



# IgG4-Related orbital disease in patients with diabetic retinopathy: Effects of glucan and vitamin D supplementation

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## Abstract

**Background:** Diabetic retinopathy represents a serious complication of diabetes.

**Methods:** In our group of 52 patients, we identified 7 individuals (13%) with elevated levels of IgG4.

**Results:** Detailed examination revealed significant clinical changes, resulting in a diagnosis of probable IgG4-RD.

**Conclusions:** Long-term evaluation and beta glucan supplementation, combined with vitamin D supplementation, during general treatment of these patients significantly improved both health and mental conditions.

**Keywords:** IgG, IgG4-RD, glucan, vitamin D

## Introduction

Diabetic retinopathy (DR) is a highly specified neurovascular complication of type 1 (DM1) or type 2 diabetes mellitus (DM2). DR is the most common cause of vision loss in people between the ages of 20 and 75 years. DR is the fifth most common preventable cause of serious vision damage and blindness. The most common risk factors involved in DR progression include the duration of diabetes, hyperglycemia, hypertension, obesity, smoking, high levels of lipids, and high insulin levels [1,2]. The prevalence of DR in different countries can reach up to 50% [1-3]. The latest studies, over a 10-year period, demonstrate that intensive monitoring and control of glycemia levels strongly lowers the risk of DR progression [1,2]. Some studies recommended evaluation of the possible effects of dyslipidemia on DR progression. In up to 10% of diabetic patients, DR was observed from the first manifestation of diabetes, which strongly suggests the importance of early diagnosis of DM2.

Monitoring nutritional parameters and their effects can be an important contribution towards the reduction of DM2 induction. Products of oxidative stress activate alternative complement pathways, triggering lower level inflammatory

reactions (pathophysiologic parainflammation) and leading to increased production of C-reactive protein. This protein, together with additional proteins, triggers chronic inflammation. It is clear that mutual relations of mechanisms mentioned above affect vascular, neural, glial, and immune systems, which are damaged by diabetes mellitus [4]. Lately, much attention is focused on the association between vitamin D deficit and risk of diabetes and subsequent DR [5-10]. Both experimental work and population studies confirmed significant positive effects of glucan supplementation in diabetics. Carbohydrates represent a key component in regulating glucose levels. Glucan can be effective either alone or as part of natural food sources [11,12].

This study was based on the hypothesis that interaction between risk factors of DR can be increased by immunological stress, particularly nonspecific immunity. We perform a detailed immunological observation of 52 patients diagnosed with DR and diabetic macular edema [4,13,14]. This complex investigation found seven individuals with high levels of IgG4 subclass.

Hamano and colleagues not only described elevated levels of IgG4 in autoimmune pancreatitis, but also prepared the basis for diagnostic and inspired health professionals from various

disciplines to follow complications of diseases connected with IgG4 levels, which are now defined as IgG4-RD [15]. A high level of IgG4 alone does not indicate a diagnosis of IgG4-RD and should be evaluated together with additional laboratory and clinical results [16-22]. IgG4-ROD (IgG4-related ophthalmic disease) is a recently recognized fibroinflammatory disorder characterized by lymphoplasmacytic infiltrates with large numbers of IgG4-positive plasma cells, eosinophil infiltration, and storiform fibrosis [7,14,23]. In addition, IgG4-ROD is the latest condition to account for some lesions previously labeled as idiopathic orbital inflammation [24]. Both orbital and extraorbital manifestations are often connected with impairments of other organs [17]. To our knowledge, IgG4-ROD has not been described in patients with DR, which led us to do an extensive evaluation of laboratory and clinical parameters of our seven patients [1,3,14,17,20].

## Material and methods

### Patients

From a group of 52 patients diagnosed with diabetic retinopathy and diabetic macular edema, we evaluated 7 patients (6 males and 1 female) with elevated levels of IgG4. Detailed characteristics of these patients are summarized in Table 1.

### Protocol

We explained the experimental protocol and obtained signed consent forms from all participating patients. This study was Institutional Review Board (Regional Masaryk University) approved and performed in full agreement with the Helsinki declaration (revised version 2000.09.01), and in full compliance with the Czech Republic's clinical testing rules.

### Glucan

Yeast-derived insoluble Glucan #300 (>85% dry w/w basis) was purchased from Transfer Point (Columbia, SC, USA). This glucan contains 96% carbohydrates and 2.1% proteins. Neutral sugar analysis confirmed 91.3% glucose and 8% mannose. Glucan, 500 mg, was taken on an empty stomach, followed by 100 ml of water and a 30-minute rest prior to any food intake.

### Vitamin D

Vitamin D (cholecalciferol, D3) was manufactured by Merck (Darmstadt, Germany). One ml of solution contains 20,000 IU of vitamin D3, one drop contains 500 IU. All patients were instructed to ingest vitamin D with fat-containing food.

### Tests

Blood was taken at regular intervals over a period of 3-months from all patients. All immunological and biochemical observations necessary to follow the development of disease, together with basic treatment using subthreshold micropulse laser of retina by an ophthalmologist, was performed.

Vitamin D levels were measured by an ELISA assay using standards recommended by the manufacturer (DRG Instru-

ments, Germany). Based on the manufacturer's information, average values for a healthy common 58-year-old Caucasian population are 26.1 ng/ml in males and 30.2 ng/ml in females. A vitamin D deficit is considered when levels are below 10 ng/ml, insufficient levels range between 10–29 ng/ml, and normal levels range between 30–100 ng/ml. Samples were taken in the morning on an empty stomach.

Serum proteins were evaluated using nephelometer Siemens BM II (Siemens Health Care, Diagnostics, Germany) as suggested by the manufacturer. Relevant reagents and controls were provided by Siemens (Siemens Health Care Diagnostic Products). We measured the levels of IgA, IgG, and IgM and subclasses IgG1, IgG2, IgG3, and IgG4 using nephelometer Siemens BM II as suggested by the manufacturer. Relevant antibodies and controls were provided by Siemens. Evaluation employed IMMULITE 20 analyzer. IgG subclasses were determined using specific antibodies (Binding Site Group, Birmingham, Great Britain). IgG4/IgG, IgG2/IgG, and IgG2/IgG4 ratio, resp., were determined as described [14,25].

Plasma levels of IL-6 were measured by IMMULITE system (Siemens) as suggested by the manufacturer. Relevant reagents and controls were provided by Siemens. Sensitivity of the test was 2 pg/ml.

Evaluations of the levels of T lymphocytes and plasmablasts were based on both available literature and our own work [7,20]. Plasmablasts are given as the percentage of IgM<sup>-</sup>/CD19<sup>+</sup> vs. CD19<sup>+</sup>. For evaluation, we used four-color cytometer FACS CALIBUR (BD Biosciences, USA) using anti-CD19-APC, anti-CD38-PE (BD Biosciences), and anti-IgM-FITC (Dako) antibodies. For Treg evaluation, we used a combination anti-CD127-PE (Beckman Coulter, USA), anti-CD4-PerCP and anti-CD25-APC (BD Biosciences). Tregs levels are shown as percentage of CD25<sup>+</sup>/CD127<sup>-</sup>/CD4<sup>+</sup>.

### Statistical analysis

Paired *t* test statistical significance was evaluated (GraphPad Prism 5.04; GraphPad Software, USA). An average and standard deviation was evaluated after determining standard value composition (D'Agostino, Pearson). In case of nonstandard composition, values were converted into logarithms.

### Results

Table 1 summarizes clinical and laboratory findings in our patients. The tested group consisted of seven patients (six males, one female) diagnosed with DR, all were found in our group of 52 patients and differed only in elevated levels of IgG4. All cases demonstrated extremely low levels of vitamin D (Table 1). Therefore, we started with supplementation with vitamin D (Vigantol) in doses based on sex, phototype, age, and weight. During the winter period, these doses were increased 50%. In all tested cases, we supplemented the food with vitamin D and yeast-derived glucan #300 at dose based on the patient weight, ranging from 500 to 140500 mg/day. In addition, all patients were overweight; one patient with

**Table 1. Basic characteristic of the IgG4-RD Subjects with diabetic retinopathy.**

Patients		HD	HM	FV	ŽP	KM	MM	HJ
Age		61	61	68	66	62	65	62
Gender		F	M	M	M	M	M	M
BMI	kg/m <sup>2</sup>	31.59	36.5	30.47		28.09	26.06	35.46
ABSI	m <sup>11/6</sup> kg <sup>-2/3</sup>	0.095	0.086	0.077	0.079	0.082	0.086	0.085
Smoker			+			+		
Former smoker								
Hypertension			+	+	+	+		+
Vitamin D	ng/ml	12.4	9.8	7.8	18.2	10.5	5	12.8
Hb 1 AC	mol/ml	87	60	57	50	61	75	64
Total cholesterol	mmol/L	4.46	6.61	5.19	5	7.59	4.7	4.29
Triglyceride	mmol/L	1.31	4.3	0.71	1.98	4.96	3.46	0.82
HDL	mnol/L	1.16	0.89	2.64	1.63	0.96	1.36	1.33
LDL	mnol/L	2.94	4.46	2.28	3.08	5.39	3.05	2.83
Aterogenic index	<4	3.84	7.43	1.97	3.07	3.45	3.45	3.23
apolipoprotein A1	g/L	1.5	1.38	1.41	1.89	1.37	1.56	1.39
apolipoprotein B	g/L	0.89	1.41	0.76	1	1.67	1	0.88
Kutners syndrom		+			+			
Lymphadenitis		+	+	+		+	+	+
Alergic disease							+	+
Microvascular disease				+				
Cough			+	+				
Fever		+	+	+	+	+	+	+
Arthralgia		+	+		+	+		+
Sialadenitis				+				
Autoimmune pancreatitis								
Autoimmune disease		+						
Malignancy		+						
Mild NPDR								
Moderate NPDR				+				
Severe PDR		+						
No DME								
NON-CIDME								
CIDME			+		+	+	+	
Diabetes I					+			
Diabetes II		12	24	3	18	22	21	17
Polyneuropathy		+	+		+	+		+
Diabetic nephropathy				+	+	+		

significantly lower BMI had a high ABSI(A Body Shape Index). Initial levels of lipid metabolism resulted from weight and dietary habits. All patients demonstrated multiple clinical impairments. Surprisingly, low rate of smoking compared to normal population was most probably reflecting socio-economic situation of our patients.

**Table 2** shows results of the laboratory examination, which focused on the definition of IgG4-RD disease. In all cases, we found higher levels of IgG4 and IgG4/IgG, and some of the IgG subclasses (IgG1, IgG2, IgG3, and IgG4) divided by IgG. Similarly, IgG4/IgG1+IgG2 and IgG2/IgG ratios were also elevated. Inflammatory reaction with persisting elevated levels

of C-reactive protein and serum amyloid A is accompanied with elevated levels of orosomucoid, which reflects long-term mild inflammatory reaction [26]. We also found elevated levels of IgE in three individuals, but increased levels of specific IgG antibodies against inhaled antigens (grass, pollen, and mites) were found only in one patient. Increased levels of plasmablasts were found in four individuals.

Local treatment of DR is laser photocoagulation (thermal burn in retinal tissue by laser-generated light), used either focally or, in more advanced conditions, panretinally. In proliferative retinopathy and in treatment of its complications, such as bleeding into vitreous body and traction retinal

**Table 2. Laboratory investigation of casis with diabetic retinopathy and IgG4 - RD.**

Parameters	reference intervals	KM		HD		HM		FV	
		sample 1	sample 2	sample 1	sample 2	sample 1	sample 2	sample 1	sample 2
IgG	7 - 16 g/l	13.3	15.9	16.1	19.6	22.4	21.8	12.8	22.7
IgG1	4,1 - 10,1 g/l	7.89	8.12	10.2	11.7	13	11.1	8.04	17
IgG2	1,7 - 7,9 g/l	4.48	4.79	4.52	4.31	8.56	6.64	4.46	5.54
IgG3	0,11 - 0,85 g/l	0.52	0.52	0.79	0.72	0.88	0.72	0.66	1.04
IgG4	0,03 - 1,8g/l	1.16	2.07	2.98	3.29	2.48	2.93	1.1	3.25
IgG1 - IgG4	14,0	14.05	15.5	18.49	20.02	24.92	21.39	14.26	26.83
IgG4/IgG (I) *	10%	9	13	19	17	11	13	9	14
IgG4/IgG (II) **	10%	9.46	13.35	11.5	13.5	11.2	9.8	11.4	11.8
IgG2/IgG4	>1	3.86	2.31	1.52	1.31	3.45	2.27	4.05	1.70
IgG2/IgG	>0,3	0.34	0.30	0.28	0.22	0.38	0.30	0.35	0.24
IgA	0,7 - 4 g/l	3.86	3.76	3.84	4.66	5.13	4.9	6.87	7.37
IgM	0,3 - 2,4 g/l	0.61	0.55	0.88	0.97	0.54	0.59	0.36	0.35
C3	0,75 - 1,4 g/l	1.27	1.33	1.48	1.47	1.49	1.49	1.28	1.41
C4	0,1 - 0,34 g/l	0.46	0.41	0.31	0.25	0.34	0.34	0.19	0.17
CRP	0 - 5 mg/l	6.3	6.43	51.1	3.3	6.36	12.6	9.08	29.9
SAA	0 - 6,4 mg/l		30.7	7	10	9.16	11.6	38.5	3.91
IL-6	0 - 20 pg/ml	2	5.1		2.6	3.2	6.1	3.1	20.5
IgE	0-150 kU/l	32		199		52.5		191	
Spec. IgE		negat		negat		negat		negat	
Orosomuroid	0,5 - 1,2 g/l	1.19	1.2	1.25	0.94	1.4	1.24	1.38	1.76
CD 38++IgM-v CD 19+	0,5 % ± 0,5		1	1.2		1			0.7

Parameters	reference intervals	ŽP		MM		HJ	
		sample 1	sample 2	sample 1	sample 2	sample 1	sample 2
IgG	7 - 16 g/l	10.8	12.9	16.4	14.3	12.8	12.5
IgG1	4,1 - 10,1 g/l	5.26	6.27	7.32	6.71	7.65	7.18
IgG2	1,7 - 7,9 g/l	5.28	5.44	6.51	6.34	4.44	4.1
IgG3	0,11 - 0,85 g/l	0.33	0.33	0.68	0.56	0.72	0.67
IgG4	0,03 - 1,8g/l	0.91	2.04	2.53	2.52	1.97	2.32
IgG1 - IgG4	14,0	11.78	14.08	17.04	16.13	14.78	14.27
IgG4/IgG (I) *	10%	8	16	15	18	15	19
IgG4/IgG (II) **	10%	10.9	10.9	10.4	11.3	14.79	16.3
IgG2/IgG4	>1	5.80	2.67	2.57	2.52	2.25	1.77
IgG2/IgG	>0,3	0.49	0.42	0.40	0.44	0.35	0.33
IgA	0,7 - 4 g/l	1.79	1.83	4.22	3.83	1.43	1.45
IgM	0,3 - 2,4 g/l	0.95	1.16	1.39	1.36	0.95	0.91
C3	0,75 - 1,4 g/l	1.25	1.2	1.12	1.1	1.25	1.31
C4	0,1 - 0,34 g/l	0.33	0.28	0.27	0.27	0.36	0.33
CRP	0 - 5 mg/l	3.74	3.3	3.3	3.17	3.17	3.17
SAA	0 - 6,4 mg/l	1.69	1.79	5.1		6.75	3.95
IL-6	0 - 20 pg/ml	2	2.2	2		2	2.6
IgE	0-150 kU/l	61.7		94.6		1240	
Spec. IgE		negat		negat		6.12	
Orosomuroid	0,5 - 1,2 g/l	0.87	0.85	0.84	0.88	0.8	0.88
CD 38++IgM-v CD 19+	0,5 % ± 0,5	0.2		1		0.4	

detachment, pars plana vitrectomy (vitreous humor gel that fills the eye cavity is removed to provide better access to the retina) is used. Treatment of edema occurring in DR is based on advancement of changes [27,28]. If laser treatment is not adequate, intravitreal application of vascular endothelial growth factor blockers or corticosteroids remain an option.

Another possibility is surgery performed pars plana vitrectomy with peeling of membrane limitans interna and epiretinal membrane.

### Discussion

Diabetes mellitus is a chronic disease characterized by high

levels of blood glucose (hyperglycemia) with typical symptoms of feeling thirsty, polyuria, polydipsia, and weight loss [29]. Medicine recognize three types of diabetes: type I caused by T cell-mediated autoimmune destruction of B lymphocytes; type II caused by cell resistance to insulin; and type III found during pregnancy manifested by both decrease of insulin level and increased resistance to insulin effects [25]. Prevalence of DM2 is steadily increasing, particularly in recent years. This trend is often associated with aging of the population, unhealthy nutritional habits, obesity, low physical activity, and other factors. Lately, we observed significant improvements in treatment of DM2, but obstacles remain such as restricted quality of life and increasing costs of treatment [6,13].

DR is one of the most common complications of diabetes mellitus and currently affects over 100 million people worldwide [1]. This neurovascular complication can occur in patients suffering from either DM1 or DM2, and its prevalence clearly correlates with the length of disease and with the quality of glycemic control [2].

IgG4-RD represents an inflammatory process characterized by tissue infiltration of IgG4-producing lymphocytes. It is a systemic disease affecting various organs previously believed to be unrelated. For detailed information of IgG4-related diseases, see review by Andrew, Kearney and Selva [24]. Since the first description of IgG4-RD with common occurrence of affected pancreas, there is an ever-increasing amount of information connecting this disease with additional tissue complications [7,19,30]. Lately, the attention is focused primarily on the correlation between IgG4-RD and orbital and periorbital impairment [7,14]. However, we found no studies describing IgG4-RD in patients with DR in the literature. In our group of 52 patients, we found 7 patients fulfilling the criteria for IgG4-RD diagnosis. Among these patients, there was a noticeable predominance of males, which is in agreement with the previous data [19,30,31]. Additional characteristics, such as obesity, advanced age, and high BMI and ABSI, suggesting high risk of sarcopenic obesity, were also consistent with current literature [1,17,19,30,32]. The fact that only two out of seven patients were smoking was interesting. Based on age and socioeconomic conditions, the percentage of smokers was significantly lower than in either diabetic or healthy population in the same region, where the percentage of smoking population exceeded 60%. Hypertension represents significant risk in diabetics, and we found this condition in all our patients. Our findings of significant vitamin D deficiency at the beginning of our study are in agreement with older studies [5,6,8-10]. In all patients with IgG4-RD, we found this deficiency to be even stronger than in the rest of diabetic patients. In addition, findings of glycosylated hemoglobin A1C were significantly higher. For some patients, lipid metabolism levels at the beginning of the study (summarized in Table 1) were in all probability distorted by long-term treatment with statins.

Elevated IgG4 levels might be connected with several

additional clinical manifestations including cancer, autoimmune diseases, vasculitis (inflammation of the blood vessels) related to ANCA, and infectious diseases [7]. As we often find elevated IgG in allergic patients, it is necessary to monitor a wide range of possible clinical manifestations, which can be connected with high IgG4 levels [19]. We based our evaluation on the frequency of their occurrence, which was established by Wolfson and Hamilos [31]. During our study, we found no additional clinical impairments which would request the need of targeted therapy. In agreement with current literature, we believe it is beneficial to continue patient monitoring at regular 8-month intervals [30]. Lymphadenopathy can be asymptomatic and persist without any clinical displays. The same is true of signalization of inflammatory reaction by activation of inflammatory proteins, which can be related only to obesity of tested individuals [13,26]. We consider clinical manifestation of IgG4-RD to be the deciding marker [14,15,19,31].

An important criterion necessary for optimal assessment of IgG4-RD diagnosis is evaluation of IgG4 levels. This level determines specificity of diagnosis to 77% and sensitivity of diagnosis to 86%. IgG4 levels higher than 2.01 mg/ml suggest specificity to be 89% and lower (80%) sensitivity [33]. Criteria for IgG4-RD are changing and different authors use limits from 1.35 mg/ml to 2.48 mg/ml [7,14,15,17-20,31,33]. Many authors now agree that the IgG4/IgG ratio is a better marker and levels above 10% are usually considered to be significant [14,16-18,22]. We believe that it would be better to use individual IgG subclasses rather than IgG only. Our findings suggest that the specificity of this evaluation is significantly higher. Lately, some groups have suggested using IgG2 levels and a ratio IgG2/IgG with limit 9.3% and above; or a ratio IgG3/IgG4 with an over 1.0 mg/ml limit [16]. It is important to note, however, that the importance of this index might be affected by allotype or isotype of Caucasian and Oriental races [34].

A better criterion for signalization of chronic inflammatory reaction could be evaluation of orosomucoid level. This acute phase plasma alpha globulin is a better marker of persistent inflammation than C-reactive protein, IL-6, or serum amyloid A [3,13]. Recent studies described galectin-3 expression in patients with IgG4-RD as an important marker of the disease activity [35]. An important benefit for precise diagnosis of IgG4-RD is evaluation of circulating plasmablasts, which is relevant during active and relapse stages of the disease [21,36]. Depressed complement levels could also be used for diagnosis, but we did not find this change in our patients [31].

The basis of DR treatment is to adhere to the suggested curative regiment [1,2]. Usually, the medical team consist of a diabetologist, an ophthalmologist, and a general practitioner. Timely involvement of these specialists is necessary for successful control of diabetes mellitus and for prevention or reduction of its common complications. It was Publilius Syrus who professed in the first century B.C.E. that it is better to use the medicine at the beginning of the disease than at the last moment [29].

Depressed vitamin D levels in patients with DM2 are associated with a higher prevalence of microvascular complications particularly nephropathy, retinopathy, and neuropathy [5,9,10]. Food supplementation with vitamins D, C, and E is recommended not only as prevention, but also for modulation of inflammatory and oxidative stress [8]. Correlation of vitamin D deficiency with risk of development of DR is not acknowledged by some authors. The same authors, however, agree with the importance of vitamin D for the risk of insulin resistance via its effects on insulin receptors with subsequent induction of systemic inflammation and obesity [6]. Extremely low levels of vitamin D were found in all tested patients; healthy population of the same age demonstrates a median level of 18 ng. Glucans have a solid history in reducing the diabetes and insulin. In human studies, glucan in food reduced glycemic index in DM2, reduced postprandial blood glucose and insulin, and, when used as glucan-enriched bedtime snacks, it reduced nocturnal blood glucose levels in diabetic children

[37-39]. In addition, glucan improved wound healing in diabetic mice and prevented diabetes and insulinitis in rats [40,41]. Beta glucans were used in the treatment of diabetes mellitus and in the prevention/reduction of cardiovascular disease risks [25]. The use of glucan resulted in significant improvement of skin conditions on lower extremities in five of seven patients with manifestations of polyneuropathy. Another study, using a cream with 3% glucan, reported significant acceleration of skin healing [42]. The role of glucan's effect on metabolism has been reported in an interesting review by Cloeten et al [43].

Functional food supplemented with glucan represents an important perspective not only for treatment, but also for prevention of diabetes mellitus and additional diseases, and possibly leading to reduce healthcare costs and disease prevalence [11,12].

#### Competing interests

The authors declare that they have no competing interests.

#### Authors' contributions

Authors' contributions	JR	MZ	VV	VK	IS	IL	JP	LRD
Research concept and design	✓	✓	--	✓	✓	✓	✓	--
Collection and/or assembly of data	✓	✓	--	✓	✓	✓	✓	✓
Data analysis and interpretation	✓	✓	✓	✓	✓	✓	✓	✓
Writing the article	✓	✓	✓	--	--	--	--	--
Critical revision of the article	✓	✓	✓	--	--	--	--	--
Final approval of article	✓	✓	✓	✓	✓	✓	✓	✓
Statistical analysis	✓	--	--	--	--	--	--	✓

#### Publication history

EIC: Anna Nasierowska-Guttmejer, Clinical Hospital of Ministry of Internal Affairs, Poland.

Received: 18-May-2018 Final Revised: 27-Jun-2018

Accepted: 03-Jul-2018 Published: 22-Jul-2018

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**Citation:**

Josef R, Martina Z, Vaclav V, Vlastimil K, Ivana S, Ivana L, Jitka P and Lucie RD. **IgG4-Related orbital disease in patients with diabetic retinopathy: Effects of glucan and vitamin D supplementation**. *Pathol Discov*. 2018; **6**:1. <http://dx.doi.org/10.7243/2052-7896-6-1>