Effect of somatotropin and IGF1 secretion on glucose metabolism: Diabetic ketoacidosis as first manifestation of acromegaly

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Introduction

Somatotropin (GH) and insulin have opposite effects in glucose and lipids metabolism and synergic effects in the promotion of protein synthesis. In a healthy individual, in the postprandial period, insulin is the most important anabolic hormone as it promotes glucose and lipids storage. During fasting, the action of GH predominates, switching the preferential energetic substrate through stimulation of lipolysis and sparing the stored proteins. Through this mechanism, GH increases plasmatic free fatty acids and ketone bodies concentration, promoting hepatic and peripheral insulin resistance (Table 1).

Healthy individual	Insulin	GH	IGF-1	Acromegaly
Carbohydrates metabolism				
Glycemia	↓	↑	↓	N /↑
Glyconeogenesis	↓	↑	↓	↑↑
Glycolysis	↑	↓	↑	↓
Insulin resistance		↑	↓	↑↑
Lipids metabolism				
Triglycerides synthesis	↑	↓	↑	↓↓
Lipolysis	↓	↑	↓	↑↑
Proteins metabolism				
Protein synthesis	↑	↑	↑	↑
Proteolysis	↓	↓	↓	↓

Tabela 1 – Main metabolic effects of insulin, GH and IGF-1

Acromegaly

- Lipolysis and glyconeogenesis induced by GH may lead to decreased pancreatic insulin secretion, changes in the expression of the insulin gene and increased beta cell apoptosis.
- If insulin production is not able to counterbalance the increased insulin resistance, glucose intolerance or diabetes may appear. Rarely, when there is a relative/absolut insulin deficit and an excess of counterregulatory hormones, diabetic ketoacidosis may occur.
- The severity of glucose metabolism disturbance may be related to GH plasmatic concentrations (>25ng/ml).

Clinical cases (Table 2)

	Case 1 Male, 26 years	Case 2 Male, 27 years	Case 3 Male, 35 years
Clinical presentation	• **Diabetic ketoacidosis as first manifestation of DM** • No family history of DM • Clinically evident acromegaly → **Pituitary macroadenoma**		
DM treatment	Metformin 2g/day Insulin 0,26U/Kg/day	Metformin 3g/day Insulin 1,28U/Kg/day	No antidiabetic drugs in the first 2 months. Metformin 2g/day, Insulin 0,8U/Kg/day
Transsphenoidal surgery	Partial remotion of the adenoma		Total remotion of the adenoma (?) (January 2013)
Histologia	GH difuse	GH dense	Necrosis
Evolution DM treatment	Suspension after 8 m	Suspension after 7 M	Metformin 3g/day, sitagliptin 100mg/day; insulin suspension after 3 months.
Acromegaly treatment	Octreotide LAR 30mg	Octreotide LAR 20mg	**Initial clinical presentation: pituitary apoplexy and panhypopituitarism.** Treatment: prednisolone, levothyroxine, testosterone.
Future	Radiosurgery	Surgery	

Table 2 – Clinical cases

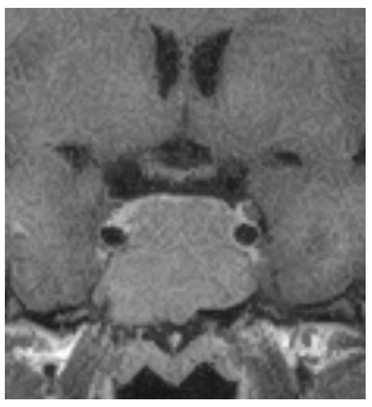

Figure 1 – Clinical case 2: before surgery

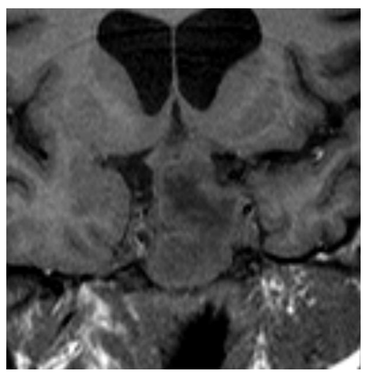

Figure 2 – Clinical case 3: before surgery

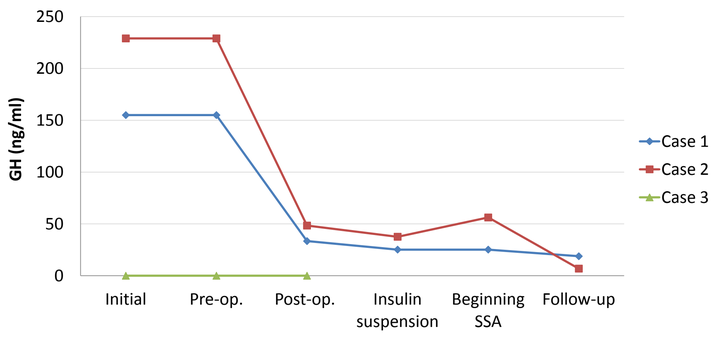

Figure 3 – Evolution of GH

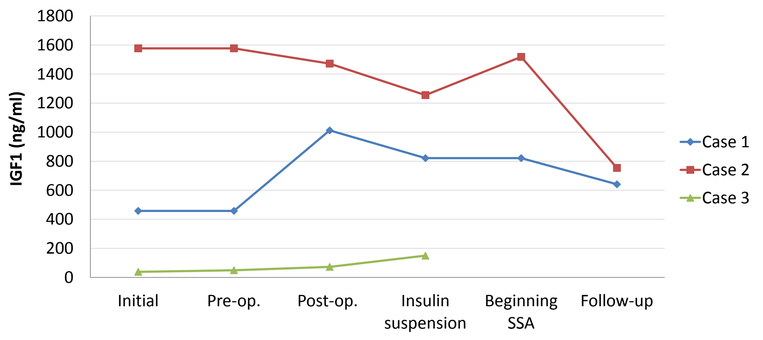

Figure 4 – Evolution of IGF1

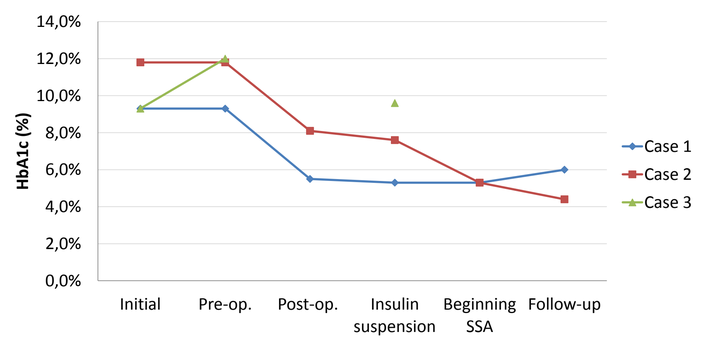

Figure 5 – Evolution of HbA1c

Conclusion:

Diabetic ketoacidosis is a very rare event in patients with acromegaly (1%). In our patients, its prevalence was 6,4% (N=47). In cases 1 and 2, initial GH secretion was very high and GH reduction led to a significant improvement in metabolic control. In case 3, glycemic control worsened probably due to the iatrogenic effect of prednisolone in a pancreas recently exposed to the glucolipotoxicity caused by GH. Somatotropin effects in carbohydrate metabolism and in the appearance of diabetic ketoacidosis in acromegaly are complex and not totally understood, but may be reversible with the reduction or normalization of GH levels.

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