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Growth Hormone & IGF Research 15 (2005) 130–135
www.elsevier.com/locate/ghir

Progression of diabetic retinopathy during improved metabolic control may be treated with reduced insulin dosage and/or somatostatin analogue administration – a case report

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Received 8 July 2004; revised 16 December 2004; accepted 16 December 2004
Available online 5 February 2005

Abstract

It is well known that intensified insulin treatment of poorly controlled type 1 diabetic patients may worsen an existing diabetic retinopathy (DR). This observation has been explained by an insulin-induced stimulation of the GH/IGF-I axis. Here, we report on three cases, where the progression of DR during intensified metabolic control was treated with manipulation of insulin therapy and/or by administration of octreotide.

Serum concentrations of IGF-I, IGFBP-3, insulin, cystatin C, creatinine, endogenous creatinine clearance and HbA1c-levels were assessed by routine laboratory methods; serum IGF-I bioactivity was estimated by a highly specific kinase receptor activation assay. Visual acuity and retinopathy stage was assessed by established clinical methods including fluorescein angiography.

After glycaemic control was improved by intensified insulin therapy, serum IGF-I levels acutely increased. Subsequently, DR progressed to an advanced stage (''florid retinopathy''), with macular edema, and proliferation of new vessels (in two cases). Immediate reduction of insulin dosage and administration of octreotide lowered serum total IGF-I levels (and IGF-I bioactivity as measured in one patient). Subsequently, macular edema resolved partly, and visual acuity improved, allowing laser photocoagulation to be performed.

In conclusion, in poorly controlled type 1 diabetic patients, intensified insulin therapy is able to cause florid DR with acute macular edema. These sight-threatening changes may improve by short-term reduction of insulin dosage or by administration of octreotide, and we speculate that this may be related to down-regulation of (serum) IGF-I.

Keywords: Intensive insulin therapy; Proliferative retinopathy; Early worsening of retinopathy; Metabolic control; Diabetes complications; Albuminuria

1. Introduction

Type 1 diabetic patients with chronic insulin deficiency and poor metabolic control are usually characterised by high serum levels of GH, while circulating IGF-I concentrations are low. This condition, which is found in type 1 diabetic patients as well as in malnutrition, is categorised as secondary GH insensitivity syndrome (SGHIS) [1]. In type 1 diabetic patients, SGHIS is reversible by intensified insulin therapy, which may, however, be associated with a transient and overshooting upregulation of serum IGF-I. Increasing serum IGF-I levels have triggered proliferation of new vessels in a clinical intervention trial [2]. Intensified insulin treatment is known to induce sight-threatening forms of diabetic retinopathy (DR), e.g. ''early worsening of DR'', ''florid DR'' or ''proliferative DR'' (PDR) with

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doi:10.1016/j.ghir.2004.12.005

macular edema in patients with a preconditioned, e.g. ischaemic, retina [3,4]. As standard laser coagulation treatment is of limited value in this condition [5], downregulation of serum IGF-I levels might be considered a treatment option. Downregulation of serum IGF-I levels in diabetic patients can be achieved by (partial) withdrawal of the adequate antidiabetic medication, e.g. by reduction of insulin dosage [6], or by drugs like octreotide [7–9].

Here, we report on three type 1 diabetic patients with SGHIS, in whom serum IGF-I levels were affected by manipulation of the insulin therapy ($n = 3$) and by administration of octreotide ($n = 2$) and in whom effects on retinopathy were observed. All patients were treated at the Düsseldorf University hospital.

2. Material and methods

Visual acuity (VA) was assessed by standard Snellen charts. Retinopathy stage was determined according to established criteria [10] by consultant ophthalmologists, using fluorescein angiography. Serum GH, total IGF-I (age adjusted normal range 101–329 μg/l), and IGFBP-3 (age adjusted normal range 3.39–7.58 mg/l) was determined by automated chemiluminiscent immunoassay (DPC Biermann, Germany) in overnight fasting blood samples. IGF-I bioactivity was determined by a highly specific kinase receptor activation assay (KIRA) as recently published by Jian-Wen Chen et al. [11]. Serum thyroid hormones, cystatin C, creatinine and endogenous creatinine clearance (ECC) were determined by routine laboratory methods. HbA1c was determined by HPLC (normal range 4–6%), albuminuria by nephelometry (normal < 20 mg/l). Serum insulin was determined by an ELISA (Mercodia AB, Uppsala, Sweden).

3. Results

3.1. Case 1

A female patient (H., born 1974) with type 1 diabetes since the age of eight had been in extremely poor control since 1992, due to deliberately omitting insulin injections. She was diagnosed with Hashimoto-thyreoiditis and depression in 1994, and with incipient diabetic neuropathy and nephropathy in 1997. In 1997 [4] and in 2000, she had experienced two bouts of "florid DR" with severe macular edema and PDR [10]. Both events had been preceded by intensified insulin therapy, lowering from approximately 12% to 8% within a few weeks. In both episodes, progression of retinopathy came to a halt only after blood glucose and HbA1c were deliberatedly elevated again, allowing extensive panretinal laser coagulation to be performed.

In June 2003, at the age of 28, H. was admitted to the diabetic ward with a neuropathic plantar ulcer with celluitis at her left big toe. VA was 0.9 in the better eye, and both fundi showed panretinal laser coagulation scars, but no neovascularisations. Blood pressure was 200/100 mmHg. Her prescribed medication consisted of approximately 20 units of Actrapid® and 35 units of Protaphane® insulin (Novo Nordisk, Denmark) daily as well as 150 μg levothyroxine daily.

Admission laboratory findings were as follows: HbA1c 16.3%, equivalent to a chronic average blood glucose of approximately 500 mg/dl [13]; serum creatinine 0.6 mg/dl; ECC 92 ml/min; serum cystatin C 0.7 mg/l; albuminuria 600 mg/l. Serum total IGF-I was 137 μg/l, and serum GH was 8.2 μg/l, consistent with the diagnosis of SGHIS. IGF-I bioactivity was 1.40 μg/l (Fig. 1). She stayed at the diabetic ward for 6 days to receive antibiotics, wound care and pressure relief of the infected foot; the acute inflammation resolved within that time. Blood pressure was controlled with lisinopril plus hydrochlorothiazide. Subcutaneous insulin therapy was carried out under routine supervision of the ward nurses, aiming at blood glucose levels between 100–200 mg/dl. As a consequence serum total IGF-I rose rapidly to a supranormal level of 421 μg/l (Fig. 1), whereas GH decreased to 5.7 μg/l. HbA1c declined more gradually. Changes in IGF-I bioactivity paralleled the changes in total serum IGF-I (Fig. 1). Increasing neuropathic leg pain was reported.

When the patient was discharged from the ward, her VA had decreased to 0.4 due to the presence of macular edema. It was assumed that the macular edema was caused by improved metabolic control and the increased serum IGF-I levels. Therefore, we aimed to reduce serum IGF-I levels by reducing her daily insulin dosage by about 30%, whereby insulin deficiency and SGHIS reappeared. As a result, blood glucose levels increased to approximately 300 mg/dl (corresponding to HbA1c-levels around 12.5%), whereas serum IGF-I declined to approximately 260 μg/l. IGFBP-3 decreased slightly, while overnight fasting GH remained normal (1.3 μg/l; Fig. 1). An appointment at the eye clinic was scheduled 4 weeks later, revealing PDR in both eyes, macular edema, and a VA of 0.4. At this time point, subcutaneous administration of octreotide (Sandostatin ®) 100 μg twice daily was started. To avoid hypoglycaemia from octreotide administration, the insulin dosage was further reduced by 20%. This therapeutic approach reduced overnight fasting serum levels of insulin (from 9 to 6 mU/l), GH (from 1.3 to 0.6 μg/l), HbA1c (from 12.5% to 10.3%), total IGF-I (from 260 to less than 200 μg/l), and IGF-I bioactivity (from approximately 1.4 to 1.0 μg/l) (Fig. 1). A VA of 0.8 was regained, but retinal proliferations, however, remained unchanged. With some delay, laser coagulation treatment was started in the left eye a week after macular edema had resolved, and it was scheduled for the right eye one week later.