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Original Article

Diabetes Mellitus is Frequent, But Retinopathy is Rare in Acromegaly: A Cross-sectional Study

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ABSTRACT

Background: The roles of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) in diabetic retinopathy (DR) are well recognized, but the prevalence and pathogenesis of retinopathy in acromegaly are not fully understood. We established the frequency and severity of glucose intolerance and retinopathy—and the relationship between them—in patients with acromegaly.

Methods: All patients with acromegaly under the care of the Department of Endocrinology, Başkent University Hospital were enrolled. Fundoscopy was carried out by two experienced ophthalmologists. Acromegaly disease state was evaluated by basal GH and IGF-1 measurements, and an oral glucose tolerance test (OGTT) when appropriate. Glucose tolerance states were assessed by means of fasting and postprandial plasma glucose concentrations, glycohemoglobin measurement and an OGTT when appropriate. The relationships between retinopathy, acromegaly disease activity and glucose tolerance states were examined.

Results: The cohort comprised 49 patients with acromegaly (24 women), with a median disease duration of 25 months (range 1–420 months). Thirty-three had active disease, with median concentrations of GH of 5.54 ng/ml (0.72–172 ng/ml) and IGF-1 of 541.5 ng/ml (203–1.985 ng/ml). The prevalence of diabetes mellitus (DM) was 30.6% (n = 15; 10 patients had active acromegaly, five of whom had uncontrolled DM). Two patients had retinopathy (4.1%); both had active acromegaly and uncontrolled DM at the time of examination.

Conclusions: The prevalence of DM was twice that of a reference population, but that of DR was lower than expected. Our findings suggest that disease activity in acromegaly might not contribute to retinopathy.

Keywords: Acromegaly, retinopathy, growth hormone, diabetes mellitus, insulin-like growth factor 1

INTRODUCTION

Diabetic retinopathy (DR) is a chronic microvascular complication of diabetes mellitus (DM) that can lead to loss of vision. Many factors have been identified that contribute to the pathogenesis of retinopathy, either independently or together with hyperglycemia and its underlying factors (1-3).

The potential roles of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) in DR have been evaluated in vitro and in vivo (3,4-6), and it has been reported that locally produced GH or IGF-1, and in some cases systemic GH and IGF-1 activity, may contribute to the onset of retinopathy or exacerbate it (5,7-10). Acromegaly is caused by the chronic hypersecretion of GH, and is often accompanied by glucose intolerance, DM or retinopathy (11). Although these complications are well recognized, understanding of their prevalence, severity and pathogenesis is incomplete, and is informed by case reports and a small number of case series, mostly of 10 to 15 cases (12-18).

Surveillance for retinopathy is not routine in acromegaly, but it would be important to establish screening programs if there are other currently unrecognized factors other than chronic hyperglycemia that might predispose patients with acromegaly to retinopathy. We aimed to assess the frequency and severity of impaired glucose tolerance and retinopathy, and the extent of any relationship between the two, in a relatively large cohort of patients with acromegaly with a variety of disease activity states treated in a tertiary referral center.

METHODS

Study participants

We consecutively recruited all patients with acromegaly who attended for regular follow-up at the Endocrinology Departments of the two main clinical centers of Baskent University Faculty of Medicine between November 2009 and December 2010 to our cross-sectional study. The Baskent University Ethics Committee for Human Studies approved the protocol, and all participants provided informed consent.

Acromegaly was diagnosed as follows. Initially, baseline blood GH and IGF-1 concentrations were measured. A 75 g oral glucose tolerance test (OGTT) was undertaken in those who had an IGF-1 concentration in excess of their age- and sex-matched upper limit of normal. Those individuals with nadir GH concentration >1 ng/ml during an OGTT were diagnosed with acromegaly. The disease was regarded as biochemically controlled when nadir GH concentration was <1 ng/ml during an OGTT, and IGF-1 concentration was within the age- and sex-matched normal range (19).

Diabetes mellitus was diagnosed in those with a fasting plasma glucose (FPG) concentration ≥126 mg/dl on at least two occasions, or those with a plasma glucose concentration ≥200 mg/dl in the second hour of an OGTT, or a random plasma glucose concentration ≥200 mg/dl for those with symptoms of hyperglycemia. Individuals with FPG concentration between 100 mg/dl and 125 mg/dl, and/or a postprandial second hour glucose concentration between 140 mg/dl and 199 mg/dl were defined as pre-diabetic. The definition of glycemic control was a glycohemoglobin (HbA1c) concentration <7% (20).

Assessment of Acromegaly

Acromegaly disease state was evaluated by basal GH and IGF-1 measurements, and GH measurement during an OGTT where appropriate. Glucose tolerance states were assessed by FPG and postprandial plasma glucose concentration, HbA1c measurements and OGTT where appropriate. Glucose tolerance state, GH and IGF-1 data, and other relevant history at the time of acromegaly diagnosis were obtained from the hospital records.

Standard fundoscopy was undertaken by two experienced ophthalmologists (DA and SS; one for each center), who were unaware of the clinical status of each patient. The pupil was dilated with one drop of 0.5% tropicamide and 2.5% phenylephrine 30 minutes beforehand. Pathologic findings in the retina were classified according to the criteria in Table 1 (21). Fundus fluorescein angiography (FFA) was performed if there was evidence of retinopathy. The relationships between retinal findings, acromegaly disease activity and glucose tolerance states were examined.

Laboratory analyses

Venous blood samples were taken after at least 8 hours of fasting between 08.00-09.00 am. Plasma glucose concentration was measured by the hexokinase method (Roche/Hitachi P modular autoanalyzer, Roche Diagnostics, Mannheim, Germany); the normal range was 70–99 mg/dl. The proportion of HbA1c was measured by means of the turbidimetric inhibition immunoassay (Roche Diagnostics); the normal range was 4% to 6%. Growth hormone concentration was measured using solid phase two-site chemiluminescence immunometric

Table 1. Classification of diabetic retinopathy (21)

Classification Level	Defining features
Retinopathy absent	No apparent lesion
Mild NPDR	Microaneurysm, hemorrhage, soft exudate, increase in vascular permeability
Moderate NPDR	Microaneurysm and hemorrhage with increased severity, vascular closure
Severe NPDR	More than 20 intraretinal hemorrhages in four quadrants or venous beading in two or more quadrants, or intraretinal microvascular abnormalities in one or more quadrant but not PDR
PDR	Presence of one or more of the following: • Neovascularization of the optic disc • Neovascularization elsewhere • Preretinal hemorrhage • Vitreous hemorrhage • Fibrous tissue proliferation

NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 2. Demographic and clinical characteristics of patients with acromegaly at diagnosis

Number of cases (F/M)	Age (years, mean ± SD)	Maximum size of adenoma (mm, mean ± SD) *	GH (ng/ml, median) (range)	IGF-1 (ng/ml, median) (range)	Glucose tolerance state, n (proportion)
49 (24 / 25)	41.4±11.4	All (49): 18.9±9.7 Micro (8): 7.5±2.5 Macro (41): 21.1±9.0	16.8 2.0–128.0	745 261–2.923	Normal: 19 (38.8%) Pre-diabetes: 18 (36.7%) Diabetes mellitus: 12 (24.5%)

F, female; M, male; SD, standard deviation; n, number of cases; Micro, microadenoma; Macro, macroadenoma; GH, growth hormone; IGF-1, insulin-like growth factor-1.* p <0.001

assays (Immulite 2000, Siemens Healthcare Diagnostics, Deerfield, IL, USA); the reference range was [0-1 ng/ml], and IGF-1 concentration using a solid-phase enzyme-labeled chemiluminescence immunometric assay (Immulite 2000, Siemens Healthcare Diagnostics); the reference range was [94-252 ng/ml].

STATISTICAL ANALYSIS

Data analysis was undertaken using SPSS software (Statistical Package for the Social Sciences, version 15.0, SSPS Inc., Chicago, IL, USA). Demographic data were subject to frequency analyses and reported as the median (range), or mean ± standard deviation (SD). The chi-squared, Student t and Mann-Whitney tests were used to evaluate numerical data. For all evaluations, a significance level of p <0.05 at a 95% confidence interval was accepted as statistically significant.

RESULTS

In total, 49 patients with acromegaly were enrolled; their characteristics at the time of diagnosis are shown in Table 2. Thirty had glucose metabolism disturbance (61.2%), and twelve had DM (24.5%). Twenty-three patients underwent surgery (46.9%) and the remaining twenty-six (53.1%) were managed medically as the primary treatment modality. Thirteen of those who had surgery underwent transsphenoidal adenomectomy (56.5%), while a transcranial approach was used in the remaining ten (43.5%). Half of the 26 treated medically were treated with octreotide and the other half were treated with monthly injections of lanreotide.

The biochemical and retinal findings, and glucose tolerance states of active and controlled cases of acromegaly at the time of evaluation, are shown in Table 3. Biochemical control had been achieved in 16 of the patients (32.7%) at the time of evaluation, a median of 25 months after diagnosis (range 1–420 months). The prevalence of DM and impaired glucose tolerance were similar in those with active or controlled disease (Table 3). Eleven patients had arterial hypertension controlled with antihypertensive drugs.

Fifteen patients in the study had DM (30.6%); their demographic and clinical characteristics are shown in Table 4. Seven of the 49 patients (14.3%) had already been diagnosed with DM before acromegaly. Diagnosis of DM and acromegaly were made simultaneously in five patients. The remaining three patients developed DM during the study period. All patients recognized to have DM had undergone fundoscopy in the previous 6 months. Of the five patients with poorly controlled DM, two had DR. Both exhibited bilateral punctuate hemorrhage and hard exudates. In one patient with an HbA1c of 9.2%, FFA revealed diffuse microaneurysms and neovascularization consistent with proliferative DR. In the other, who had an HbA1c of 8.6%, there was no evidence of neovascularization, and the findings were

Table 3. Clinical, laboratory features and retinal findings of the study group during evaluation

Acromegaly cases (n=49)	**Age yerars, mean ± (SD)****	**Time since diagnosis (months, median)**(range)**	**Basal GH (ng/ml), median)***(range)**	**IGF-1 (ng/ml), median)****(range)**	**Glucose tolerance state, n (proportion)**	**Retinopathy, n (proportion)**
Active disease* (n=33)	46.1±11.7	12.5 (1–104)	5.54 (0.72–172.0)	541.5 (203.0–1,985.0)	Normal: 12 (37%) Pre-diabetes: 11 (33%) Controlled DM: 5 (15%) Uncontrolled DM: 5 (15%)	2 (6.1%)
Controlled disease* (n=16)	44.5 ±12.9	40 (7–420)	1 (0.17–2.5)	162.0 (68.9–348.0)	Normal: 4 (25%) Pre-diabetes: 7 (44%) Controlled DM: 5 (31%) Uncontrolled DM: 0 (0%)	0 (0%)

N, number; SD, standard deviation; min, minimum; max, maximum; GH, growth hormone; IGF-1, insulin-like growth factor-1; DM, diabetes mellitus. * Biochemical control; ** p>0.05; *** p<0.01; **** p<0.001

Table 4. Clinical features of individuals diagnosed with diabetes mellitus during the study period

Case no.	At the time of acromegaly diagnosis				At the time of evaluation			
	DM duration (years)	FPG (mg/dl)/ HbA1c (%)	DM therapy	Basal GH/ IGF-1 (ng/ml)	FPG (mg/dl)/ HbA1c (%)	DM therapy	Basal GH/ IGF-1 (ng/ml)	Acro duration (years)/disease state
1[#]	10	268/9.0	MNT, OAD	38.5 / 597	186/8.6	MNT, insulin	15.3 / 447	0.5 / A
2	0	112/5.8	recent dx	98.0 / 905	121/6.1	MNT, OAD	4.3 / 880	2 / A
3	0	161/6.8	recent dx	3.2 / 550	93/5.5	MNT, OAD	0.2 / 223	5 / C
4	6	148/8.4	MNT, OAD	41.5 / 1.850	116/7.4	MNT, OAD	0.8 / 397	1 / A
5	0	88 / 6.6	recent dx	17.2 / 504	91/5.6	MNT	0.5 / 158	4 / C
6	0	87/6.5	recent dx	19.4 / 859	87/6.1	MNT	1.0 / 221	2.5 / C
7	3	134/6.9	MNT, OAD	27.5 / 938	115/6.5	MNT, OAD	17.6 / 593	4.5 / A
8[¥]	-	123/ -	-	4.5 / 745	126/6.7	MNT	1.5 / 475	1 / C
9[¥]	-	109/-	-	23.0 / 735	131/6.6	MNT	1.4 / 212	3 / C
10[¥]	-	121/-	-	11.7 / 2.923	136/6.6	MNT	12.0 / 1970	0.5 / A
11	10	154/6.4	MNT, OAD, insulin	40.0 / 1.985	154/6.4	MNT, OAD, insulin	40.0 / 1.985	0 / A
12	0	137/5.5	recent dx	7.3 / 477	121/6.3	MNT, OAD	5.7 / 715	1 / A
13	10	186/10	insulin	16.3 / 517	186/10.0	insulin	16.3 / 517	0 / A
14	5	176/8	MNT, OAD	11.2/ 980	115/7.9	MNT, OAD	5.7 / 812	7 / A
15 [#]	12	312/10	MNT, insulin	21.4/ 550	174/9.2	MNT, insulin	5.37 / 553	3 / A

DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, glycohemoglobin; GH, growth hormone; IGF-1, insulin-like growth factor-1; Acro, acromegaly; MNT, medical nutrition therapy; OAD, oral antidiabetic drug; A, active disease; dx, diagnosis; C, controlled disease. [#]cases with retinopathy, [¥] pre-diabetic at diagnosis of acromegaly

suggestive of mild to moderate non-proliferative DR (Table 4) (21). Progression or deterioration of the retinal changes was not detected in both cases during the study period.

Other than these two established cases of retinopathy, fundoscopy undertaken as part of this study did not identify any other affected patients, including the three other patients with active acromegaly and poorly controlled DM (Tables 3 and 4). The biochemically controlled acromegaly group included five patients with controlled DM (Tables 3 and 4).

There was no significant difference in the proportion of patients with controlled or active acromegaly in the subgroup with normal glucose tolerance (n=4 (25%) vs n=12 (75%)) and the group with abnormal glucose tolerance (pre-diabetes [n=7 (38.9%) vs n=11 (61.1%)] and DM [n=5 (33.3%) vs n=10 (66.7%)], respectively, $p<0.05$ for all).

Approximately 80% (n = 39) of patients were being treated with somatostatin receptor ligands (SRL) at the time of evaluation. Eight patients had received radiotherapy; acromegaly was controlled only in two of these cases, but neither had DM.

DISCUSSION

Glucose intolerance is one of the most important sequelae of acromegaly; when DM is diagnosed in a patient with acromegaly, it adds substantial additional therapeutic and pathophysiologic burdens (11). In our group of 49 patients with acromegaly, the prevalence of DM was 30.6% and DR was 4.1%. A national survey conducted in 2010 (TURDEP 2) reported that the prevalence of DM in the adult population of Turkey was 13.7% (22). The high prevalence of DM in our cohort of patients with acromegaly was not a surprising finding, given that acromegaly is a well-recognized cause of impaired glucose homeostatis (20). Moreover, in a study of 2,270 patients with DM and pre-diabetes, the prevalence of acromegaly was 0.13%, and that was higher than the general population (23,24). The prevalence was not sufficiently high to warrant a recommendation for screening for acromegaly in patients with DM, but strategies have been recommended to detect this chronic, slowly progressing disease more promptly (23).

The prevalence of DM in patients with acromegaly was

reported between 17-60% (15,25-30) in previous studies. These cohort studies included 34-200 participants (15,25-29). Our findings were broadly comparable with the study of Fieffe et al, which is the most comprehensive study in the field (30). The prevalence of DM was 22.3% among 519 patients in the French Acromegaly Registry and that while age, body mass index (BMI) and arterial hypertension were risk factors, blood GH and IGF-1 concentrations were not (30).

In a more recent study, besides age and BMI, a family history of DM and elevated IGF-1 (but not GH) concentration were found to be associated with impaired glucose metabolism in patients with acromegaly (29). Schneider and colleagues investigated whether IGF-1 concentration predicts the development of DM in two large prospective cohort studies. The blood IGF-1 concentration of 7,777 non-diabetic individuals was measured and they were followed prospectively. Abnormally high and low IGF-1 concentrations were associated with new onset DM in 464 cases during a 5-year follow-up period (31).

Diabetic retinopathy generally appears about 5 to 10 years after the onset of hyperglycemia. Receptors for GH and IGF-1 are strongly expressed in the retina; stimulation of these receptors by their ligands results in proliferation of the retinal epithelium (32). However, reports on the role of the GH/IGF-1 system, locally or systemically, in the pathogenesis of DR are inconsistent. As the IGF-1 receptors are expressed by groups of cells with diverse functions, and the findings of studies of activation or inhibition of the systemic GH/IGF-1 system on retinal neovascularization are inconsistent, the roles of the GH/IGF-1 axis in the pathogenesis of retinopathy are complex and probably indirect. Therefore, the activity of the GH/IGF-1 system in the retina and its role in the pathogenesis of DR has been debated (3,4-10, 33-39). Given the over-activity of the GH/IGF-1 system in acromegaly, the reported rates of retinopathy in acromegaly are surprisingly low, and severe retinopathy is rare (13,14).Retinopathy caused by DM developing secondary to acromegaly is a very unusual complication (40). Understanding of retinopathy in acromegaly is somewhat limited; most evidence is based on case reports (12-18). Despite the findings of elevated intraocular GH and IGF-1 concentrations in many of these studies and case reports, a direct relationship between acromegaly and retinopathy has not yet been established (3,4,41). While retinopathy may be a consequence of dysfunction of the GH/IGF-1 system, it is more likely that it is a complication of impaired glucose homeostasis in patients with uncontrolled DM (12,17,41).

Cases of unexpectedly severe DR in the context of mild glucose intolerance have been reported in patients with acromegaly, in which the retinopathy has been attributed to elevated GH concentration (42). Tran and colleagues reported a patient with recently diagnosed diet-controlled type 2 DM, active acromegaly and severe DR, in whom the retinopathy and DM recovered almost completely about 18 months after surgery for acromegaly (16). The authors proposed that the severity of DR in this case could not be explained by DM alone, and that high GH concentration was probably the cause of the retinal angiogenesis. Similarly, the prevalence of proliferative retinopathy was determined to be 9.3% among both 43 cases with acromegaly and 129 cases with type 2 DM in a recent study. No non-proliferative retinopathy was observed among acromegaly cases. The authors suggested that IGF-1 may play an important role in proliferative retinopathy (43). In one recent prospective observational study, 8.8% of 91 acromegalic and 9.8% of 123 cases with impaired fasting glucose developed retinopathy at the end of a median follow-up of 64 months. Patients with acromegaly had the same incidence of non-proliferative retinopathy and a non-statistically significantly higher incidence of proliferative retinopathy (OR 2.461; 95% CI 0.404–14.988). The authors concluded that GH and IGF-1 might play a crucial role in the development of proliferative retinopathy and acromegalics should be screened similar to diabetes patients (44).

The median disease duration of our cohort was more than 2 years after diagnosis (one patient had a greater than 30-year history of acromegaly). Some patients had markedly elevated blood GH concentration (>100 ng/dl) or an IGF-1 concentration of approximately 2,000 ng/ml, but nonetheless, there were only two cases of retinopathy. DM was longstanding (>9 years), poorly controlled (HbA1c >8%), and retinopathy had been detected before the diagnosis of acromegaly in both cases. Our finding that there were no additional cases of retinopathy, even among 33 patients with active acromegaly, suggests that disease activity may not contribute to DR in acromegaly. A nationwide multicenter study undertaken in Turkey in 2000 found that the prevalence of DR was 30.5% in 2,362 patients with DM (45). Our finding of only two cases of DR (13.3% of the 15 patients with DM) is therefore lower than expected, but could be explained by the relatively short history of DM in our cohort: about two-thirds of patients had not been diagnosed with DM before acromegaly.

The results of a similar study by Ballintine and colleagues are broadly comparable with ours: they detected one case of retinopathy in 44 patients with acromegaly (2.2%), compared with two cases (4.1%) in our cohort of 49 (13). More than half of their patients had pre-diabetes with a mean duration of 2 years, supporting the hypothesis that DR is a consequence of uncontrolled DM rather than dysfunction of the GH/IGF-1 system. In other, differently designed studies, the prevalence

of retinopathy in acromegaly has been reported to vary between 0% and 20% (14,15,18). In one of these studies, 10 of the 15 patients with acromegaly had DM, and three of the 10 were reported to have DR (14). There was also reportedly just one case of DR (2.9%) in a patient who also had DM, in another cohort of 34 patients with acromegaly (15). In one study, DR was detected in 12.5% of 40 patients with acromegaly, all of whom also had DM. The duration and severity of DM was not clear in all patients. There was a significant relationship between DR and hyperglycemia, but no correlation was determined between DR and GH concentration (18). The variety of study designs and cohort sizes (most of which comprise 10–15 patients with acromegaly) probably account for these diverse findings (12-18).

A relatively high proportion of patients in our study group received primary medical therapy (49%). This was partially due to the presence of comorbidities that increased perioperative anesthetic and surgical risk for some patients, and personal preference in others. This likely explains the lower rates of disease control in our group (39%) compared with other tertiary referral centers (11).

As there were only two cases of DR in our group, we could not reliably establish the influence of age, disease duration, or GH and IGF-1 concentrations, on the risk of developing retinopathy. However, in the light of the body of evidence in the literature and our findings, it is our opinion that the onset and progression of DM and DR are likely independent of the GH/IGF-1 dysfunction seen in acromegaly.

Preclinical data on the therapeutic role of somatostatin in DR is encouraging, and there are an increasing number of clinical trials, especially of octreotide (46,47). Somatostatin receptor ligands have two mechanisms of action, exerting direct anti-angiogenic, anti-proliferative and anti-apoptotic effects, and acting indirectly by suppressing the GH/IGF-1 axis (47). Considering that almost 80% of our group were being treated with an SRL, we cannot exclude the possibility that this therapy effectively prevented retinopathy in the majority of the active acromegaly group other than the two patients in whom DR had already been documented. The active acromegaly group comprised all five of the cases of uncontrolled DM, including the two patients with retinopathy, which makes it difficult to draw any firm conclusions about the effect of SRLs on retinopathy in acromegaly. Recently, multimodal management of a patient with proliferative diabetic retinopathy and diabetic macular edema associated with active acromegaly, who presented with deteriorated eyesight, was reported. Anti-vascular endothelial growth factor treatments, cataract surgeries and retinal direct laser photocoagulation were performed together with gradual glycemic control with basal insulin to prevent worsening of the visual impairment. She was given an injection of a long-acting somatostatin analog (octreotide LAR), followed by a trans-sphenoidal adenomectomy. Her visual acuity improved without worsening of retinopathy (48).

Our study has several limitations: the sample size was relatively small, and the lack of a control group made it difficult to account for all the potentially confounding factors. Nonetheless, our findings enlighten about the relationship between retinopathy, DM and acromegaly in an era where the prevalence of DM has doubled in almost 10 years (22). It is also encouraging that we found no new cases of retinopathy, even in those with active acromegaly and uncontrolled DM. Most of our patients with acromegaly are treated with an SRL. While these drugs can influence glucose metabolism, it is thought that the clinical consequences are minimal (11,49).

It will be important to undertake prospective controlled studies of large cohorts of patients to fully understand the role of the GH/IGF-1 system in the onset and progression of retinopathy in acromegaly, allowing subgroup analysis to be undertaken to establish the influence of DM or other potentially confounding factors.

CONCLUSION

The prevalence of DM in patients with acromegaly was more than twice that of a reference population, but that of diabetic retinopathy was surprisingly low in a group in which biochemically active cases of acromegaly predominated. Those cases with retinopathy had uncontrolled DM, which suggests that disease activity in acromegaly might not contribute to retinopathy. Prospective long-term studies of larger cohorts will be needed to validate our findings.

DECLARATIONS

Conflict of interest: The authors declare that they have no conflict of interest.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Authors' contributions: All authors contributed in some way to the concept and design of the study; acquisition, analysis and interpretation of data; and writing or revising the manuscript.

Ethics Committee: Başkent University, IRB; 2009/KA09/334

REFERENCES

1. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet*. 2010;376(9735):124-136. doi:10.1016/S0140-6736(09)62124-3
2. Aiello LP, Gardner TW, King GL, et al. Diabetic retinopathy. *Diabetes Care*. 1998;21(1):143-156. doi:10.2337/diacare.21.1.143
3. Grant MB, Afzal A, Spoerri P, Pan H, Shaw LC, Mames RN. The role of growth factors in the pathogenesis of diabetic retinopathy. *Expert Opin Investig Drugs*. 2004;13(10):1275-1293. doi:10.1517/13543784.13.10.1275
4. Meyer-Schwickerath R, Pfeiffer A, Blum WF, et al. Vitreous levels of the insulin-like growth factors I and II, and the insulin-like

growth factor binding proteins 2 and 3, increase in neovascular eye disease. Studies in nondiabetic and diabetic subjects. *J Clin Invest*. 1993;92(6):2620-2625. doi:10.1172/JCI116877
5. Alzaid AA, Dinneen SF, Melton LJ 3rd, Rizza RA. The role of growth hormone in the development of diabetic retinopathy. *Diabetes Care*. 1994;17(6):531-534. doi:10.2337/diacare.17.6.531
6. Chantelau E. Evidence that upregulation of serum IGF-1 concentration can trigger acceleration of diabetic retinopathy. *Br J Ophthalmol*. 1998;82(7):725-730. doi:10.1136/bjo.82.7.725
7. Merimee TJ, Zapf J, Froesch ER. Insulin-like growth factors. Studies in diabetics with and without retinopathy. *N Engl J Med*. 1983;309(9):527-530. doi:10.1056/NEJM198309013090904
8. Lee HC, Lee KW, Chung CH, et al. IGF-I of serum and vitreous fluid in patients with diabetic proliferative retinopathy. *Diabetes Res Clin Pract*. 1994;24(2):85-88. doi:10.1016/0168-8227(94)90024-8
9. Arner P, Sjöberg S, Gjötterberg M, Skottner A. Circulating insulin-like growth factor I in type 1 (insulin-dependent) diabetic patients with retinopathy. *Diabetologia*. 1989;32(10):753-758. doi:10.1007/BF00274537
10. Sévin R. The correlation between human growth hormone (HGH) concentration in blood plasma and the evolution of diabetic retinopathy. *Ophthalmologica*. 1972;165(1):71-77. doi:10.1159/000308471
11. Melmed S, Kleinberg D. Williams Textbook of Endocrinology. *Pituitary Masses and tumors*. Philelphia: Elsevier Saunders, 2011:229-290.
12. Inokuchi N, Ikeda T, Yasuda F, Shirai S, Uchinori Y. Severe proliferative diabetic retinopathy associated with acromegaly. *Br J Ophthalmol*. 1999;83(5):629-630. doi:10.1136/bjo.83.5.628c
13. Ballintine EJ, Foxman S, Gorden P, Roth J. Rarity of diabetic retinopathy in patients with acromegaly. *Arch Intern Med*. 1981;141(12):1625-1627.
14. Amemiya T, Toibana M, Hashimoto M, Oseko F, Imura H. Diabetic retinopathy in acromegaly. *Ophthalmologica*. 1978;176(2):74-80. doi:10.1159/000308696
15. Arya KR, Pathare AV, Chadda M, Menon PS. Diabetes in acromegaly--a study of 34 cases. *J Indian Med Assoc*. 1997;95(10):546-547.
16. Tran HA, Petrovsky N, Field AJ. Severe diabetic retinopathy: a rare complication of acromegaly. *Intern Med J*. 2002;32(1-2):52-54.
17. Malhotra C. Proliferative diabetic retinopathy in acromegaly. *Oman J Ophthalmol*. 2010;3(2):96-97. doi:10.4103/0974-620X.64237
18. Azzoug S, Chentli F. Diabetic retinopathy in acromegaly. *Indian J Endocrinol Metab*. 2014;18(3):407-409. doi:10.4103/2230-8210.131207
19. Giustina A, Barkan A, Casanueva FF, et al. Criteria for cure of acromegaly: a consensus statement. *J Clin Endocrinol Metab*. 2000;85(2):526-529. doi:10.1210/jcem.85.2.6363
20. American Diabetes Association. Standards of medical care in diabetes--2009. *Diabetes Care*. 2009;32 Suppl 1(Suppl 1):S13-S61. doi:10.2337/dc09-S013
21. Wilkinson CP, Ferris FL 3rd, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology*. 2003;110(9):1677-1682. doi:10.1016/S0161-6420(03)00475-5
22. Satman I, Omer B, Tutuncu Y, et al. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. *Eur J Epidemiol*. 2013;28(2):169-180. doi:10.1007/s10654-013-9771-5
23. PW. Frequency of acromegaly in adults with diabetes or glucose intolerance and estimated prevalence in the general population. *Pituitary*. 2011;14(3):217-221. doi:10.1007/s11102-010-0281-0
24. Melmed S. Medical progress: Acromegaly [published correction appears in N Engl J Med. 2007 Feb 22;356(8):879]. *N Engl J Med*. 2006;355(24):2558-2573. doi:10.1056/NEJMra062453
25. Biering H, Knappe G, Gerl H, Lochs H. Diabetes-Häufigkeit bei Akromegalie und Cushing-Syndrom [Prevalence of diabetes in acromegaly and Cushing syndrome]. *Acta Med Austriaca*. 2000;27(1):27-31. doi:10.1046/j.1563-2571.2000.200106.x
26. Stelmachowska-Banaś M, Zdunowski P, Zgliczyński W. Abnormalities in glucose homeostasis in acromegaly. Does the prevalence of glucose intolerance depend on the level of activity of the disease and the duration of the symptoms?. *Endokrynol Pol*. 2009;60(1):20-24.
27. Kreze A, Kreze-Spirova E, Mikulecky M. Risk factors for glucose intolerance in active acromegaly. *Braz J Med Biol Res*. 2001;34(11):1429-1433. doi:10.1590/s0100-879x2001001100009
28. Rodrigues TC, Costenaro F, Fedrizzi D, et al. Diabetes mellitus in a cohort of patients with acromegaly. *Arq Bras Endocrinol Metabol*. 2011;55(9):714-719. doi:10.1590/s0004-27302011000900008
29. Alexopoulou O, Bex M, Kamenicky P, Mvoula AB, Chanson P, Maiter D. Prevalence and risk factors of impaired glucose tolerance and diabetes mellitus at diagnosis of acromegaly: a study in 148 patients. *Pituitary*. 2014;17(1):81-89. doi:10.1007/s11102-013-0471-7
30. Fieffe S, Morange I, Petrossians P, et al. Diabetes in acromegaly, prevalence, risk factors, and evolution: data from the French Acromegaly Registry. *Eur J Endocrinol*. 2011;164(6):877-884. doi:10.1530/EJE-10-1050
31. Schneider HJ, Friedrich N, Klotsche J, et al. Prediction of incident diabetes mellitus by baseline IGF1 levels. *Eur J Endocrinol*. 2011;164(2):223-229. doi:10.1530/EJE-10-0963
32. Rymaszewski Z, Cohen RM, Chomczynski P. Human growth hormone stimulates proliferation of human retinal microvascular endothelial cells in vitro. *Proc Natl Acad Sci U S A*. 1991;88(2):617-621. doi:10.1073/pnas.88.2.617
33. Smith LE, Kopchick JJ, Chen W, et al. Essential role of growth hormone in ischemia-induced retinal neovascularization. *Science*. 1997;276(5319):1706-1709. doi:10.1126/science.276.5319.1706
34. Hyer SL, Sharp PS, Brooks RA, Burrin JM, Kohner EM. A two-year follow-up study of serum insulinlike growth factor-I in diabetics with retinopathy. *Metabolism*. 1989;38(6):586-589. doi:10.1016/0026-0495(89)90222-9
35. Wang Q, Dills DG, Klein R, Klein BE, Moss SE. Does insulin-like growth factor I predict incidence and progression of diabetic retinopathy?. *Diabetes*. 1995;44(2):161-164. doi:10.2337/diab.44.2.161
36. Janssen JA, Lamberts SW. Circulating IGF-I and its protective role in the pathogenesis of diabetic angiopathy. *Clin Endocrinol (Oxf)*. 2000;52(1):1-9. doi:10.1046/j.1365-2265.2000.00922.x
37. Laron Z, Weinberger D. Diabetic retinopathy, nephropathy and cardiovascular disease in a patient with GH gene deletion. *Clin Endocrinol (Oxf)*. 2005;63(6):699-700. doi:10.1111/j.1365-2265.2005.02402.x
38. Koller EA, Green L, Gertner JM, Bost M, Malozowski SN. Retinal changes mimicking diabetic retinopathy in two nondiabetic, growth hormone-treated patients. *J Clin Endocrinol Metab*. 1998;83(7):2380-2383. doi:10.1210/jcem.83.7.4953
39. Wilkinson-Berka JL, Wraight C, Werther G. The role of growth hormone, insulin-like growth factor and somatostatin in diabetic retinopathy. *Curr Med Chem*. 2006;13(27):3307-3317. doi:10.2174/092986706778773086
40. Sönksen PH, Russell-Jones D, Jones RH. Growth hormone and diabetes mellitus. A review of sixty-three years of medical research and a glimpse into the future?. *Horm Res*. 1993;40(1-3):68-79. doi:10.1159/000183770
41. 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(2):161-167. doi:10.1076/orbi.21.2.161.7186
42. Barnes AJ, Kohner EM, Johnston DG, Alberti KG. Severe retinopathy and mild carbohydrate intolerance: possible role of insulin deficiency and elevated circulating growth hormone. *Lancet*. 1985;1(8444):1465-1468. doi:10.1016/s0140-6736(85)92250-0
43. Wu TE, Chen HS. Increased prevalence of proliferative retinopathy in patients with acromegaly. *J Chin Med Assoc*. 2018;81(3):230-235. doi:10.1016/j.jcma.2017.09.013
44. Wu TE, Chen HS. The role of growth hormone and IGF-1 in retinopathy: a prospective study of retinopathy in patients with acromegaly and impaired fasting glucose. *Diabetol Metab Syndr*. 2022;14(1):38. Published 2022 Mar 5. doi:10.1186/s13098-022-00806-z
45. Tas A, Bayraktar MZ, Erdem U, Sobaci G, Ucar M. Prevalence and risk factors for diabetic retinopathy in Turkey. *Gulhane Medical Journal*. 2005; 47(3):164-174.
46. Hernández C, Simó R; European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Somatostatin replacement: a new strategy for treating diabetic retinopathy. *Curr Med Chem*. 2013;20(26):3251-3257. doi:10.2174/09298673113209990024
47. Grant MB, Caballero S Jr. The potential role of octreotide in the treatment of diabetic retinopathy. *Treat Endocrinol*. 2005;4(4):199-203. doi:10.2165/00024677-200504040-00001
48. Yuno A, Ikota A, Koizumi S, et al. Advanced proliferative diabetic retinopathy and macular edema in acromegaly: a case report and literature review. *Diabetol Int*. 2022;13(3):575-579. Published 2022 Jan 25. doi:10.1007/s13340-022-00571-4
49. Colao A, Auriemma RS, Galdiero M, et al. Impact of somatostatin analogs versus surgery on glucose metabolism in acromegaly: results of a 5-year observational, open, prospective study. *J Clin Endocrinol Metab*. 2009;94(2):528-537. doi:10.1210/jc.2008-1546