

# Serum Immunoglobulin G4 is Closely Related to Develop Graves' Ophthalmopathy.

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## Introduction

Grave's ophthalmopathy (GO) is most common extrathyroidal manifestation of Grave's disease (GD). It affects about 25-50 % of Graves' patients with variable severity (mild, moderate to severe, and sight-threatening). The possible pathogenesis of GO can be swelling of extraocular muscle and adipose tissue following cytokine induced accumulation of glycosaminoglycans. But we do not know precise mechanism of onset of GO.

In 2001, Hamano *et al.* first reported IgG4-related disease (IgG4-RD) with regard to autoimmune pancreatitis. IgG4-RD is characterized by hypergammaglobulinemia with elevated IgG4 levels. So, variety of IgG4-RD were proposed, such as Riedel's thyroiditis, Mikulicz's syndrome, retroperitoneal fibrosis, multifocal fibrosclerosis (affecting the orbits, thyroid gland, retroperitoneum and other tissues), periaortitis, peirarteritis, and mediastinal fibrosis. However, there are limited data about the relationship between IgG4 and Graves' ophthalmopathy (GO). In this study, we investigated the association between IgG4 and GO.

## Methods

### 1. Subjects

This cross-sectional study was performed on subjects who were visited or referred to Endocrinology and Metabolism Outpatient Clinic of the Hallym University Sacred Heart Hospital, Republic of Korea, from January 2013 to August 2015. The patients initially diagnosed as Graves' disease (GD) were enrolled, and thus none of the patients underwent antithyroid drug medication or surgery or radioiodine treatment in the time of enrollment. The diagnosis of GD was based on the presence of hyperthyroidism, positive TSH receptor antibody (TR Ab), and/or increased <sup>131</sup>I thyroid uptake. GD patients were divided into two groups depending on the presence of Graves' ophthalmopathy (GO) on the basis of NOSPECS and clinical activity score (CAS). Control group composed of euthyroid healthy subjects who did not have any thyroid disorder history.

### 2. Methods

#### 1) Measurement of serum thyroid hormones and thyroid autoantibodies

- Serum T3, free T4, and TSH
- TR Ab, thyroglobulin antibody (Tg Ab), and thyroid peroxidase antibody (TPO Ab)
- Serum IgG and IgG4

#### 2) Ophthalmological evaluation

- NOSPECS' classification system
- CAS

#### 3) Ultrasonographic evaluation

- Hypoechogenicity
- Grade 0, diffuse high-amplitude echoes throughout whole lobe; Grade 1, low-amplitude and nonuniform echoes in whole or several regions; Grade 2, several sonolucent regions; Grade 3, no apparent echoes or very low amplitude echoes throughout whole lobe.

### 3. Statistical analysis

All data are expressed as mean  $\pm$  standard deviation (SD). SPSS program version 23.0 (SPSS, Chicago, IL, USA).

## Results

### 1. Basic characteristics of GD and control groups

Sixty four treatment naïve GD patients were enrolled in the study. And 65 euthyroid healthy subjects who did not have any thyroid disease history were enrolled to the control group. Basic characteristics including age, sex, hormone, autoantibodies, IgG, and IgG4 level of GD and control group are summarized in Table 1.

### 2. IgG4 levels were higher in GD with GO (Table 2, Figure 1)

### 3. IgG4 levels were significantly higher in the severe form of GO (Figure 2)

Table 1. Basic characteristics between Control and GD groups.

	Control (n=65)	GD (n=64)	p
Sex (M/F)	14/51	18/46	0.420
Age (yr)	47.5 $\pm$ 12.7	37.2 $\pm$ 14.9	<0.001*
Family history of AITD [n (%)]	15 (23.1)	17 (26.6)	0.687
Smoking history [n (%)]	11 (16.9)	12 (18.8)	0.822
IgG (mg/dL)	1178.3 $\pm$ 166.9	1299.7 $\pm$ 320.6	0.135
IgG4 (mg/dL)	25.4 $\pm$ 12.8	42.0 $\pm$ 25.9	<0.001*
IgG4/IgG (%)	2.2 $\pm$ 1.1	3.3 $\pm$ 1.9	<0.001*
T3 (ng/dL)	105.3 $\pm$ 19.4	288.3 $\pm$ 140.5	<0.001*
Free T4 (ng/dL)	1.20 $\pm$ 0.18	3.37 $\pm$ 1.89	<0.001*
TSH (mIU/L)	2.101 $\pm$ 1.124	0.002 $\pm$ 0.007	<0.001*
TR Ab (IU/L)	0.28 $\pm$ 0.33	13.03 $\pm$ 13.09	<0.001*
Tg Ab (IU/mL)	70.8 $\pm$ 118.7	663.8 $\pm$ 1114.6	<0.001*
TPO Ab (IU/mL)	27.2 $\pm$ 56.9	245.0 $\pm$ 232.4	<0.001*
Thyroid size (mm <sup>2</sup> )	1132.1 $\pm$ 93.8	1386.5 $\pm$ 270.4	<0.001*
Hypoechogenicity	0.12 $\pm$ 0.33	1.25 $\pm$ 0.47	<0.001*
Color Doppler flow	0.08 $\pm$ 0.27	1.00 $\pm$ 0.69	<0.001*

\*p < 0.05. Data are presented as mean  $\pm$  SD. GD, Graves' disease; AITD, autoimmune thyroid disease; IgG, immunoglobulin G; IgG4, immunoglobulin G4; TR Ab, thyroid stimulating hormone receptor antibody; Tg Ab, thyroglobulin autoantibody; TPO Ab, thyroid peroxidase antibody.00

Table 2. Comparison between GD without and with GO groups.

	GD without GO (n=42)	GD with GO (n=22)	p
Sex (M/F)	16/26	2/20	0.019*
Age (yr)	39.3 $\pm$ 14.2	33.2 $\pm$ 15.7	0.060
Family history of AITD [n (%)]	11 (26.2)	6 (27.3)	1.000
Smoking history [n (%)]	4 (9.5)	8 (36.4)	0.016*
IgG (mg/dL)	1194.5 $\pm$ 175.1	1500.5 $\pm$ 429.2	0.022*
IgG4 (mg/dL)	28.9 $\pm$ 13.7	66.9 $\pm$ 25.4	<0.001*
IgG4/IgG (%)	2.5 $\pm$ 1.3	4.7 $\pm$ 1.9	<0.001*
T3 (ng/dL)	246.5 $\pm$ 99.9	368.1 $\pm$ 171.9	0.002*
Free T4 (ng/dL)	2.84 $\pm$ 1.33	4.40 $\pm$ 2.35	0.010*
TSH (mIU/L)	0.003 $\pm$ 0.009	0.001 $\pm$ 0.003	0.522
TR Ab (IU/L)	7.98 $\pm$ 9.06	22.68 $\pm$ 14.31	<0.001*
Tg Ab (IU/mL)	302.3 $\pm$ 304.3	1353.9 $\pm$ 1669.0	0.005*
TPO Ab (IU/mL)	229.9 $\pm$ 237.4	273.8 $\pm$ 225.2	0.589
Thyroid size (mm <sup>2</sup> )	1376.4 $\pm$ 246.5	1405.8 $\pm$ 316.4	0.702
Hypoechogenicity	1.17 $\pm$ 0.38	1.41 $\pm$ 0.59	0.069
Color Doppler flow	0.98 $\pm$ 0.60	1.05 $\pm$ 0.84	0.855

\*p < 0.05. Data are presented as mean  $\pm$  SD. GD, Graves' disease; GO, Graves' ophthalmopathy; AITD, autoimmune thyroid disease; IgG, immunoglobulin G; IgG4, immunoglobulin G4; TR Ab, thyroid stimulating hormone receptor antibody; Tg Ab, thyroglobulin autoantibody; TPO Ab, thyroid peroxidase antibody.

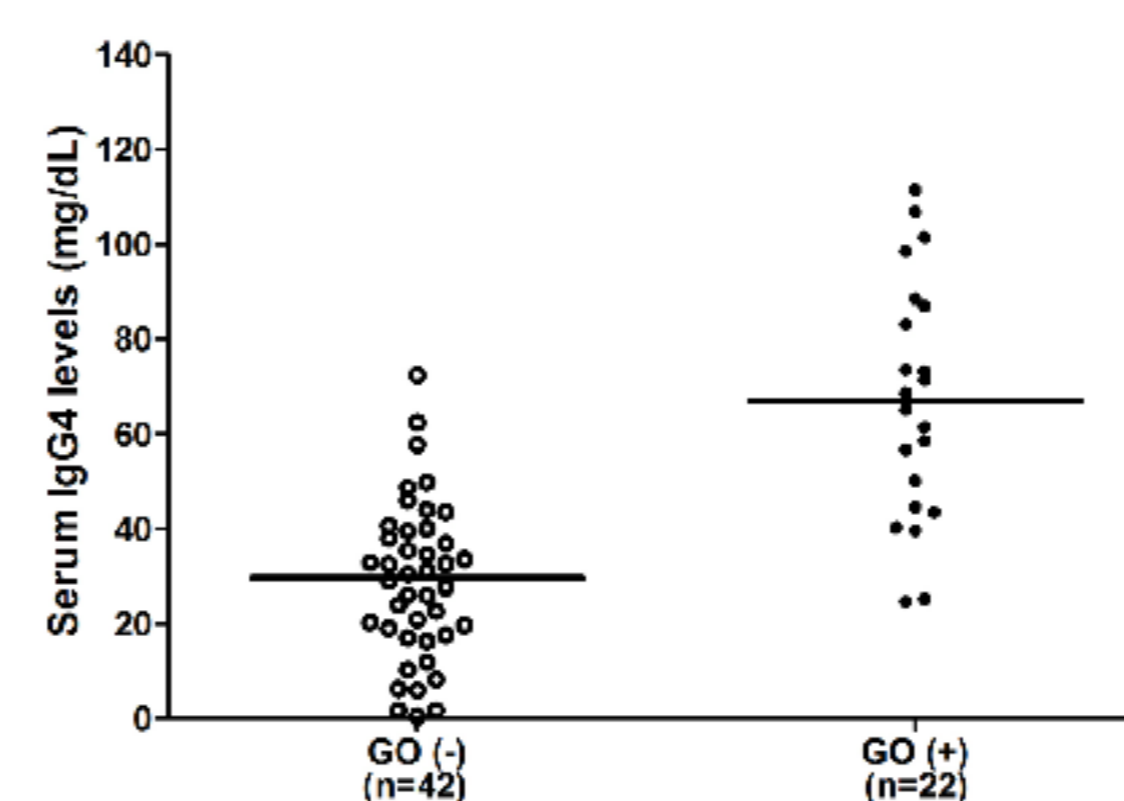


Figure 1. Distribution of IgG4 between GD without and with GO groups.

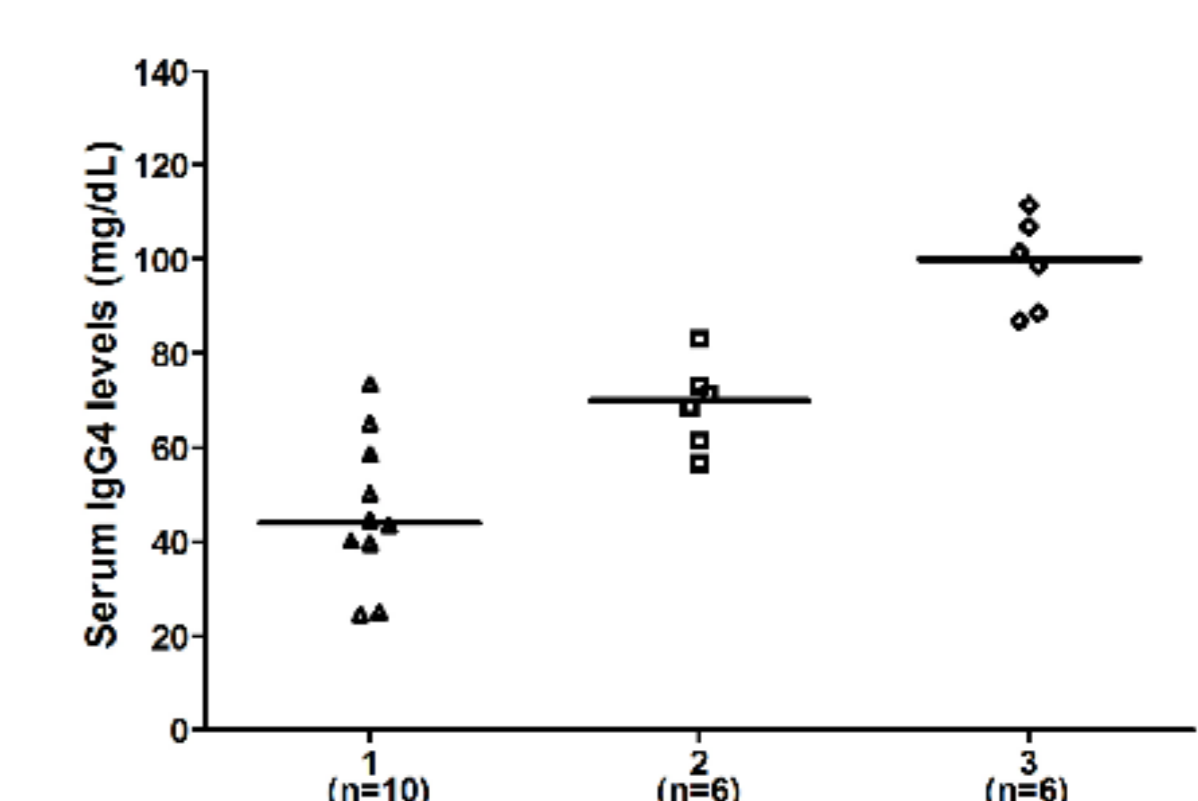


Figure 2. IgG4 levels were significantly higher in the severe form of GO based on CAS assessments in GD with GO patients

Table 3. Correlation of serum IgG4 levels to clinical and laboratory parameters in GD with GO group.

	IgG4	
	r	p
Age	0.067	0.767
IgG	0.063	0.779
T3	0.185	0.411
Free T4	0.400	0.065
TSH	0.0	1.000
TR Ab	0.462	0.031*
Tg Ab	0.386	0.076
TPO Ab	-0.040	0.860

\*p < 0.05. GD, Graves' disease; GO, Graves' ophthalmopathy; IgG, immunoglobulin G; IgG4, immunoglobulin G4; TR Ab, thyroid stimulating hormone receptor antibody; Tg Ab, thyroglobulin autoantibody; TPO Ab, thyroid peroxidase antibody.

## Conclusions

Serum IgG4 levels are elevated in patients with treatment naïve GD. And IgG4 levels were significantly increased according to the severity of GO. Therefore, measuring serum IgG4 levels in treatment naïve GD may help to provide potential therapeutic options for GO.

