Available online at www.sciencedirect.com

ScienceDirect

Journal of the Chinese Medical Association 81 (2018) 230–235

www.jcma-online.com

Original Article

Increased prevalence of proliferative retinopathy in patients with acromegaly

Tzu-En Wu [c], Harn-Shen Chen [a,b,*]

[a] Division of Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC
[b] Faculty of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC
[c] Department of Ophthalmology, Shin-Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan, ROC

Received March 31, 2017; accepted August 3, 2017

Abstract

Background: This pilot study was carried to determine the prevalence of retinopathy, especially proliferative retinopathy, in patients with acromegaly.
Methods: We analyzed 43 acromegalic patients and 129 age- and gender-matched patients with type 2 diabetes. The retinopathy status was determined from the medical records based on the ophthalmologist consultations of patients with acromegaly. Color photographs of the macula- and disc-centered views were obtained at an angle of 45° with a fundus camera after pharmacologic-induced mydriasis in patients with type 2 diabetes.
Results: Compared with age- and gender-matched patients with type 2 diabetes, the acromegalic patients had lower fasting plasma glucose levels and lower systolic and diastolic blood pressures, but were taller and had higher IGF-1 levels. Any degree of retinopathy was present in 9.3% (4 of 43) of patients with acromegaly and 34.9% (45 of 129) of patients with type 2 diabetes (odds ratio [OR] = 0.191; 95% confidence interval [CI] = 0.064–0.570). Proliferative retinopathy was present in 9.3% (4 of 43) of patients with acromegaly and 9.3% (12 of 129) of patients with type 2 diabetes (OR = 1.000; 95% CI = 0.305–3.281). Non-proliferative retinopathy was absent in patients with acromegaly, but present in 25.9% (33 of 129) of patients with type 2 diabetes.
Conclusion: The high proliferative, but absence of non-proliferative retinopathy in our patients with acromegaly may reflect the pathogenic effect of IGF-1 on neovascularization. IGF-1 may play an important role in proliferative retinopathy, but may play no role in non-proliferative retinopathy.

Keywords: Acromegaly; Growth hormone; IGF-1; Proliferative retinopathy

1. Introduction

Acromegaly is a rare chronic disease that is characterized by hypersecretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) and is caused by pituitary adenomas in >95% of patients.[1] GH hypersecretion leads to excessive skeletal growth, soft tissue enlargement, insulin resistance or diabetes, and cardiovascular, cerebrovascular, and respiratory diseases.[1]

Neovascularization is the final common pathway in diabetic retinopathy and IGF-1 has been associated with retinal neovascularization.[2] The retina has also been identified as a target of excessive IGF-1, and increased serum and intraocular IGF-1 have been reported in acromegalic patients with diabetic retinopathy.[3,4] IGF-1 modulates the function of retinal endothelial precursor cells, drives retinal angiogenesis in response to hypoxia, and may play a role in the pathogenesis of

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Dr. Harn-Shen Chen, Division of Endocrinology and Metabolism, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC.
E-mail address: chenhs@vghtpe.gov.tw (H.-S. Chen).

https://doi.org/10.1016/j.jcma.2017.09.013

proliferative diabetic retinopathy.[5] There is a significant amount of data to suggest that an increase in IGF-1 activity may contribute to retinal neovascularization, which is characteristic of conditions, such as proliferative diabetic retinopathy.[6,7] Some studies have reported an association between the plasma or intraocular levels of IGF-1 and the occurrence or progression of diabetic retinopathy.[8–10]

Although there is strong experimental evidence that IGF-1 plays a role in the development of proliferative retinopathy, the prevalence of retinopathy in patients with acromegaly has not been well-documented.[2–10] This pilot study was conducted to determine the prevalence of retinopathy, especially proliferative retinopathy, in patients with acromegaly.

2. Methods

2.1. Subjects

This analysis combined two study populations (acromegalic patients and a diabetes control group). The acromegalic patients were recruited first then the gender- and age-matched controls were selected from a cohort of type 2 diabetes at a 1:3 ratio.

There were 163 patients with acromegaly admitted to the Taipei Veterans General Hospital for trans-sphenoidal surgery between 1979 and 2007. Forty-three patients (16 males and 27 females) had undergone examinations by an ophthalmologist during the hospitalization. Another 480 type 2 diabetic patients consented to participate in the study and were enrolled between 1 August 2001 and 31 December 2002. All participants provided a medical history and underwent a physical examination, biochemical assessment, and fundus examination. We selected 129 gender- and age-matched controls from this diabetes cohort. The Medical Ethics Committee of Taipei Veterans General Hospital approved the two study protocols.

2.2. Clinical examination

Height and weight were measured while each participant wore light indoor clothes without shoes. The body mass index (BMI) was calculated as the body weight in kilograms divided by the square of the height in meters. Blood pressure was measured with a sphygmomanometer and calculated as the mean of two measurements from the left arm of subjects who had been resting for 5 min in a sitting position. We also queried the participants for disease duration, cigarette use, and medications prescribed. The disease duration was defined from known diagnosis of diabetes or acromegaly to the time of fundus examination.

2.3. Eye examinations

The retinopathy status was reviewed from the medical reports prepared by ophthalmologists of patients with acromegaly. In patients with type 2 diabetes, color photographs of the retinas were obtained according to the ETDRS.[11] Macula- and disc-centered views were taken at an angle of 45° with a fundus camera after pharmacologic-induced mydriasis. The fundus photographs were evaluated by one ophthalmologist who was unaware of the medical conditions. The scale has 17 steps, ranging from no retinopathy in either eye to high-risk proliferative retinopathy in both eyes. We combined the severity of retinopathy into three categories in both study populations, as follows: no apparent retinopathy; non-proliferative retinopathy; and proliferative retinopathy.

2.4. Statistical analysis

SPSS for Windows (version 18.0; SPSS, Inc., Chicago, IL, USA) was used to perform data analysis. All data are described as the mean ± SD unless stated otherwise. The nadir GH level was defined as the lowest value at any time after oral ingestion of glucose. Non-normally distributed values were log-transformed. The differences in the prevalence of retinopathy were evaluated using a χ^2 test. Statistical significance was defined as a p value < 0.05.

3. Results

Among the 43 acromegalic patients, there were 7 patients who had visual field defects and 4 had proliferative retinopathy. Another 2 patients had optic neuropathy, but had normal visual field tests. The mean age at diagnosis was 45.1 ± 15.9 years, the mean fasting GH level was 31.38 ± 36.35 μg/L, the mean fasting IGF-1 level was 506.0 ± 308.4 μg/L, and the mean SD score for IGF-1 was 5.21 ± 5.31. According to the results of the oral glucose tolerance tests, 16 patients had normal glucose tolerance, 11 patients were glucose intolerant, and 16 patients had diabetes. Among the 129 type 2 diabetes controls, the mean age was 48.7 ± 6.2 years, the mean diabetes duration was 6.5 ± 5.7 years, the mean fasting plasma glucose level was 165.3 ± 47.8 mg/dL, and mean the HbA1c was 8.07 ± 1.56% (Table 1). Compared with age- and gender-

Table 1
Clinical characteristics of patients with acromegaly and type 2 diabetes.

	Acromegaly (N = 43)	Type 2 diabetes (N = 129)	p
Age (years)	45.1 ± 15.9	48.7 ± 6.2	0.350
Gender (male/female)*	16/27	48/81	1.000
Fasting GH (μg/L)	31.38 ± 36.35	NA	
Fasting IGF-1 (μg/L)	524.4 ± 301.9	216.7 ± 118.7	<0.001
IGF-1 SD score	5.21 ± 5.31	0.97 ± 2.42	<0.001
Fasting plasma glucose (mg/dL)	109.7 ± 37.1	165.3 ± 47.8	<0.001
2-h glucose during OGTT (mg/dL)	196.4 ± 90.8	NA	
HbA1C (%)	6.65 ± 1.12	8.07 ± 1.56	<0.001
Disease duration (years)	0.6 ± 0.6	6.45 ± 5.7	<0.001
Body height (cm)	165.6 ± 9.9	160.6 ± 9.1	0.004
Body weight (kg)	71.6 ± 13.6	67.5 ± 13.1	0.086
Body mass index (kg/m^2)	25.96 ± 3.42	26.45 ± 4.14	0.491
Systolic BP (mmHg)	128.1 ± 18.2	137.4 ± 16.1	0.002
Diastolic BP (mmHg)	77.5 ± 8.4	84.3 ± 10.1	0.001

GH = growth hormone; IGF-1 = insulin-like growth factor-1; OGTT = oral glucose tolerance test; HbA1C = glycated hemoglobin; BP = blood pressure.
* Fisher's Exact test. Data are described as the mean ± SD.

matched patients with type 2 diabetes, the acromegalic patients had lower fasting plasma glucose levels and lower systolic and diastolic blood pressures, but were taller and had higher IGF-1 levels.

Any level of retinopathy was present in 9.3% (4 of 43) of patients with acromegaly and 34.9% (45 of 129) of patients with type 2 diabetes (odds ratio [OR] = 0.191; 95% confidence interval [CI] = 0.064–0.570). Proliferative retinopathy was present in 9.3% (4 of 43) of patients with acromegaly and 9.3% (12 of 129) of patients with type 2 diabetes (OR = 1.000; 95% CI = 0.305–3.281); however, non-proliferative retinopathy was absent in patients with acromegaly, but present in 25.9% (33 of 129) of patients with type 2 diabetes (Table 2).

Fig. 1 shows the prevalence of retinopathy according to the quartiles of IGF-1 and HbA1c levels. In patients with type 2 diabetes, the prevalence of any retinopathy and proliferative retinopathy increased with increasing HbA1c levels (Fig. 1B), unlike the IGF-1 levels (Fig. 1A). The prevalence of any retinopathy was significantly higher in patients with type 2 diabetes than patients with acromegaly regarding any IGF-1 and HbA1c levels. The mean HbA1c value was 6.65% in our acromegalic patients, with a range of 5.6%–9.9%. The prevalence of proliferative retinopathy in type 2 diabetic patients with HbA1c was between 4.9% and 8.8%, and was similar to the patients with acromegaly (Fig. 1B). Compared with acromegalic patients, the prevalence of proliferative retinopathy in patients with type 2 diabetes was greater in the highest quartile of HbA1c.

Among patients with acromegaly accompanied with proliferative retinopathy, three patients had diabetes and one patient had IGT. Fig. 2 shows one example of fundus photographs from one acromegalic patient. The clinical characteristics of the patients are shown in Table 3. The age, gender, HbA1c and fasting blood glucose levels, and GH/IGF-1 profiles had no significant differences between acromegalic patients with and without proliferative retinopathy; however, the patients with acromegaly accompanied with proliferative retinopathy had higher blood glucose levels at 120 min during the oral glucose tolerance test.

4. Discussion

In the current study we analyzed 43 acromegalic patients and 129 age- and gender-matched patients with type 2 diabetes. Proliferative retinopathy was present in 9.3% (4 of 43) of patients with acromegaly and 9.3% (12 of 129) of patients with type 2 diabetes; however, non-proliferative retinopathy was absent in patients with acromegaly, but present in 25.9% (33 of 129) of patients with type 2 diabetes. Although there was no non-proliferative retinopathy in our patients with acromegaly, proliferative retinopathy was as frequent as in patients with type 2 diabetes.

Table 2
Prevalence of retinopathy in patients with acromegaly (n = 43) and type 2 diabetes (n = 129).

	Acromegaly	Type 2 diabetes		
	N (%)	N (%)	Odds ratio	95% Confidence interval
No apparent retinopathy	39 (90.7)	84 (65.12)		
Any level of retinopathy	4 (9.30)	45 (34.88)	0.191	0.064–0.570
Non-proliferative retinopathy	0 (0)	33 (25.58)	NA	NA
Proliferative retinopathy	4 (9.30)	12 (9.30)	1.000	0.305–3.281

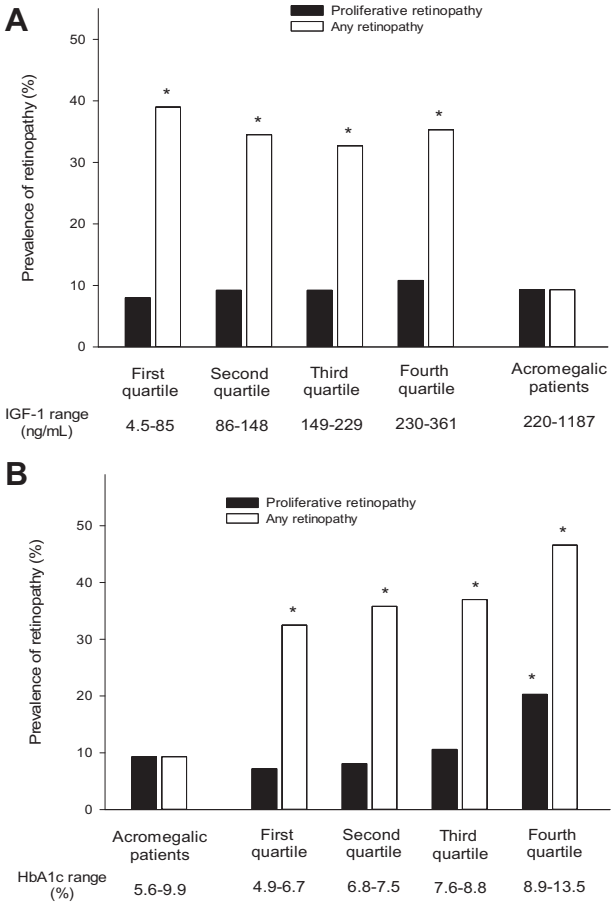

Fig. 1. The prevalence of retinopathy according to the quartiles of (A) IGF-1 and (B) HbA1c levels in patients with type 2 diabetes. *, $p < 0.05$ compared with acromegaly.

The high prevalence of proliferative retinopathy in our patients with acromegaly, but absence of non-proliferative retinopathy, was likely attributable to several underlying mechanisms. First, IGF-1 plays no role in non-proliferative retinopathy. Second, IGF-1 can accelerate the progression of non-proliferative retinopathy into proliferative retinopathy and shorten the non-proliferative phase. Third, bitemporal hemianopia occurs from the mass effect of acromegaly and is well-known to ophthalmologists. Indeed, ophthalmologists might not perform a retinal examination unless the patient suffers from visual loss. The classic signs of non-proliferative diabetic retinopathy are microaneurysms, retinal hemorrhage, hard exudates, cotton-wool spots, venous dilatation, and intraretinal microvascular abnormalities.[5] With time, the resulting retinal ischemia is a potent inducer of angiogenic growth factors. Retinal neovascularization is the final common

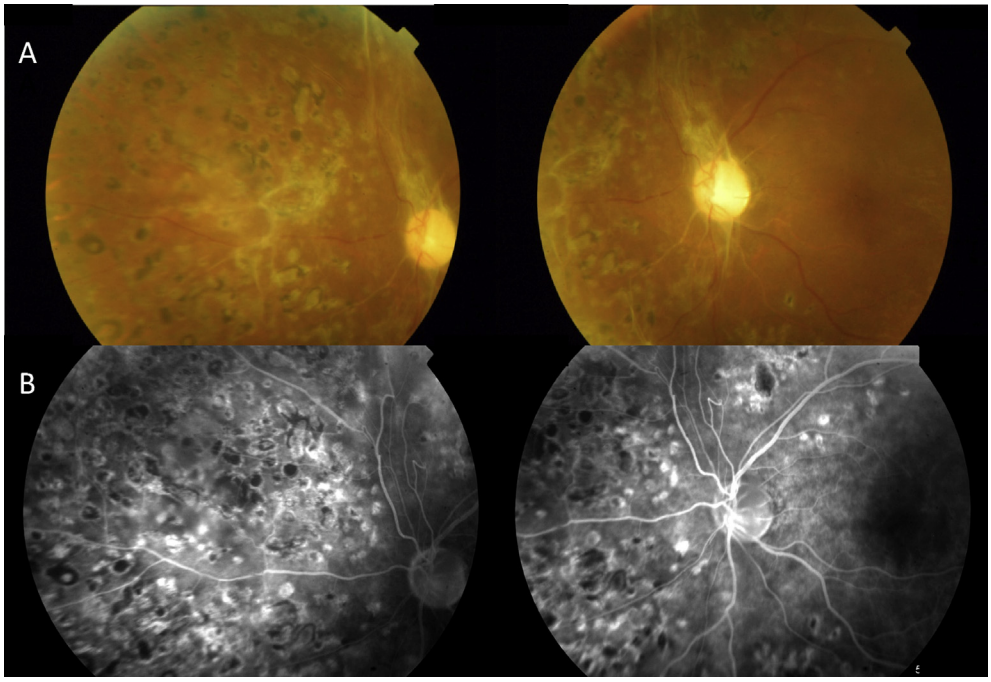

Fig. 2. One example of fundus photographs from one acromegalic patient.

Table 3
Clinical characteristics in acromegalic patients with and without proliferative retinopathy.

	Age	Gender	Fasting glucose	Glucose at 120 min	HbA1c %	Fasting GH (μg/L)	Nadir GH (μg/L)	Fasting IGF-1 (μg/L)	IGF-1 SD score
PR-1	50	Female	89	224	5.8	28.6	5.36	307	2.65
PR-2	66	Male	84	155	5.6	10.15	9.29	320	3.39
PR-3	55	Female	109	334	7.4	17.46	16.87	735	11.86
PR-4	32	Female	235	398	8.8	12.81	12.81	790	6.54
No PR (N = 39)	44.6 ± 16.1	M/W = 15/24	106.1 ± 30.1	186.4 ± 83.7*	6.63 ± 1.10	18.2 (IQR 6.5–47.2)	17.3 ± 8.2	522.8 ± 309.8	5.11 ± 5.47

PR = Proliferative retinopathy; HbA1C = glycated hemoglobin; GH = growth hormone; IGF-1 = insulin-like growth factor-1; OGTT = oral glucose tolerance test; IQR = Inter-quartile range; *, $p < 0.05$.

pathway in diabetic retinopathy, retinopathy of prematurity, and age-related macular degeneration, and retinal neovascularization the most common cause of blindness.[6] Vascular endothelial growth factor (VEGF) is an essential cytokine in hypoxia-induced proliferative retinopathy, and IGF-1 may accompany VEGF to stimulate new vessel growth.[6] High proliferative, but not non-proliferative retinopathy, in patients with acromegaly may be due to the pathogenic effect of IGF-1 in the neovascularization and lead to rapid progression of retinopathy from non-proliferative retinopathy to proliferative retinopathy.

We previously investigated the association between serum IGF-1 levels and retinopathy in patients with type 2 diabetes.[12] We found that the serum IGF-1 levels were not associated with the prevalence of retinopathy, and did not predict the progression of retinopathy in all participants; however, increased serum levels of IGF-1 were associated with the cumulative incidence of severe retinopathy and predicted the progression of retinopathy in patients with relatively good glycemic control. The diabetes cohort in the current study was a sub-group from this previous study.[12] We found that the HbA1c level significantly increased the risk of retinopathy and the serum IGF-1 level may not play a role in any retinopathy and proliferative retinopathy. This finding may provide alternative evidence that IGF-1 plays an important role in proliferative retinopathy and may influence the progression of retinopathy, but IGF-1 may not play a role in non-proliferative retinopathy.

In patients with acromegaly, retinopathy has seldom been investigated; the frequency varies from 2.2% to 20%.[13–16] Ballintine et al.[16] studied 44 acromegalic patients with fluorescein angiography to detect retinopathy. Ballintine et al.[16] reported retinopathy in only 1 patient (2.2%), and concluded that retinopathy is uncommon in patients with acromegaly. Azzoug and Chentli[15] revealed the prevalence of diabetic retinopathy in 40 patients with acromegaly and diabetes. Azzoug and Chentli[15] reported that there were three patients with non-proliferative retinopathy and two patients with proliferative retinopathy. The prevalence of retinopathy in our acromegalic patients was 9.3% and similar to previous reports.[13–16] Although the number of subjects in the current study was only 43, all of the previous studies had only 15–40 patients.

The limitations of our study include a retrospective analysis and few retinopathies were detected in patients with acromegaly. The present study was a cross-sectional, retrospective analysis. Thus, the study lacked comprehensive retina screening at baseline and during the follow-up period for both

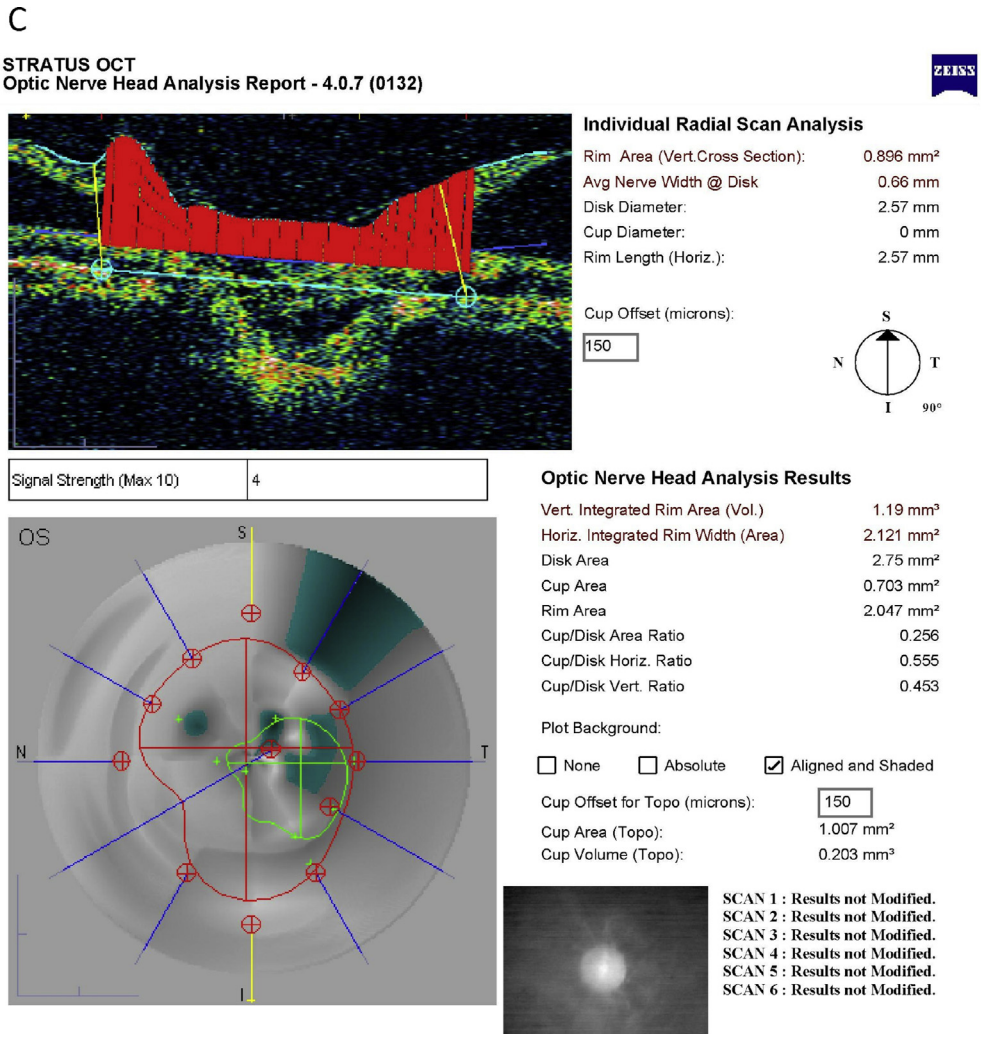

Fig. 2. (*continued*).

groups. Therefore, we cannot provide the time that elapsed for development of retinopathy in patients with acromegaly and type 2 diabetic. Glycemic control was poor in the group of patients with type 2 diabetes, which may be a source of bias. Therefore, a well-designed prospective study with a well-controlled glycemic group, and consistent examinations for retina screening at baseline and follow-up period in both groups is warranted. Another limitation involved retinopathy, which developed in different ways. The retinopathy status was reviewed from the medical records provided by ophthalmologists for patients with acromegaly, and color photographs of the macula- and disc-centered views in patients with type 2 diabetes. The same source of material to examine retina status should be used in corollary studies.

In conclusion, although there was no non-proliferative retinopathy in our patients with acromegaly, the prevalence of proliferative retinopathy was as high as well-matched patients with type 2 diabetes. We suggest that IGF-1 may play an important role in proliferative retinopathy and may influence the progression of retinopathy, but IGF-1 may not play a role in non-proliferative retinopathy.

Acknowledgments

This work was supported by grants from Taipei Veterans General Hospital (V98C1-154) and the National Science Council (NSC 101-2314-B-010-023).

References

1. Melmed S. Medical progress: acromegaly. *N Engl J Med* 2006;**355**:2558–73.
2. Smith LEH, Kopchick JJ, Chen W, Knapp J, Kinose F, Daley D, et al. Essential role of growth hormone in ischemia-induced retinal neovascularization. *Science* 1997;**276**:1706–9.
3. Inokuchi N, Ikeda T, Yasuda F, Shirai S, Uchinori Y. Severe proliferative diabetic retinopathy associated with acromegaly. *Br J Ophthalmol* 1999;**83**:629–30.
4. van Setten G, Brismar K, Algvere P. Elevated intraocular levels of insulin-like growth factor I in a diabetic patient with acromegaly. *Orbit* 2002;**21**:161–7.
5. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet* 2010;**376**:124–36.
6. Smith LE, Shen W, Perruzzi C, Soker S, Kinose F, Xu X, et al. Regulation of vascular endothelial growth factor-dependent retinal neovascularization by insulin-like growth factor-1 receptor. *Nat Med* 1999;**5**:1390–5.

7. Kondo T, Vicent D, Suzuma K, Yanagisawa M, King GL, Holzenberger M, et al. Knockout of insulin and IGF-1 receptors on vascular endothelial cells protects against retinal neovascularization. *J Clin Invest* 2003;**111**:1835−42.
8. Dills DG, Moss SE, Klein R, Klein BE. Association of elevated IGF-I levels with increased retinopathy in late-onset diabetes. *Diabetes* 1991; **40**:1725−30.
9. Janssen JA, Jacobs ML, Derkx FH, Weber RF, van der Lely AJ, Lamberts SW. Free and total insulin-like growth factor I (IGF-I), IGF-binding protein-1 (IGFBP-1), and IGFBP-3 and their relationships to the presence of diabetic retinopathy and glomerular hyperfiltration in insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1997;**82**:2809−15.
10. Frystyk J. The growth hormone hypothesis − 2005 revision. *Horm Metab Res* 2005;**37**(Suppl 1):44−8.
11. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. *Ophthalmology* 1991;**98**:823−33.
12. Chen HS, Wu TE, Hsiao LC, Lin SH. Interaction between glycaemic control and serum insulin-like growth factor 1 on the risk of retinopathy in type 2 diabetes. *Eur J Clin Invest* 2012;**42**:447−54.
13. Amemiya T, Toibana M, Hashimoto M, Oseko F, Imura H. Diabetic retinopathy in acromegaly. *Ophthalmologica* 1978;**176**:74−80.
14. Arya KR, Pathare AV, Chadda M, Menon PS. Diabetes in acromegaly: a study of 34 cases. *J Indian Med Assoc* 1997;**95**:546−7.
15. Azzoug S, Chentli F. Diabetic retinopathy in acromegaly. *Indian J Endocrinol Metab* 2014;**18**:407−9.
16. Ballintine EJ, Foxman S, Gorden P, Roth J. Rarity of diabetic retinopathy in patients with acromegaly. *Arch Intern Med* 1981;**141**:1625−7.