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学位論文

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Analysis of pancreatic endocrine function in patients with IgG4-related diseases, in whom autoimmune pancreatitis was ruled out by diagnostic imaging

Running title: Glucose intolerance in IgG4-RD

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Abstract

IgG4-related disease (IgG4RD) is a newly recognized systemic disease characterized by the elevation of serum IgG4 levels and abundant IgG4-positive plasma cell infiltration into the involved organs. Few data exist regarding the relationship between diabetes or glucose intolerance and IgG4RD in the absence of obvious type 1 autoimmune pancreatitis (AIP). Therefore, we are characterizing pancreatic endocrine function in IgG4RD patients with no signs of type 1 AIP. 28 patients (12 men, mean age 62.1 years old) were diagnosed as having IgG4RD from serum IgG4 levels, histopathology and images. Diagnostic imaging ruled out obvious type 1AIP. We used 75g oral glucose tolerance tests (OGTT) and arginine tolerance tests (ATT) to evaluate pancreatic endocrine function. Patients' serum IgG4 and HbA1c levels were 603±437 mg/dL and 6.6±1.0%, respectively. The results of OGTT on 23 patients showed that 12 patients had diabetes, 4 had impaired glucose tolerance, and 7 had normal glucose tolerance. Interestingly, insulin secretion was preserved in most of the patients, even in diabetic patients, on OGTT and ATT. Glucagon hyperreactivity was observed in 10 of the 19 patients who underwent ATT. Twenty-three patients were treated for IgG4RD with glucocorticoids. Their HbA1c levels were significantly elevated during the first six months of treatment, but improved after twelve months in parallel with glucocorticoid therapy. These results demonstrate the high frequency of pancreatic endocrine dysfunction in IgG4RD even when there is no indication of AIP, thus revealing that pancreatic endocrine dysfunction frequently occurs in IgG4RD without obvious type 1AIP.

Key words

IgG4-related disease, autoimmune pancreatitis, glucagon hyperreactivity

Introduction

IgG4-related disease (IgG4RD) is a newly recognized systemic inflammatory disease entity characterized by serum IgG4 level elevation and IgG4-positive plasma cell infiltration into the interstitial space of the involved organs [1-6]. Previous reports indicated that involved organs were the pancreas (type 1 autoimmune pancreatitis: type 1 AIP), lacrimal and salivary glands (chronic sclerosing dacryoadenitis and chronic sclerosing sialadenitis), lungs (interstitial pneumonia; pulmonary pseudotumor), kidneys (tubulointerstitial nephritis), retroperitoneum (retroperitoneal fibrosis) and prostate [1-6]. Usually, the swelling and enlargement of the involved organs, which reflect interstitial inflammation in IgG4RD, are reversible and quickly resolved with anti-inflammatory therapy including glucocorticoid [1]. Several studies have reported on diabetes in type 1 AIP [7-11] and its remission after glucocorticoid therapy [7-11].

Recently, chronic interstitial inflammation has been thought to play a significant role in the initiation and progression of diabetes and its vascular complications [12-15]. So the patients with IgG4RD constitute an excellent study population for using observational data to determine the prognosis for diabetes with chronic interstitial inflammation. However, few data exist regarding the effects of pancreatic endocrine function on IgG4RD, although some patients with IgG4RD frequently had diabetes mellitus or glucose intolerance independent from obvious type 1 AIP and glucocorticoid therapy. Therefore, we examined the pancreatic endocrine function in the IgG4RD patients even though they did not have obvious type 1 AIP.

Material and Methods

Materials

Between January 2000 and April 2011, a total of 36 patients were diagnosed as having IgG4RD (Figure 1). Twenty-eight patients (15 males, mean age 62.1±9.9 years old) met the following inclusion criteria: (1) definite or probable IgG4RD using comprehensive diagnostic criteria for IgG4RD 2011 or diagnostic criteria for IgG4-related kidney disease [16,17]; (2) possible IgG4RD (if biopsy was not possible because of the difficulty of reaching the affected organ(s)) with typical clinical findings and images for IgG4RD [CT, gallium (^{67}Ga) scintigraphy, or FDG-PET] with successful corticosteroid therapy; (3) without malignant disease, vasculitis, tuberculosis, or Castleman's disease. We excluded (1) patients who were diagnosed with type 1 AIP by using 'Clinical Diagnostic Criteria of Autoimmune Pancreatitis 2006 in Japan' [18]; (2) patients who showed accumulation of fluorodeoxyglucose (FDG) in the pancreas with positron-emission tomography (PET), and also had inflammation in the pancreas; (3) patients with no clinical data about glucose tolerance, such as HbA1c, before glucocorticoid therapy (Figure 1). We checked for history of AIP when noting the patients' medical history or from their medical records; those with a history of this condition were excluded. However, it was impossible to exclude patients with AIP who did not have subjective symptoms. With respect to chronic AIP, patients with evidence of pancreatic calcification or pancreatic atrophy on computed tomography scans were excluded; pancreatic atrophy was determined according to a radiologist's interpretation.

Evaluations for the pancreatic endocrine function

Oral glucose tolerance tests (OGTT) were performed with a standard World Health Organization 75g glucose load. Arginine tolerance tests were performed as follows; briefly, arginine (L-Arginine hydrochloride, Ajinomoto Pharma, Tokyo, Japan; 10% arginine, 300 mL/body) was infused for 30 minutes and blood samples were drawn at 0, 15, 30, 45, 60, 90 and 120 minutes after injection of arginine [19,20]. C-peptide reaction (CPR) and immunoreactive glucagon (IRG) concentration were measured each time, and the maximal value was selected to evaluate β-cell and α-cell function.

All of the subjects were assigned to one of three groups; normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and diabetes mellitus (DM) according to World Health Organization (WHO) criteria [21]. Briefly, NGT was defined as fasting plasma glucose (FPG)

≤ 109 mg/dL and 2 hours postload plasma glucose (2h-PPG) ≤ 139 mg/dL. DM was defined as FPG ≥ 126 mg/dl or 2h-PPG ≥ 200 mg/dl. Subjects who didn't meet either of these criteria were designated IGT.

Insulin resistance was estimated using the homeostasis model of assessment-insulin resistance (HOMA-IR) and Matsuda index [22], and insulin secretion was assessed using the homeostasis model of assessment of β-cell function (HOMA-β), insulinogenic index and disposition index [23]. The standard value of each index was follows; HOMA-IR≦1.6, Matsuda index≦2.5, HOMA-β 40-60%, Insulinogenic index >0.4, and Disposition index >1.0. We evaluated the α-cell function by arginine load test. The peak level of IRG equal or more over than 300 pg/mL was evaluated as glucagon hyperreactivity.

Serum IRI and CPR were determined by enzyme immunoassay (Tosoh Co, Tokyo, Japan). Plasma IRG was measured by radioimmunoassay using antiserum monoiodinated ^{125}I-labeled glucagon (TFB Inc., Tokyo, Japan). HbA1c was measured by high performance liquid chromatography (HPLC) using an automated glycohemoglobin analyzer, HLC-723G7 (Tosoh Co., Tokyo, Japan).

The prevalence ratio for DM and IGT in IgG4RD without obvious type1 AIP was evaluated by using the database of the National Health and Nutrition Survey in 2007 by the Ministry of Health, Labor and Welfare in Japan [24].

Statistical analysis

Statistical analyses were performed using JMP 9.0 (SAS Institute Inc. Cary, NC, USA). The data are presented as mean ± standard deviation (SD). Paired-T test, Fisher's exact test and Tukey's HSD test were used for statistical analysis. A *p*-value of less than 0.05 was considered significant for all analysis.

This clinical study was approved by the Ethics Committee of the Kanazawa School of Medicine, and informed consent was obtained from each patient.

Results

1. Frequency of DM and IGT in IgG4RD

The clinical characteristics of all 28 subjects were shown in Table 1. A total of 9 patients had a family history of diabetes mellitus and 16 patients did not; the status of family history was unknown in 3 patients (added to Table 1). All patients tested negative for anti-glutamic acid decarboxylase antibodies. OGTTs were performed in 23 patients, all except those who had been previously diagnosed as having diabetes and treated with oral hypoglycemic agents (OHAs) (case 2, 7, 20, 23 and 27). According to the results of OGTT of these 23 patients, 12 were DM (52.1%), 4 were IGT (17.4%) and 7 were NGT (30.4%). Thus, the frequencies of DM (n=17) and IGT (n=4) in IgG4RD without obvious type 1 AIP was significantly higher than those in the general population, particularly in patients >50 years old, concluded from information reported in the database of the database of the National Health and Nutrition Survey by the Ministry of Health, Labor and Welfare in Japan (2007) [24] (Table 2).

2. Evaluation of pancreatic endocrine function

No reduction in insulin secretion was observed in an arginine tolerance test (ATT), which was performed in 19 patients (10 DMs, 3 IGTs and 6 NGTs) (Table 3). Actually, delta CPR, which reflects intrinsic insulin secretion capacity, in DM was 4.0±2.1, that in IGT was 3.3±1.6 and that in NGT was 4.5±2.1. On the contrary, glucagon hyperreactivity (peak IRG level ≥300 pg/mL) was found in 10 patients on ATT (Table 3). Additionally, delta IRG in DM was 353±284, that in IGT was 219±103 and that in NGT was 195±112.

3. Change in glucose intolerance with glucocorticoid therapy in IgG4RD

The initial dose of prednisolone was 26.7±7.3 mg/day. Twenty-two patients were followed for 12 months after initiation of corticosteroids (Figure 1). The dose of glucocorticoids was reduced to 6.8±2.1 mg/day of prednisolone after 12 months. Actually, seven patients had changes in their treatment for diabetes after glucocorticoid therapy. In 11 patients taking medication for diabetes, 2 patients switched from OHAs to insulin, 4 patients continued OHAs or insulin, and the remaining 5 patients started medication for diabetes with OHAs or insulin. Of the 11 patients who did not receive medication for diabetes, 4 patients were DM, 2 were IGT, and 5 were NGT. Average HbA1c levels of all subjects changed from 6.4±0.8% at baseline to 6.8±1.0% at 3 months (p=0.0368). Surprisingly, their HbA1c level declined to 6.7±0.8% at 6 months (p=0.0417) and 6.5±0.8% at 12 months (p=0.3422) after the initiation of

glucocorticoid therapy (Figure 2). These results showed no statistically significant change in HbA1c levels even after strict glucocorticoid therapy. As for patients taking medication for diabetes (n=11), their HbA1c level completely returned to baseline after 12 months of glucocorticoid therapy.

Discussion

The three main findings of this study were as follows. First, a high frequency of pancreatic endocrine dysfunction was observed in IgG4RD patients without obvious type 1 AIP. Second, the pancreatic endocrine dysfunction was characterized by glucagon hyperreactivity rather than an insulin secretion defect. Third, no significant further deterioration of glucose tolerance due to intensive glucocorticoid therapy was observed in the majority of the cases. These results suggest that IgG4RD-related DM could be treated with glucocorticoid, probably through suppression of glucagon heperreactivity.

IgG4RD sometimes exhibits type 1 AIP accompanied by both endocrine and exocrine dysfunction in the pancreas. Pancreatic endocrine dysfunction has been observed in 83% to 88% of AIP [7-11]. Additionally, 66.5% of Japanese AIP cases were associated with DM; of those, 51.6% developed DM around the same time as the onset of AIP, and 33.3% had DM before the onset of AIP [8]. Following glucocorticoid therapy, 55% and 36% of these AIP patients showed improvement in DM control [8]. On the other hand, 14% of patients showed newly developed DM after corticosteroid therapy [7, 8]. However, few data exist regarding the impact of IgG4RD without AIP on the occurrence of DM and its treatment. The present data revealed that about 70% of the IgG4RD patients had DM or IGT even without obvious type 1 AIP, which is similar to the frequency of DM associated with type 1 AIP.

In this study, glucagon hypersecretion, rather than an insulin secretion defect, could play a central role in the initiation and progression of glucose intolerance in IgG4RD. This finding is relevant to the pathogenesis of glucose intolerance with IgG4RD, since glucagon hypersecretion could be the antecedent findings of general type 2 diabetic patients [25-28]. This finding also suggests the possible involvement of pancreatic islets in IgG4RD even (without AIP. Interestingly, in contrast to present results with IgG4RD without type 1 AIP, the subjects with this association show significant reduction in both glucagon and insulin responses against several stimuli including glucose and arginine [20]. The endocrine dysfunction in AIP is caused by fibrosis due to the inflammatory cells infiltration into the whole pancreas, resulting in secretion defects in the islets of α-cells and β-cells [20]. In addition, Tanaka *et al*. reported that the beta cell count decreased in AIP by immunohistologic examination [29], but did not mention about the change in insulin secretion. In our patients, insulin secretion was comparatively well maintained, indicating that a decline in beta cell count was unlikely. This suggests that IgG4-RD, without AIP, has a different mechanism compared with that of AIP.

Some reports showed that hyperglycemia during the course of corticosteroid therapy occurred within three months in 5-25% of patients who started taking oral glucocorticoids [30-32]. Furthermore, almost all cases with glucocorticoid therapy show deterioration in glucose tolerance and rarely show improvement in glycemic control. The underlying molecular mechanisms for this glucose intolerance were accelerated hepatic glyconeogenesis, reduced glucose uptake in skeletal muscles, and hyperglucagonemia. It depended on the duration of glucocorticoid administration rather than the timing of the first dose of glucocorticoid. In our study, the HbA1c levels of 22 patients became significantly elevated for the first 6 months. After that, they improved, returning to a level not significantly different from the baseline at 12 months. Moreover, half of the patients did not require medication for diabetes. In 11 patients without medication for diabetes, HbA1c levels elevated from 5.8% to 6.4% within 3 months, and then, declined to 6.3%. Thus, in this patient group, glucocorticoid therapy resulted in the elevation of HbA1c by only 0.5%. From this point of view, 11 patients taking medication for DM did not exhibit elevation of HbA1c after 12 months. This may be explained by the DM drugs taken by patients in the latter group.

There are some limitations in the present study. First, we could not obtain histological findings for the pancreas in IgG4RD without obvious type 1 AIP because of difficulty in pancreatic tissue sampling. However, pancreatic imagings strongly suggested the absence of type I AIP in the present cohorts. Second, medication for DM was not consistent in this study. Therefore, medication for diabetes might have altered the clinical course of diabetes. However, the finding of HbA1c reduction even with glucocorticoid therapy, clearly showed that there was improvement in glucose tolerance throughout the present study.

In conclusion, this is the first report that pancreatic endocrine dysfunction without obvious AIP frequently occurs in IgG4RD. Under these conditions, intensive glucocorticoid therapy is effective in improving glucose tolerance. We suggest that evaluation of pancreatic endocrine dysfunction provides clinical information indicating the early pancreatic involvement of IgG4RD even without significant morphological changes.

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No potential conflicts of interest relevant to this article were reported. N.I. designed and performed the study, analyzed the data, and wrote the manuscript. K.Y., M.K., Y.M., S.O., D.C., Y.T., J.K. contributed to discussion and reviewed and edited the manuscript. M.Y. is the guarantor of this work and, such as, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors would like to thank Reiko Ikeda for their assistance with the data collection.

Disclosure

None of the authors have any conflicts of interest associated with this study.

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Table 1

Characteristics of subjects with IgG4-related disease

No.	Age	Gender	BMI (kg/m2)	IgG /IgG4 (mg/dL)	IgE (IU/mL)	Diagnosis by patho-histology	Diagnosis by image	FH of DM	HbA1c (%)	OGTT type	HOMA -IR	Matsuda index	HOMA -β (%)	I.I.	Disposition index	GC	Medications for DM	
																	before CG	after GC
1	65	M	29.5	3310/1420	74	LG		+	9.7	DM	1.37	7.63	6.8	0	0.01	-	GL, BG	-
2	58	F	32.1	1960/164	1621	SG		unknown	8.3	-						-	SU, BG, αGI	-
3	64	F	30.9	1820/486	90	LG		+	5.6	NGT	2.72	1.73	155.6	1.04	1.80	+	none	none
4	46	F	29.4	1350/209	170	LG, SG		-	7	DM	7.5	1.38	141.1	0.33	0.46	+	αGI	αGI
5	60	M	17.1	1480/463	5310	LG, Skin		+	6.8	DM	0.68	13.13	14.5	0.08	1.01	+	none	Insulin, GL, αGI
6	53	F	27	2260/359	611	LG, SG		+	7.2	DM	4.11	1.96	67.2	0.21	0.40	+	none	Insulin, GL
7	66	M	19.9	1457/173	-		RP	unknown	6.7	-						+	GL	GL
8	66	M	25	1900/575	151	LG, SG, Skin		unknown	5.6	IGT	1.34	2.71	84.5	1.47	4.00	+	none	none
9	76	F	27.4	2840/769	414	LG, Kidney		-	5.9	DM	2.79	2.00	109.9	0.56	1.12	+	none	none
10	58	M	18.7	2850/1280	456	Kidney, Liver		-	5.5	IGT	1.09	6.28	54.6	0.42	2.26	+	GL	GL
11	64	M	28.7	3070/1800	302	SG, Lung		+	7.3	DM	5.86	1.40	110.3	0.22	0.31	+	none	Insulin, BG
12	75	F	23.1	3695/500	1226	Lung, Kidney		-	5.6	DM	2.49	3.68	102.2	0.17	0.61	+	none	none
13	61	F	20.5	2152/345	1935	SG		-	5.7	NGT	1.71	3.57	108.0	1.17	4.16	+	none	none
14	68	M	28.3	4661/1120	335	Kidney		-	6.9	DM	2.63	3.18	72.0	0.28	0.89	+	none	unknown
15	58	F	25.2	1674/606	3		LG	+	6.7	DM	2.52	2.45	66.9	0.57	1.39	+	none	none
16	44	M	23.3	1332/599	351	LG		+	6	NGT	0.77	7.97	30.2	0.18	1.40	+	none	none
17	77	M	18.7	1813/438	375	SG		-	5.7	IGT	1.21		69.4	0.38	2.32	+	none	none
18	73	M	22.8	1487/196	47		RP	-	6.6	IGT	2.38	2.90	58.2	0.38	1.10	-	none	-
19	61	M	20.1	3323/916	1500	SG, Lung		-	5.6	NGT	2.32	5.20	102.7	1.02	5.32	+	none	none
20	68	M	24.7	3391/736	-	Kidney, LN		-	6	-						+	SU, αGI	Insulin
21	61	F	24.9	1481/152	1938		Lung, Kidney	-	6.1	DM	2.36	2.78	80.8	0.22	0.62	+	none	none
22	46	M	23.2	1865/860	83	LG, SG		-	6	NGT	0.99	7.98	42.2	0.74	5.94	+	none	none
23	70	M	24.9	2081/870	1285	SG, Prostate		-	8.6	-						+	Insulin, BG	Insulin, BG
24	79	F	22.5	1261/260	301	SG		+	6.7	DM	1.32	6.43	43.7	0.19	1.20	+	none	BG, DPP-4
25	60	M	22.3	2141/1100	459	LG, Kidney		-	6.8	DM	0.8	9.13	30.3	0.06	0.56	+	SU, TZD	Insulin, TZD
26	41	F	22.1	1554/260	134	LG		+	5.1	NGT	1.06	8.14	87.4	0.98	7.94	-	none	-
27	64	F	26	1214/67.6	47	SG		-	7.2	-						-	SU, αGI	-
28	57	F	24.5	1686/173	188	LG		−	6.5	NGT	1.17	6.73	38.6	0.44	2.93	+	none	αGI
Mean ±SD	62.1 ±9.9		24.4 ±3.8	2182±877 /603±437	476 ±1112				6.6 ±1.0		2.23 ±1.66	4.93 ±3.14	72.9 ±38.5	0.48 ±0.40	2.08 ±2.07			

FH, family history; I.I., Insulinogenic index; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; DM, diabetes mellitus; GL, glinide; SU, slufonylurea; αGI, αglucosydase inhibitor; BG, biganide; TZD, thiazolidine; DPP-4, dipeptidyl peptidase-4 inhibitor; LG, lacrimal gland; SG, salivary gland; LN, lymph nodes; RP, retroperitoneum; GC, glucocorticoid therapy.

Table 2

Comparison of the prevalence rate of DM or IGT patients with Japanese general population and IgG4RD without obvious type 1 AIP

	Standard population (2007)			IgG4RD without obvious type1 AIP			
Age	Total	DM/IGT	%	Total	DM/IGT	%	*p**
40-49	557	85	15.3	4	1	25.0	0.6153
50-59	711	194	27.3	5	4	80.0	0.0145
60-69	934	331	35.4	13	10	76.9	0.0024
70-	1008	379	37.6	6	6	100	0.0006

Data of standard population was quoted by National Health and Nutrition Survey in 2007 by Ministry of Health, Labor and Welfare in Japan. * Fisher's exact test.

Table 3

Serum level of C-peptide and plasma level of glucagon in arginine tolerance test

OGTT pattern	Patient No.	CPR 0' (ng/mL)	CPR peak (ng/mL)	ΔCPR	IRG 0' (pg/mL)	IRG peak (pg/mL)	ΔIRG
DM	5	1.1	3.2	2.1	87	312	225
	6	2.7	6.7	4	134	611	477
	9	2.1	6.8	4.7	123	225	102
	11	2.6	5.1	2.5	151	731	580
	12	4.5	9.5	5	150	523	373
	14	4.5	11.1	6.6	464	1423	959
	15	3.3	11.4	8.1	140	365	225
	24	1.8	5.3	3.5	96	178	82
	25	4.6	5.9	1.3	95	248	153
	27	2.0	4.5	2.5	ND	ND	ND
Mean±SD		2.9±1.3	7.0±2.8	4.0±2.1	160±117	513±389	353±284
IGT	8	2.9	7.6	4.7	125	429	304
	17	1.0	2.6	1.6	79	183	104
	18	2.1	5.8	3.7	94	343	249
Mean±SD		2.0±1.0	5.3±2.5	3.3±1.6	99±23	318±125	219±103
NGT	13	1.7	8.4	6.7	128	510	382
	16	1.1	3.2	2.1	145	292	147
	19	1.8	5.5	3.7	112	218	106
	22	1.1	8.4	7.3	88	367	279
	26	1.2	5.7	4.5	71	225	154
	28	2.2	4.8	2.6	62	166	104
Mean±SD		1.5±0.5	6.0±2.1	4.5±2.1	101±33	296±126	195±112

ND, not done

Figure 1

Study enrollment and flow of patients

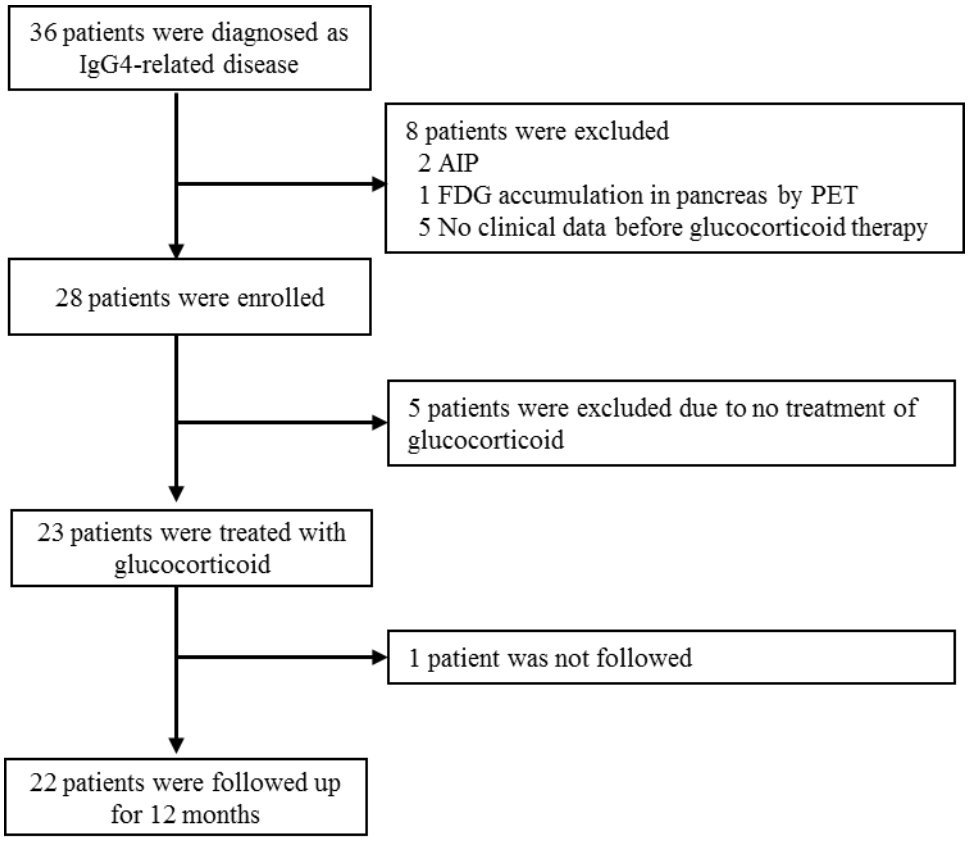
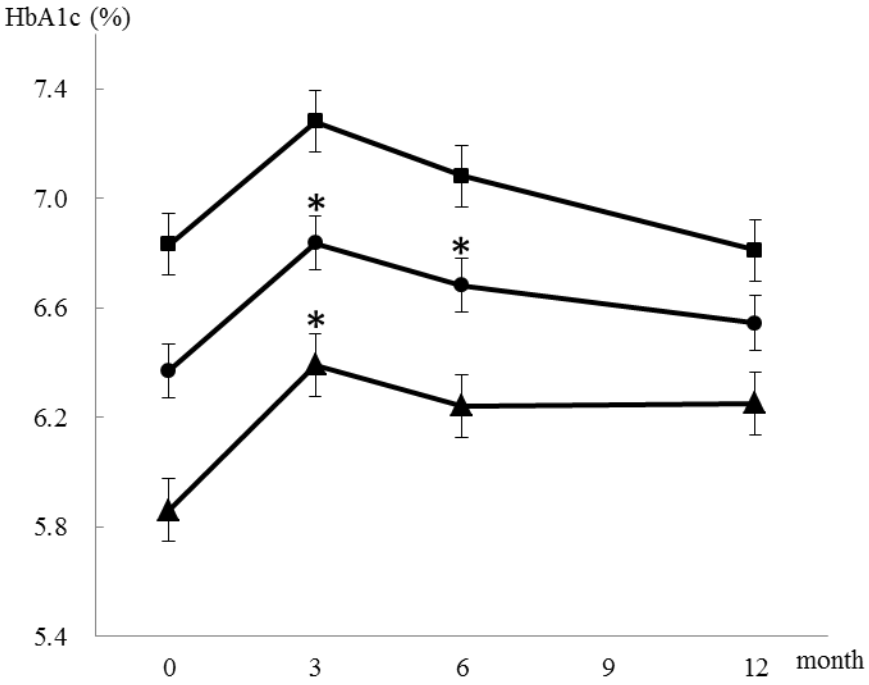


Figure 2

Change of HbA1c level after initiation of glucocorticoid



Twenty-two patients were followed for 12 months after initiation of glucocorticoid. In 11 patients with medication for diabetes with filled squares (■), 2 patients switched from OHAs to insulin, 4 patients continued OHAs, and the remaining 5 patients newly started medication for diabetes with OHAs or insulin. In 11 patients without medication for diabetes with filled triangles (▲), 4 patients were DM, 2 were IGT, and 5 were NGT. HbA1c levels of all subjects with filled circles (●) changed from 6.4±0.8% at baseline to 6.8±1.0% at 3 months (p=0.0368). HbA1c level declined to 6.7±0.8% at 6 months (p=0.0417) and 6.5±0.8% at 12 months (p=0.3422) after the initiation of glucocorticoid therapy. * p value is <0.05 vs baseline.