Immunopathologia Persa
http www.immunopathol.com
DOI:10.34172/ipp.2021.06

Clinical and biochemical aspects between "stress" and "non-stress" induced Graves' disease

Mostafa Najafipour[1,2], Masoumeh Zareizadeh[3], Farzad Najafipour[3,4*]

[1]Young Researchers and Elite Club, Ardabil Branch, Islamic Azad University, Ardabil, Iran
[2]Faculty of Medicine, Azad Ardabil University of Medical Sciences, Ardabil, Iran
[3]Endocrine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Department of Internal Medicine, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

***Correspondence to**
Farzad Najafipour, Email;
Farzadnajafipour@gmail.com
Najafipourf@tbzmed.ac.ir

Received 14 April 2020
Accepted 27 June 2020
Published online 17 July 2020

Keywords: Graves' disease, Autoimmunity, Antithyroid peroxidase, Thyroid disease, Stress induced

Abstract

Introduction: The role of stress in the pathogenesis of Graves' disease has been highlighted in many studies. The hereditary pattern of Graves' disease is uncertain because various genetic and environmental factors are known. One of the most important environmental factors is stress. Any kind of stress, such as physical and emotional, can flare or create Graves' disease.
Objectives: The aim of this study was to evaluate the clinical and biochemical aspects of "stress-induced" and "non-stress induced" Graves' disease.
Patients and Methods: This study evaluated 148 patients with Graves's disease. According to perceived stress scale (PSS) all patients were divided into two groups; stress and non-stress induced Graves' group. Chi-square test was used to determine statistical difference in qualitative variables.
Results: The mean ± standard deviation perceived stress scale score in 53 patients in stress induced Graves' disease was 40.24±6.53 and in 95 patients in non-stress induced Graves' disease was 18.47±3.90. In this study the onset of Graves' disease is more severe in the stress induced Graves' disease, however the level of anti-thyroid peroxidase was significantly lower. Duration of methimazole since diagnosis and doses of methimazole in the stress induced Graves' group was shorter than non- stress induced Graves' group ($P<0.001$ and 0.032 respectively) and percent of male was significantly higher in stress induced Graves' group ($P=0.002$).
Conclusion: According to this study, clinical characteristics of stress induced Graves' disease differ with non-stress induced Graves' disease. Generally, severity of disease in stress induced Graves' group was initially more severe (higher FT4 in this group), but duration of disease was shorter than non-stress induced Graves' disease, and these patients had smaller size of goiter and lower anti-thyroid peroxidase (anti-TPO) antibody (anti-TOP Ab).

Citation: Najafipour M, Zareizadeh M, Najafipour F. Clinical and biochemical aspects between "stress" and "non-stress" induced Graves' disease. Immunopathol Persa. 2021;7(1):e06. DOI:10.34172/ipp.2021.06.

Introduction

The first people reporting goiter and ophthalmopathy were Iranian philosophers, Avicenna and Al-Jorjani. These manuscripts were written in 1000 and 1100 AD (1). Graves' disease is an autoimmune disorder, in which the body produces autoantibody-stimulatory receptor on the thyroid (2). The reason of generation of these antibodies is unknown and it is unclear why some people develop, thyroid-stimulating immunoglobulin antibody (TSI Ab) (3). The most important features of this disease are goiter and ophthalmopathy (4). For this reason, in patients with thyrotoxicosis who have ophthalmopathy, Graves' disease is confirmed. Various factors contribute to the development of this disease such as gender, genetic and environmental factors (4, 5). One of these environmental factors is stress. Stress is known as a flam or causative agent. Emotional or physical stress or severe illness may be a factor for the onset of Graves' disease among people who are genetic susceptibility to the disease (6). Stress stimulates the immune system by mechanism of activity of Th17, Th1 and Th2. Increasing these cells stimulates B cells since these cells secrete TSI antibodies (7). Psychological and physical stress can stimulate this mechanism (6), while during the Second World War, the incidence of Graves' disease increased sharply

Key point

Several factors contribute to flare up in Graves' disease, one of which is stress. We evaluated stress induced and non-stress induced Graves' disease. Severity of disease in stress induced Graves' group was more severe, but duration of disease was shorter than that of non-stress induced Graves' group.

in Nazi prisons (8). Paunkovic et al in a prospective study showed while the incidence of Graves' disease had been stable since 1971, it significant increased in eastern Serbia during the civil war in the former Yugoslavia between 1992 and 1995 (9).

Other stresses include; divorce, death of relatives, emigration, change jobs, bankruptcy, torture, accident, falling and thunderbolt (4,7,10). The perceived stress scale is a classic stress assessment instrument. The perceived stress questionnaire was developed by Cohen et al in 1983 and contains 14 questions that measure how much stress a person experienced during his last month (11). Numerous studies have focused on the role of genetics in Graves' disease. Genetics plays an important role in the development of Graves' disease. The study of Brix et al, on monozygot twins, strongly supports the idea that genetic factors play a major role in the etiology of Graves' disease (12). Winsa et al on 208 Graves' patients showed that negative events in life and genetic susceptibility play an important role in the development of Graves' disease (13). However, in addition to genetics, stress also plays a major role in the development and severity of Graves' disease. We therefore decided to do this study on stress induced and non-stress induced Graves' patients.

Objectives

The aim of this study was to evaluate the association between stress and onset or worsening of Graves' disease and differences between "stress induced" and "non-stress induced" Graves' group.

Patients and Methods

Study design

This prospective study was conducted in 2017. This study evaluated 148 patients with Graves' disease in Endocrine Research Center, Tabriz University of Medical Sciences in Iran. The perceived stress scale (PSS) questioner (11) form was filled up for patients and laboratory information was extracted based on information in the records. According to PSS all patients were divided into two groups; stress and non-stress induced Graves' group. Individual scores on the PSS can range from 0 to 56 with higher scores indicating higher perceived stress. PSS score questionnaire was filled after the onset of the disease or long afterwards. Hence the questionnaire was originally a reminder of the past.

Scores ranging from 0-14 are considered low-stress. Scores ranging from 15-28 are considered moderate stress. Scores ranging from 29-56 are considered high perceived stress. All of the patients were divided into two groups: stress induced and non-stress induced Graves' group. In this study, specific stress was considered, thereby score more than the 28 was entry criteria in stress induced Graves' group. Thus patients with scores "between" 0 to 28 were in non- stress induced" Graves' group and those with scores of more than 28 were in stress induced" Graves' group. Mean ± standard deviation of PSS score in stress induced Graves's group and in non-stress induced Graves's group was 40.24 ± 6.53 and 18.47± 3.90 respectively. Graves' disease was diagnosed by assessment of serum TSH, free thyroxin (FT4), diffused goiter and ophthalmopathy. Anti-thyroid peroxidase (anti-TPO) was measured in all of them. To estimate thyroid volume, a clinical examination by an endocrinologist was conducted; since thyroid ultrasound was not used due to reducing the cost. The degree of goiter and ophthalmopathy and rate of relapse or no response to methimazole were determined from available information for all patients. In both groups, the dose and duration of treatment were determined. Patients who did not respond to anti-thyroid drugs were treated with ablative therapy such as radioactive iodine and thyroidectomy.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Tabriz University of Medical Sciences approved this study (IR.TBZMED.REC.1397.067). Accordingly, written informed consent taken from all participants before any intervention.

Statistical analysis

Statistical analysis was done by SPSS 21. The data are shown as mean ± SD and 95% confidence interval. Univariate test for all parameters was adjusted relative to gender and age to check difference between the means of two groups. Chi-square test was used to determine statistical difference in qualitative variables. *P* value less than 0.05 was considered as statistically significant.

Results

This study was performed on 148 patients with Graves' disease. In stress induced Graves' group 53 patients and in non-stress induced Graves' group 95 patients selected. Basic demographic information (before drug therapy) was extracted from the patients' records. Demographic information such as age at the time of diagnosis, thyroid size (estimated by endocrinologist), TSH, FT4 and anti-TPO is shown in Table 1. Patients were divided into two groups according to PSS score. The mean ± standard deviation of PSS score in 53 patients in stress induced Graves' group was 40.24 ± 6.53 and in 95 patients in non-stress induced Graves' group was 18.47 ± 3.90 ($P < 0.001$). The average age of patients in stress induced Graves' group was 27.81 ± 7.49 and in 95 patients in non-stress induced Graves' group was 26.06 ± 7.05 ($P = 0.16$) was not significantly different (Table 1).

Average dose of methimazole per day and average duration of treatment per months are shown in Table 1. The mean ± standard deviation methimazole consumption in the stress induced Grave's group was 5.3 mg/d and in the non-stress induced Graves' disease group was 6.59 mg/d. The duration of taking methimazole in the stress induced Graves' disease and non-stress induced Graves' disease group was 11.92 months and 14.49 months respectively

Table 1. Demographic information in the patients with stress induced and non-stress induced Graves' disease

Parameters	Stress induced Graves' disease (n= 53)	Non-stress induced Graves' disease (n = 95)	*P* value
Age (year)	27.81 ± 7.49	26.06 ± 7.05	0.16[a]
Gender (female/male)	39/14	83/12	0.002[a,*]
PSS (score)	40.24 ± 6.53	18.47 ± 3.90	<0.001[b,**]
TSH (mIU/L)	0.089 ± 0.076	0.109 ± 0.121	0.568[b]
FT4 (ng/dL)	4.109 ± 1.186	3.64 ± 1.30	0.034[b,*]
Anti-TPO (IU/mL)	31.69 ± 18.47	63.88 ± 43.45	<0.001[b,**]
Goiter (g)	34 ± 10.21	44.94 ± 9.03	<0.001[b,**]
ATD (mg/d)	5.3 ± 4.87	6.59 ± 2.38	0.384[b]
ATD (months)	11.92 ± 3.95	14.49 ± 3.185	<0.001[b,**]
Recurrence(negative/positive) number	43/10	79/16	0.461[a]
I131 (no/yes) number	43/10	82/13	0.27[a]
Surgery (no/yes) number	53/0	92/3	<0.001[a,*]

ATD: Anti-thyroid drug (methimazole); PSS, perceived stress scale; TSH, thyroid stimulating hormone.
Variables are expressed as mean ± standard deviation (SD).
* Statistically significant ($P<0.05$); ** Statistically significant ($P<0.001$)
[a] Chi-square test; [b] Univariate test all parameters were adjusted relative to gender and age.

(Table 1). The thyroid size in the stress induced Graves' disease group was smaller than non-stress induced Graves' disease group (34 ± 10.21 g versus 44.94 ± 9.03 g; P=0.002).

In the stress induced Grave's group, percent of men was higher than in non- stress induced Graves' disease group (26.4% versus 12.6%; P=0.02) however, there was no significant difference in recurrence and ablation therapy between two groups (Table 1).

In this study, 122 patients were women and 26 patients were men. All of demographic data by gender are shown in Tables 2 and 3.

As seen in Tables 2 and 3 in male and female groups, methimazole dosage and duration, thyroid size, anti-TPO antibodies were significantly different between stress induced and non-stress induced Graves' disease group.

Discussion

In this study, clinical and biochemical aspects were compared between stress and non-stress induced Graves' disease group. So far, there has been no comprehensive study on the comparison between two groups. One of the important findings in this study was the proportion of men to women. Numerous studies showed that Graves' disease is higher in women than in men. Thus, men account for 10% of Graves' disease patients (14-17). However in this study, the percentage of men in stress induced Graves' disease group was 26% and in non-stress induced Graves' disease group was 12% (P= 0.002). Whether stress in men has contributed more to development of Graves' disease is not yet proven. Our study showed that in stresses induced Graves' disease, FT4 was significantly higher than non-stress induced Graves' disease. The level of TSH in the stress induced Graves' disease group was lower than the non- stress induced Graves' disease group, however this finding was not significant.

Falgarone et al reported the important role of emotional stress in development of Graves' disease (18). They recommended reduction of stress for better response to treatment. Benzodiazepine is given occasionally to reduce stress. Propranolol in addition to reducing heart rate and decreased peripheral conversion of T4 to T3 reduces stress and can also be beneficial by affecting mood. However, some investigators do not accept this theory (5,7,15,16,).

Methimazole dosage and duration of treatment were evaluated between the two groups. The first step in the treatment of Graves' disease is drug therapy. The duration of drug therapy in these patients is 1 to 2 years. If patients do not respond to treatment during this period,

Table 2. Demographic information in 122 females with stress induced and non-stress induced Graves' disease

Parameters	Stress induced Graves (n = 39)	Non-stress induced Graves (n = 83)	*P* value[a]
Age (y)	27.62 ± 6.73	26.09 ± 7.25	0.32
TSH (mIU/L)	0.103 ± 0.084	0.109 ± 0.125	0.82
FT4 (ng/dL)	3.94 ± 1.20	3.50 ± 1.18	0.09
Anti-TPO (IU/mL)	31.75 ± 16.52	63.81 ± 44.34	<0.001**
Goiter (g)	34.48 ± 10.20	44.60 ± 9.12	<0.001**
ATD (mg/d)	4.56 ± 1.22	6.59 ± 2.42	<0.001**
ATD (months)	11.55 ± 4.18	14.24 ± 3.19	0.001**

ATD: Anti-thyroid drug (methimazole); TSH, thyroid stimulating hormone.
Variables are expressed as mean ± standard deviation (SD).
* Statistically significant ($P<0.05$); ** Statistically significant ($P<0.001$)
[a] Independent samples *t* test.

Table 3. Demographic information in 26 males with stress induced and non-stress induced Graves' disease

Parameters	Stress induced Graves (n = 14)	Non-stress induced Graves (n = 12)	*P* value[a]
Age (y)	28.04 ± 8.47	25.95 ± 6.45	0.37
TSH (mIU/L)	0.071 ± 0.063	0.11 ± 0.108	0.152
FT4 (ng/dL)	4.30 ± 1.16	4.15 ± 1.60	0.715
Anti-TPO (IU/mL)	31.62 ± 20.15	64.15 ± 41.06	0.002*
Goiter (g)	33.41 ± 10.41	44.100 ± 8.89	0.001**
ATD (mg/d)	6.18 ± 7.09	6.59 ± 2.28	0.807
ATD (months)	12.37 ± 3.69	15.45 ± 3.01	0.005*

ATD: Anti-thyroid drug (methimazole); TSH, thyroid stimulating hormone.
Variables are expressed as mean ± standard deviation (SD).
* Statistically significant ($P<0.05$); ** Statistically significant ($P<0.001$); [a] Independent samples *t* test.

methimazole should be discontinued and final treatment (ablation therapy) should be given to them (15, 19).

The discontinuation of methimazole in our patients was due to improvement or because of lack of response to drug and then, ablation was conducted. In some cases, lack of response to a medication was not due to time of drug therapy alone, while it could be due to inability to reduce methimazole dosage during a specified time, which in such cases ablation was performed. Ablation therapy with iodine 131 occurred in both groups, which was not statistically significant. Nevertheless ablation therapy with surgery only occurred in non- stress induced Graves' disease.

Clinical aspects of Graves' disease are more strongly associated with higher levels of FT4 (7,10,17). The onset of Graves' disease is more severe (higher FT4) in stress induced Graves' disease, however, the level of anti-TPO was significantly lower than of non-stress induced Graves' disease. The hypothesis in this regard is that stress is a trigger for the autoimmune Graves' disease.

In this study the dosage and duration of methimazole therapy in the stress induced Graves' group was shorter than non- stress induced Graves' disease group.

Another important finding in this study was a shorter period of treatment in stress induced Graves' disease group. In this group, size of thyroid was smaller and anti-TPO was lower than another group. Another hypothesis for these findings is response to treatment in stress induced Graves' disease group. Our observation showed that treatment in this group occurred faster.

Overall, according to evidence of this study, Graves' disease is somewhat milder in stress induced Graves' disease.

Unfortunately, in our country, thyroid-stimulating immunoglobulin antibody (TSI Ab) is not routinely measured. If we could measure TSI Ab in our study, the reasons for difference between two groups were more specific.

In this study, the parameters were measured separately between men and women with stress and non-stress induced Graves' disease group. There were no significant differences in the parameters in men and women group except in methimazole dose, which was less in women with stress induced Graves' disease group than non- stress induced Graves' disease group.

Several parameters are involved in developing and severity of Graves' disease, such as thyroid size, free T4, free T3, TSI Ab and exophthalmia (3,9,18,19). In our study, stress was a major contributor to severity of disease and duration of treatment.

Conclusion

The stress induced Graves' disease had initially more severe manifestation, but severity of disease is lower in this group. In addition, in stress induced Graves' disease goiter was smaller and anti-TPO was lower than non-stress induced Graves' group. Additionally, doses and duration of treatment with methimazole were also lower. While stress affects Graves 'disease, therefore management of stress is an important part of therapy.

Limitations of the study

Unfortunately, in Iran, TSI Ab is not routinely measured. If we could measure TSI Ab in our study, the reasons for difference between two groups were more specific.

Author's contribution

MN and FN contributed to literature search, study design, data collection, data analysis, data interpretation and writing. FN and MZ participated in the literature search and data collection. MN contributed to study design and data analysis. FN and MZ participated in study design and data interpretation. All authors read and signed the final manuscript.

Conflicts of interest

All authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

This study was supported by Tabriz University of Medical Sciences.

References

1. Nabipour I, Burger A, Moharreri MR, Azizi F. Avicenna, the

first to describe thyroid-related orbitopathy. Thyroid. 2009 Jan 1;19(1):7-8. doi: 10.1089/thy.2008.0299
2. Vargas-Uricoechea H, Bonelo-Perdomo A, Sierra-Torres CH, Meza-Cabrera I. Autoimmune thyroid disease (Flajani-Parry-Graves-von Basedow Disease): an overview of treatment. In: Imam S, Ahmad S, eds. Thyroid Disorders. Cham: Springer; 2016. p. 169-184. doi: 10.1007/978-3-319-25871-3_9
3. Xia N, Ye X, Hu X, Song S, Xu H, Niu M, Wang H, Wang J. Simultaneous induction of Graves' hyperthyroidism and Graves' ophthalmopathy by TSHR genetic immunization in BALB/c mice. PLoS One. 2017;12:e0174260. doi: 10.1371/journal.pone.0174260.
4. Živanović D, Šipetić S, Stamenković-Radak M, Milašin J. Graves-Basedow disease and potential risk factors. Vojnosanit Pregl. 2008;65(8):633-8. doi: 10.2298/vsp0808633z.
5. Tomer Y, Huber A. The etiology of autoimmune thyroid disease: a story of genes and environment. J Autoimmun. 2009;32:231-9. doi: 10.1016/j.jaut.2009.02.007.
6. Sonino N, Girelli ME, Boscaro M, Fallo F, Busnardo B, Fava GA. Life events in the pathogenesis of Graves' disease. A controlled study. Acta Endocrinol. 1993;128:293-6. doi: 10.1530/acta.0.1280293.
7. Zhao SX, Xue LQ, Liu W, Gu ZH, Pan CM, Yang SY, et al. Robust evidence for five new Graves' disease risk loci from a staged genome-wide association analysis. Hum Mol Genet. 2013;22:3347-62. doi: 10.1093/hmg/ddt183.
8. Vita R, Lapa D, Trimarchi F, Benvenga S. Stress triggers the onset and the recurrences of hyperthyroidism in patients with Graves' disease. Endocrine. 2015;48:254-63. doi: 10.1007/s12020-014-0289-8.
9. Paunkovic N, Paunkovic J, Pavlovic O, Paunovic Z. The significant increase in incidence of Graves' disease in eastern Serbia during the civil war in the former Yugoslavia (1992 to 1995). Thyroid. 1998;8:37-41. doi: 10.1089/thy.1998.8.37.
10. Tsatsoulis A. The role of stress in the clinical expression of thyroid autoimmunity. Ann N Y Acad Sci. 2006;1088:382-95. doi: 10.1196/annals.1366.015.
11. Warttig SL, Forshaw MJ, South J, White AK. New, normative, English-sample data for the short form perceived stress scale (PSS-4). J Health Psychol. 2013;18:1617-28. doi: 10.1177/1359105313508346.
12. Brix TH, Kyvik KO, Christensen K, Hegedüs L. Evidence for a major role of heredity in Graves' disease: a population-based study of two Danish twin cohorts. J Clin Endocrinol Metab. 2001;86:930-4. doi: 10.1210/jcem.86.2.7242.
13. Winsa B, Adami HO, Bergstrom R, Gamstedt A, Dahlberg PA, Adamson U, Jansson R, Karlsson A. Stressful life events and Graves' disease. Lancet. 1991;338:1475-9. doi: 10.1016/0140-6736(93)91402-8.
14. Weetman AP. Graves' disease. N Engl J Med. 2000;343:1236-48. doi: 10.1056/NEJM200010263431707.
15. Marcocci C, Leo M, Altea MA. Oxidative stress in Graves' disease. Eur Thyroid J. 2012;1:80-7. doi: 10.1159/000337976
16. Anagnostis P, Boboridis K, Adamidou F, Kita M. Natural course of mild Graves' orbitopathy: is it a chronic remitting or a transient disease? J Endocrinol Investn. 2017;40:257-61. doi: 10.1007/s40618-016-0555-0.
17. Ranabir S, Reetu K. Stress and hormones. Indian J Endocrinol Metab. 2011;15:18. doi: 10.4103/2230-8210.77573.
18. Falgarone G, Heshmati HM, Cohen R, Reach G. Mechanisms in endocrinology: role of emotional stress in the pathophysiology of Graves' disease. Eur J Endocrinol. 2013;168:R13-8. doi: 10.1530/EJE-12-0539.
19. Boelaert K, Newby PR, Simmonds MJ, Holder RL, Carr-Smith JD, Heward JM, Manji N, Allahabadia A, Armitage M, Chatterjee KV, Lazarus JH. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. Am J Med Sci. 2010;123:183-e1. doi: 10.1016/j.amjmed.2009.06.030.