880.
19 Weetman AP. *Horm Res*. 2003;59(Suppl 1):114–118.
20 Brent GA. Graves' disease. *N Engl J Med*. 2008;358:2544–2554.
21 Katakura M, Yamada T, Aizawa T, et al. Presence of antideoxyribonucleic acid antibody in patients with hyperthyroidism of Graves' disease. *J Clin Endocrinol Metab*. 1987;64:405.
22 KGMM, Zimmet P. Shaw J.Metabolic syndrome–a new world-wide definition. A consensus statement from the international diabetes federation. *Diabet Med*. 2006 May;23(5):469, 80.