Increased number of retinal vessels in acromegaly

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Abstract

Objective: Excess of growth hormone (GH) and insulin-like growth factor 1 (IGF-1), as in acromegaly, is associated with increased risk of diabetes, but whether retinal vessels are altered is unknown. The aim of this study was to evaluate retinal vessel morphology in patients with acromegaly at diagnosis and after treatment and to describe the prevalence of diabetic retinopathy in patients with long-standing acromegaly and diabetes.

Design: Two independent observational studies, one being prospective and the other retrospective and cross-sectional.

Methods: Retinal vessel morphology of 26 patients with acromegaly was examined at diagnosis and 1 year after treatment and compared to 13 healthy controls. Cross-sectional evaluation of 39 patients with long-standing acromegaly and diabetes was performed. Fundus photographs were digitally analyzed for vessel morphology.

Results: Patients with acromegaly had a median (interquartile range) of 34.3 (30.0–39.0) vessel branching points compared to 27.0 (24.0–29.0) for healthy controls ($P < 0.001$). Tortuosity of arterioles and venules remained unchanged. Vessel morphology did not change significantly after treatment. Patients with acromegaly and diabetes for a median of 14 years also had a high number of branching points (34.2 (32.5–35.6)), but the prevalence of diabetic retinopathy was not higher than expected in diabetic patients without acromegaly.

Conclusions: Patients with acromegaly have an increased number of vascular branching points in the retina without an alteration of macroscopic vessel morphology. This is consistent with an angiogenic effect of GH/IGF-1 in humans. The prevalence of diabetic retinopathy was not increased in patients with acromegaly and diabetes.

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Introduction

Patients with acromegaly have elevated serum concentrations of growth hormone (GH) and insulin-like growth factor 1 (IGF-1), which is associated with excess mortality, mainly due to cardiovascular diseases (1). There is evidence that normalization of GH and IGF-1 levels negates the increased mortality of the condition (2). As the disease develops slowly and initially has unspecific symptoms, diagnosis is often delayed by many years. Increased GH exposure in acromegaly leads to insulin

resistance (3) with hypertension and diabetes mellitus (DM) among the main comorbidities affecting patients (4).

Patients with DM may develop microangiopathy with abnormal vessel growth and permeability, which can affect various organs. Presence and severity of changes in the retina may predict changes in other organs (5). The retina therefore provides a unique possibility to study microvascular morphology by direct and non-invasive examination.

The roles of GH and IGF-1 as trophic factors in the eye have been discussed in this context. As insulin inhibits IGF-binding protein-1 (IGFBP-1) and induces hepatic production of IGF-1, patients with type 1 DM have low serum levels of IGF-1 and increased IGFBP-1 and GH levels (6). In type 2 DM, the situation is more complex, but most studies in type 2 DM find serum IGF-1 levels comparable to healthy controls (7, 8). Correlations between serum IGF-1 concentrations and the presence and severity of diabetic retinopathy have shown conflicting results (9, 10), but high levels of intravitreal IGF-1 have been seen in patients with proliferative retinopathy (11).

Early reports of improvement of diabetic retinopathy after pituitary infarction or ablation in patients with type 1 DM (12, 13) may support the hypothesis of a pathogenic role of GH and IGF-1 in diabetic retinopathy. We would therefore expect that patients with active acromegaly and diabetes would have a higher prevalence of diabetic retinopathy; however, previous small studies have not consistently shown this (14, 15, 16).

The aim of this study was, for the first time, to evaluate retinal vessel morphology by an objective method using digital imaging analysis of fundus photographs in patients with acromegaly at diagnosis and after biochemical control. In a different cohort of patients with long-standing acromegaly and type 2 DM, we aimed to describe retinal findings and the prevalence of diabetic retinopathy.

Subjects and methods

Study protocol

This report contains two independent studies. The first is a case-control study followed by a prospective cohort study of retinal vessel morphology in patients with acromegaly. The second is a retrospective cross-sectional study on retinal findings in patients with long-standing acromegaly and type 2 DM. In the first study, patients were included in Gothenburg, Sweden, at the time of diagnosis when fundus photographs were taken before any type of intervention. Measurements were compared to healthy controls. Patients were then treated according to best clinical practices, with surgery, medical treatment, or both. If necessary, patients received hormonal replacement therapy (Table 1). Follow-up fundus photographs were available in 16 patients after a median time of 1.4 years (range, 0.8–3.5). In the second study, fundus photographs at a regular check-up of patients with long-standing and

well-treated acromegaly and type 2 DM were examined in patients from Rotterdam, the Netherlands.

Subjects

Recruitment of 26 consecutive patients with acromegaly was performed at the Sahlgrenska University Hospital (Gothenburg, Sweden) between 2004 and 2011. Acromegaly was diagnosed by the presence of clinical features, serum IGF-1 levels 1.2 times above the age-adjusted upper limit of normal (ULN), GH nadir >1 µg/L after oral glucose tolerance test (OGTT), or GH-day curve with a minimum value >1 µg/L in the presence of a pituitary adenoma. GH-day curve, OGTT, and serum IGF-1 measurements were performed at follow-up. Patients were considered to have controlled disease if two or more of these tests were normal.

For the cross-sectional study, clinical data and fundus findings at the last clinical check-up (as of September 2018) were obtained for patients at the Erasmus University Medical Center (Rotterdam, the Netherlands). Fundus photographs were dated between 2005 and 2018 in this part of the study.

Reference populations

Results were compared with fundus photographs of 13 healthy adults of similar age as the acromegalic patients. As fundus morphology of healthy individuals does not change after 3 years of age (17), the acromegalic patients in this study were also compared to normal fundus photographs from 100 young (3–19 years of age), healthy individuals who were analyzed with the same equipment (18).

For comparison of the prevalence of diabetic retinopathy, we used data from the Swedish National Diabetes Registry. We extracted data on diabetic retinopathy during 2018 for patients with type 2 DM treated in primary care with a disease duration of 7–14 years. This analysis was conducted at both a nationwide level and a regional level, including 121 603 and 22 564 patients, respectively, with a completeness for data of 86% and 81%, respectively (19).

Ethical considerations

Informed consent was obtained from all patients. The study was approved by the Regional Ethics Review Boards/Local Institutional Review Boards in Gothenburg, Sweden, and in Rotterdam, the Netherlands.

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Table 1 Characteristics of acromegalic patients from Gothenburg and Rotterdam.

Characteristics	Gothenburg patients (n = 26)	Rotterdam patients (n = 39)
Sex, n (%), Male/Female	13 (50)/13 (50)	23 (59)/16 (41)
Median age at diagnosis, year (range)	47.9 (23–75)	45.9 (18–69)
Median age at follow-up, year (range)	51.0 (31–73)	60.2 (33–84)
Adenoma type, n (%), micro/macro	5 (19)/21 (81)	1 (3)/38 (97)
Treatment at diagnosis, n (%)		
Surgery	23 (63.9)	24 (61.5)
Somatostatin receptor ligands	2 (7.7)	NR
Dopamine agonist	1 (3.8)	NR
Pre-operative treatment, n (%)		
Somatostatin receptor ligands	3 (11.5)	18 (46.2)
Pegvisomant	0	6 (15.4)
Dopamine agonist	1 (3.8)	0
Current treatment, n (%)		
Somatostatin receptor ligands	–	35 (89.7)
Pegvisomant	–	33 (84.6)
Dopamine agonist	–	3 (7.7)
Radiotherapy	0	4 (15.4)
Mean IGF-1, xULN (s.d.)	3.20 (1.32)	0.92 (0.38)
Mean BMI, kg/m ² (s.d.)	26.7 (4.2)	30.6 (4.2)
Diabetes, n (%)	7 (26.9)	39 (100)
Impaired glucose tolerance, n (%)	6 (23.1)	ND
Mean fasting glucose, mmol/L (s.d.)	6.2 (2.3)	ND
Mean glucose 2 h after OGTT, mmol/L (s.d.)	9.6 (4.5)	ND
Mean HbA1c at last follow-up, % (s.d.)	ND	6.8 (0.9)
Mean SBP/DBP, mmHg (s.d.)	136 (17)/79 (11)	135 (11)/83 (10)
Mean total cholesterol, mmol/L (s.d.)	5.0 (0.8)	4.6 (1.0)
Mean LDL-cholesterol, mmol/L (s.d.)	2.3 (1.3)	2.8 (0.8)
Mean HDL-cholesterol, mmol/L (s.d.)	1.5 (0.3)	1.4 (0.5)
Mean triglycerides, mmol/L (s.d.)	1.5 (1.1)	1.4 (0.6)
Treatment with statin/RAS inhibitor, n (%)	2 (8)/5 (19)	23 (59)/25 (64)
Ischemic heart disease, n (%)	1 (3.8)	NR
Hormone insufficiency, n (%)		
Thyroid hormone	4 (15.4)	9 (23.1)
Testosterone	6 (23.1)	16 (41.0)
Estrogen	4 (15.4)	8 (20.5)
Adrenocorticotrophic hormone	0	6 (15.4)
Hormone replacement, n (%)		
Thyroid hormone	2 (7.7)	9 (23.1)
Testosterone	1 (3.8)	14 (35.9)
Estrogen	1 (3.8)	2 (5.1)
Hydrocortisone	0	6 (15.4)

One additional Swedish patient received thyroxine after thyroid surgery.

DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ND, not done; NR, not reported; OGTT, oral glucose tolerance test; RAS, renin-angiotensin system; SBP, systolic blood pressure; ULN, upper limit of normal.

Biochemical analysis

The technique for measuring serum IGF-1 concentrations changed during the study period. The individual results were therefore compared to the age- and sex-matched/adjusted reference ranges supplied by the producer to acquire a percentage of the ULN. In Sweden before September 2006, serum IGF-1 was measured using a chemiluminescent immunoassay (Advantage, Nichols Institute Diagnostics, San Juan Capistrano, CA). After September 2006, an Immulite automated

chemiluminescence system was used (Immulite 2500/200Xpi, Siemens Medical Solutions Diagnostics). The method for measuring serum GH also changed during the study period. Before 2008, an immunofluorometric assay was used (DELFI[®], Wallac, Sweden), whereas after 2008, a one-step immunoenzymatic method was used (Access2, Beckman Coulter, Bromma, Sweden).

In the Netherlands before 2013, serum IGF-1 was measured with the Immulite 2000 assay (DPC Biermann GmbH/Siemens), which is a solid-phase, enzyme-labeled chemiluminescent immunometric assay with an intra-

assay variability of 2–5% and an inter-assay variability of 3–7%. IGF-1 age- and sex-adjusted reference ranges were used from the publication by Elmlinger *et al.* (20). From 2013, serum total IGF-1 concentrations were analyzed by the commercially available immunometric assay (IDS-iSYS, Immunodiagnostic Systems Limited, Boldon, UK), which has intra-assay and inter-assay coefficients of variation for IGF-1 of 8.1% and 2.1%, respectively, using recently reported reference intervals (21).

Fundus photography and digital image analysis

In Sweden, fundus photographs were taken with a Canon 60° fundus camera (CF-60UD) and developed as dias slides. These were then digitalized by a CCD flatbed scanner and analyzed by a computer-assisted digital mapping system as described previously (22). Briefly, the retinal vessels (arteries, veins, and unspecified small vessels) were traced manually from their origin on the optic disc to a reference circle 3.0 mm from the geometric center of the optic disc. Tortuosity index was obtained by dividing the vessel's path length by the linear distance from its origin to the reference circle. The number of branching points on all vessels within the reference circle were identified manually and counted automatically. In the Netherlands, fundus photographs were taken locally for clinical diabetic retinopathy assessment and, thus, by different cameras and at different angles. Some were analyzed manually and some digitally.

Conventional retinal analysis

All fundus photographs were thoroughly analyzed in a masked fashion with respect to acromegalic patients and controls by two independent ophthalmologists. If there was disparity between the retinal evaluation, a consensus was reached. The optic disc was analyzed for glaucoma and retina for abnormal retinal vessel appearance, where abnormalities associated with hypertension were graded according to the Keith–Wagener–Barker classification (23), and abnormalities associated with diabetic retinopathy were graded according to the modified Airlie House classification. In addition, macular morphology abnormalities were noted.

Statistical analysis

The primary outcome measures of this study were retinal vascular branching points and tortuosity index of

arterioles and veins. Secondary outcome measures were the prevalence of diabetes retinopathy, morphometric measures of the optic disc, and prevalence of other retinopathies.

Since the size of the groups were limited, results for retinal measurements are shown as median and interquartile ranges (IQRs). Comparison of results to the reference populations was performed using the non-parametric Mann–Whitney *U*-test. For the follow-up analyses, the results were compared using a two-tailed Wilcoxon signed-rank test. Adjusted analyses for age and sex were performed using regression models (ANOVA). *P* values of <0.05 were considered significant. IBM SPSS (version 21; SPSS Institute) software was used to perform the statistical analyses.

Results

Baseline

The clinical characteristics of patients with acromegaly from Gothenburg (*n*=26) and Rotterdam (*n*=39) are summarized in Table 1. At diagnosis, in the Gothenburg cohort, 13 patients had abnormal glucose metabolism, one patient had type 1 DM, six patients had type 2 DM, and six patients had impaired glucose tolerance following OGTT. All patients from Rotterdam had type 2 DM and acromegaly. Morphometric measurements of the retinal vessels of 26 patients with untreated acromegaly and 13 healthy controls are shown in Table 2. An example of a fundus photograph is shown in Fig. 1. Retinal vessel tortuosity and optic disc dimensions did not differ between cases and controls. Compared to healthy adult and child controls, patients with acromegaly had an increased number of retinal vessels as reflected by more branching points. Patients with hypertension (systolic blood pressure >135 mmHg) and abnormal OGTT including DM did not differ in number of branching points from patients without these abnormalities (data not shown). There was no correlation between serum IGF-1 levels or age and number of retinal vascular branching points (Pearson's coefficient 0.15 and –0.12, respectively). Eighteen of the acromegalic patients had a normal retina, two had grade 1 hypertensive retinopathy, three had pre-proliferative diabetic retinopathy (one had previously been laser treated), one had glaucoma, and two had macular abnormalities. Conventional analysis of the fundus photographs was normal for the healthy controls.

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Table 2 Retinal vessel and optic nerve morphometry.

	Gothenburg			Rotterdam (n = 39)
	Patients (n = 26)	Controls (n = 13)	P values patients vs adult controls	
Sex, n (%)				
Men	13 (50)	4 (30.8)		23 (59.0)
Women	13 (50)	9 (69.2)		16 (41.0)
Median age, year (range)	47.9 (23–75)	53.8 (32–67)		60.2 (33–84)
Median tortuosity index (IQR)				
Arteries	1.06 (1.05–1.08)	1.06 (1.05–1.07)	0.6	1.06 (1.05–1.06)
Veins	1.06 (1.05–1.08)	1.05 (1.05–1.06)	0.4	1.06 (1.05–1.06)
Median branching points, n (IQR)*	34.3 (30.0–39.0)	27.0 (24.0–29.0)	0.0003	34.2 (32.5– 35.6)
Median optic papilla areas, mm ² (IQR)				
Disc	1.22 (1.11–1.47)	1.18 (1.06–1.35)	0.6	ND
Cup	0.12 (0.07–0.35)	0.00 (0.00–0.12)	0.058	ND
Rim	1.17 (1.01–1.32)	1.17 (1.03–1.30)	0.9	ND
Retinal examination, n (%)				
Normal medical retina	18 (69.2)	13 (100)		32 (82.1)
Grade 1 hypertensive retinopathy	2 (7.7)	0		2 (5.1)
Pre-proliferative diabetic retinopathy	3 (11.5)	0		2 (5.1)
Proliferative diabetic retinopathy	0	0		3 (7.7)
Glaucoma	1 (3.8)	0		0
Macula abnormalities	2 (7.7)	0		2 (5.1)

*An adjusted model (adjusted for age and sex) showed a similar significant difference between the groups ($P = 0.0022$).

Effect of Acromegaly treatment

In 16 patients after a median follow-up of 1 year (range, 0.8–3.5) after primary treatment, the tortuosity of the vessels and retinal fundus abnormalities were unchanged. Patients still had a higher median (IQR) number of retinal vascular branching points than controls (35 (27.5–38.5) vs 27 (23.3–29.0), respectively). There was no difference in branching points between the patients that obtained biochemical control and those who did not ($P = 0.30$) (Fig. 2). The variation in branching points in the acromegalic population was larger than in the healthy controls. This is reflected in the large IQR shown in Fig. 3.

Cross-sectional study of patients with acromegaly and diabetes

In 39 patients with known acromegaly for a median (IQR) of 14 years (10–19) and a type 2 DM diagnosis for a median of 14 years (4–19.5), morphometric analysis of retinal vessels confirmed findings of the longitudinal study. Patients had increased number of branching points but unchanged tortuosity of the vessels (Table 2). In this cohort, diabetic retinopathy was diagnosed in five (13%) patients (two pre-proliferative and three proliferative diabetic retinopathy), with two having grade 1 hypertensive retinopathy and two having macular abnormalities. Medical retinal examination was normal

in 32 patients. Individuals with diabetic retinopathy from both cohorts had a tendency toward higher mean (s.d.) systolic blood pressure compared to other patients (141.6 ± 9.9 vs 135.1 ± 11.1 mmHg, $P = 0.06$).

For comparison, data obtained from the Swedish Diabetes Registry for patients with type 2 DM and a DM duration of 7–14 years treated in primary care showed a prevalence of diabetic retinopathy of 21% in the region around Gothenburg (Västra Götaland) and 24% at the Swedish national level.

Discussion

We have shown that patients with acromegaly have an increased number of retinal vascular branching points, suggesting that this is an effect of long-standing excessive exposure of GH and IGF-1. However, the frequency of diabetic retinopathy among patients with concomitant acromegaly and DM was not higher than that expected for patients with type 2 DM alone.

Few other studies have examined the effects of GH on human microvasculature, as this would require invasive techniques in most organs. However, the skin, just like the eye, allows for direct examination of microvasculature. One such study using nail-fold capillaroscopy found a decreased number of capillaries and increased tortuosity in acromegalic patients, which stands in contrast to our

Figure 1

Fundus photography of (A) patient with acromegaly and (B) healthy control. Examples of branching points marked with arrows.

results from the retina (24). However, such findings in the nail fold are also common in other medical conditions such as hypertension (even subclinical forms) and diabetes, which are both common comorbidities in acromegaly (25). On the other hand, and more in line with our findings, GH-deficient (GHD) patients have reduced skin capillary density and microvascular perfusion, both of which are normalized after 6 months of GH replacement therapy (26, 27). Children with GHD (28), GH receptor defects (Laron syndrome) (29), and adult patients with congenital isolated GHD (30) have reduced numbers of branching points in the retina, supporting the hypothesis of a crucial role of the GH/IGF-1 system in vasculogenesis in humans. One cross-sectional study, assessing the safety of long-term GH replacement therapy in adult GHD patients, found no evidence of retinopathy, but in this study serum IGF-1

Figure 2

Number of retinal vascular branching points in Swedish acromegalic patients at diagnosis and at follow-up. Cured disease at follow-up represented by solid lines and active disease at follow-up by dashed lines.

was normal and vessel density or branching points were not evaluated, as the focus was on diabetic retinopathy changes (31). We propose that the increased number of branching points found in the acromegalic patients in our study may reflect the angiogenic effects of GH/IGF-1 in humans, which might explain some of the effects of GH

Figure 3

Number of retinal vascular branching points in healthy adults and children compared to patients with acromegaly from Gothenburg at diagnosis and after 1 year of treatment and patients from Rotterdam. Data are presented as a box and whiskers plot with the interquartile range, median, and maximum and minimum values.

in other highly vascularized organs such as the thyroid gland (32). As we could detect an increase in branching points after a median of 14 years of optimal treatment, these changes are most likely among the irreversible changes that come with the disease.

The effect of GH on angiogenesis is thought to be direct and indirect through IGF-1. IGF-1 is known to be essential for normal retinal development (33). GH can directly stimulate endothelial proliferation, migration, and extracellular matrix production as well as the formation of capillary structures *in vitro* (34). Also, GH treatment increases vascularization in the brain (35) and heart (36) of aged rats. Endothelial cells themselves produce little IGF-1, but express IGF-1 receptors and thus respond to circulating IGF-1 (37). IGF-1 promotes angiogenesis by promoting chemotaxis *in vitro* (38). The angiogenic effects by IGF-1 are thought to be both direct and through stimulation of vascular endothelial growth factor (39, 40). It is known that other angiogenic factors in the blood, such as angiogenin and endostatin, are elevated in acromegaly (41) but also in several other physiological and clinical settings (42). This underscores the complexity of angiogenesis and might explain some overlap in branching points in our study groups and control groups. Whether the elevated intraocular IGF-1 in diabetic retinopathy is due to leakage across the blood-retina barrier or represents intraocular production remains a subject of debate (11, 43).

We report on a total of 46 patients with acromegaly and DM, eight of whom had some degree of diabetic retinopathy. The overall prevalence of diabetic retinopathy was thus 17%, with the prevalence being higher in the Gothenburg patients (3/7, 43%) than in the Rotterdam patients (5/39, 13%). One difference between the two cohorts is the treatment regime for acromegaly. Most of the Swedish patients received surgery and, if not cured, they received a somatostatin receptor ligand (SRL), whereas most Dutch patients received pegvisomant in addition to SRL (Table 1). GH receptor blockade by pegvisomant may therefore have favorable effects on diabetic retinopathy, although this was not supported by a 24-week treatment trial in patients with DM and retinopathy (44).

In the general diabetic population, the prevalence of diabetic retinopathy varies locally and over time and direct comparison is therefore difficult. Data from the Swedish National Diabetes Register show a prevalence of retinopathy after a similar duration of diabetes in primary care patients to be just above 20%. We did not have access to detailed population based data from the Netherlands on diabetes retinopathy; however, one study from the city

of Einthoven found a prevalence of diabetes retinopathy of 31% after a median disease duration of 12.5 years (45). These patients, however, were referred to specialists due to a complicated medical situation that could explain the higher prevalence of retinopathy. Taken together, our data do not support the hypothesis of a higher prevalence of diabetic retinopathy in patients with acromegaly and DM. In a recent retrospective study including 16 patients with acromegaly and diabetes, prevalence of proliferative diabetic retinopathy was similar to matched controls with diabetes, whereas no patient had pre-proliferative retinopathy (46). In our study, half of the patients with diabetic retinopathy had pre-proliferative retinopathy. Together these data do not support the hypothesis of IGF-1 exclusively playing a role in proliferative retinopathy. Interestingly, in our patients there was no correlation between blood glucose OGTT results and the number of branching points in retinal vessels. Also, the increased number of branching points was also present in the patients treated with pegvisomant, suggesting that blocking the GH receptor has no effect on this finding.

The impact of acromegaly on diabetic retinopathy may be more complicated than the mere effects of GH and IGF-1 on vascularization as many factors influence the development of retinopathy, not all of which are aggravated by acromegaly. For example, it is well known that markers of inflammation such as C-reactive protein and interleukin-6 are elevated in diabetic patients with retinopathy compared to patients without retinopathy and are even positively correlated with the severity of retinopathy (47). However, in acromegaly, acute-phase reactants are decreased, suggesting that GH/IGF-1 may have anti-inflammatory effects that potentially counteract the development of retinopathy (48). It could be argued that the increased number of retinal vessels in acromegaly might be due to increased blood pressure, altered body composition, or other comorbidities common in acromegaly. We could not find any such correlations in our data. Our conclusion is, therefore, that the increase in vascularization of the retina in both diabetic and non-diabetic patients with acromegaly is a direct effect of increased hormone levels leading to formation of new but seemingly healthy vessels without a significant impact on the development of diabetic retinopathy.

This study has both strengths and limitations. It includes a relatively large number of patients with acromegaly and is based on all available patients treated in the two study centers. The Swedish part of the study was designed in a prospective manner. Limitations of our

study are that the retinal photographs in our patients and the adult control group were taken with different cameras and at a different location than the retinal photographs of the child cohort, which has been previously published (18). Camera settings and magnification factors were the same for all Swedish patients. However, the tortuosity index, which is dependent on magnification, seemed to differ between the child and the adult control groups, which is why the data from the child cohort was used with caution. The number of branching points is less dependent on minor differences in magnification and the two control groups showed similar results, both of which were significantly different from the acromegalic patients. As the technique of fundus photographs and analysis was different for the Rotterdam patients, fundus morphology data could not be directly compared between the two cohorts of patients with acromegaly.

In conclusion, this unique study shows by objective measures that patients with acromegaly have increased retinal vascular density with apparently normal vessels and that those subjects with diabetes had a prevalence of diabetic retinopathy equal to or lower than what would be expected. The findings support the role for the GH/IGF-1 system in angiogenesis but not in the development and progress of diabetic retinopathy.

Declaration of interest

D S O has been a consultant for Sandoz, Ipsen, and Pfizer. G J has been a consultant for AstraZeneca, Novo Nordisk, and Shire and has received lecture fees from Merck Serono, Novo Nordisk, Novartis, Otsuka, Pfizer, and Shire. S N has been a consultant for Pfizer and Ipsen and has received study grants from Pfizer, Novartis, and Ipsen. A H is a medical consultant for Takeda/Shire. G J is on the editorial board of EJE. G J was not involved in the review or editorial process for this paper, on which he is listed as an author. The other authors have nothing to disclose.

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Author contribution statement

A Hellström and G Johannsson contributed equally to this work.

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