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EVOLUTION OF GLUCOSE TOLERANCE STATUS AFTER TREATMENT OF ACROMEGALY : A PROSPECTIVE STUDY IN 57 PATIENTS.

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INTRODUCTION

➢ Active acromegaly is frequently associated with alterations of glucose metabolism. The prevalence of diabetes mellitus (DM) and impaired glucose tolerance (IGT) in acromegaly ranges in several studies from 19 to 56% and from 16 to 46%, respectively.

➢ The prevalence of reported abnormal glucose metabolism after treatment of acromegaly is more variable (0 to 46% for DM and 0 to 58% for IGT).

➢ The medical treatment of acromegaly may have an impact on glucose metabolism.

AIMS

➢ To study in 57 acromegalic patients the evolution of glucose metabolism from diagnosis until last visit according to disease activity and treatment.

➢ To identify possible risk factors associated with an abnormal glucose tolerance after treatment of acromegaly .

PATIENTS AND METHODS

• Hormonal and metabolic evaluation were performed in all patients at diagnosis and at last follow-up.

• Insulin sensitivity (HOMA-S) and ß-cell function (HOMA- ß) were evaluated by the homeostasis model assessment (HOMA).

• All patients underwent an oral glucose tolerance test (OGTT), with the exception of diabetic patients.

• Categories of glucose tolerance status were defined according to current criteria of the American Diabetes Association (ADA):

The NFG/NGT group had a normal fasting glucose (NFG; < 100 mg/dl) and a normal glucose tolerance (NGT; 2h-post glucose load < 140 mg/dl).

The IFG/IGT group had either an impaired fasting glucose (IFG; FG 100-125 mg/dl) or an impaired glucose tolerance (IGT; 2h-post glucose load 140-199 mg/dl).

The DM group had diabetes mellitus (DM; FG ≥ 126 mg/dl or 2h-post glucose load ≥ 200 mg/dl).

• Activity of acromegaly at the last visit was determined on the basis of the following criteria:

The cured group had a normal age-related IGF-I level and a nadir GH post-OGTT < 0.40 µg/L

The controlled group had a normal age-related IGF-I level under medical treatment

The active disease group had a high IGF-I concentration and a nadir GH post-OGTT ≥ 0.40 µg/L

RESULTS

Table 1 : Basal characteristics of the study population at diagnosis of acromegaly according to glucose tolerance

	At diagnosis				
	All patients (n=57)	NGT (n = 28)	IFG and/or IGT (n = 15)	DM (n = 14)	p
Age (years)	43.3 ± 12.7	38.2 ± 10.1	49.7 ± 12.5 $	46.9 ± 13.9 $	<0.05
Sex ratio H/F	31/26	17/11	5/10	9/5	NS
BMI (kg/m²)	27.6	26.7 ± 4.9	26.6 ± 4.6	30.5 ± 3.7 *	<0.05
Macro/microadenome	48/8	23/5	12/2	13/1	NS
HTA (%)	36.8	18	40	71 $	<0.05
Family history of diabetes (%)	45.5	32	47	75 $	<0.05
Fasting glucose (mg/dl)	97.5 [78-500]	92.5 [78-99]	102.0 [82-120] $	152.0 [100-500] *	<0.001
Fasting insulinemia (µU/ml)	17.6 ±10.6	14.9 ± 7.3	14.7 ± 10.0	29.0 ± 11.9 *	<0.001
HbA1c (%)	6.5 ±1.7	5.5 ± 0.4	5.9 ± 0.4	7.8 ± 2.0 *	<0.001
HOMA-β (%)	135.9 [26.6-252]	171.5 [62.4-252.0]	132.1 [40.6-200.8] $	115.5 [26.6-213.3] $	<0.05
HOMA-S (%)	40.8 [10.2-155.5]	43.3 [24.0-131.1]	43.6 [17.1-155.5]	22.1 [10.2-59.3] *	<0.05
IGF-I z-score	4.8 ± 1.5	4.3 ± 1.3	4.8 ± 1.2	5.9 ± 1.5 *	<0.001
GH basal (ng/ml)	8.2 [0.3-80.0]	7.2 [0.3-48.5]	8.2 [0.3-80.0]	9.5 [1.0-53.1]	NS

Values are shown as mean ± SD or median [min-max]. * p < 0.05 vs NGT and IFG/IGT $ p < 0.05 vs NGT

• NGT patients were younger and had a higher HOMA- β than IFG/IGT and DM patients.

• Acromegalic patients had a reduced insulin sensitivity which was more severe in DM patients

• Overweight, hypertension and positive family history of diabetes were more frequent in DM patients compared to NGT patients.

Table 2 : Characteristics at last visit and evolution according to disease activity

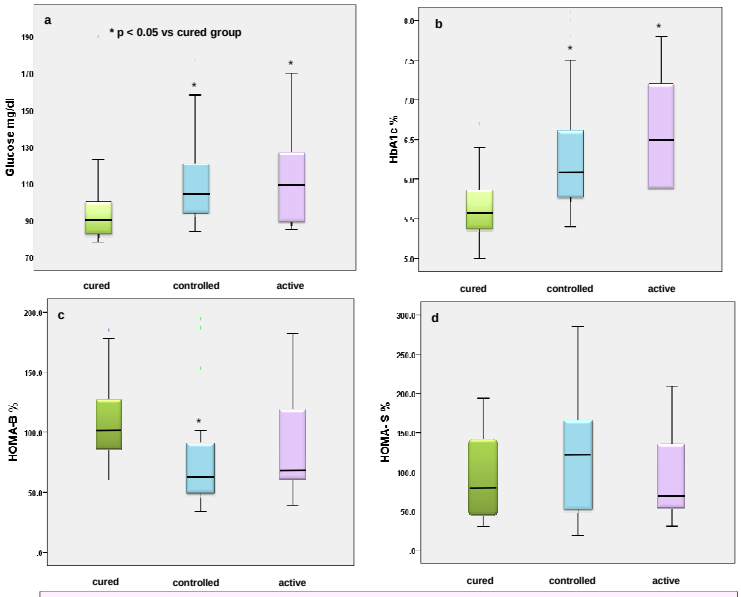
	At last visit				
	All patients (n=57)	Cured (n=20)	Controlled (n=28)	Active (n=9)	p
Age (years)	52.2 ±12.4	48.0 ± 12.8	53.5 ± 11.6	57.0 ± 12.7	NS
IGF-I z-score	1.2 ±1.2	0.8 ± 1.0	0.9 ± 0.9	2.9 ± 0.6 *,$	<0.001
N patients NGT/IGT/DM	24/15/18	14/2/4	7/11/10	3/2/4	<0.05
Δ Age (years)	+8.8 ±6.8	+7.8 ± 6.2	+10.1 ± 7.6	+6.9 ± 5.1	NS
Δ BMI (Kg/m²)	+1.2 ±2.7	+0.8 ± 2.6	+1.0 ± 2.8	+2.7 ± 2.1	NS
Δ IGF-I z-score	-3.6 ±1.8	-4.3 ± 1.5	-3.6 ± 1.9	-2.2 ± 1.5 *,$	<0.05
Δ fasting glucose (mg/dl)	-1.0 [-55.0 ; 79]	-7.0 [-55.0 ; 9.0]	+2.0 [-32.0 ; 79.0] *	+4.0 [-17.0 ; 65.0]	<0.05
Δ fasting insulinemia (µU/ml)	-9.0 [-36 ; 10]	-7.0 [-21.0 ; 10.0]	-12.0 [-36.0 ; 10.0]	-2.5 [-21.6 ; 1.0]	NS
Δ HbA1c (%)	-0.2 ±1.5	-0.4 ± 1.3	+0.2 ± 0.8	-1.0 ± 3.2	NS
Δ HOMA-β (%)	-48.5 [-191 ; 107]	-30.4 [-158.5 ; 150.0]	-87.9 [-190.9 ; 106.5] *	-36.9 [-62.2 ; -18.4]	<0.05
Δ HOMA-S (%)	+47 [-108 ; 234]	+43.5 [-108.1 ; 142.3]	+59.4 [-95.8 ; 234.1]	+11.6 [-21.9 ; 133.0]	NS

Values are shown as mean ± SD or median [min-max]. * p < 0.05 vs cured group $ p < 0.05 vs controlled group

• Fasting glucose decreased in cured patients while it increased in the two other groups.

• Insulin sensitivity (HOMA-S) improved in all patients (but less in active disease) while beta-cell function (HOMA-β) was mostly decreased in controlled patients under medical treatment.

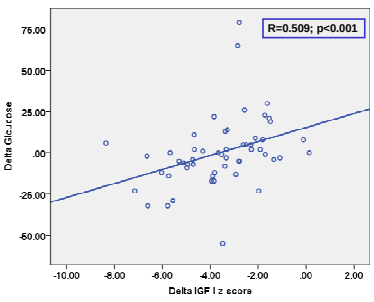
Figure 1 : Biological parameters at last visit according to disease activity



• Fasting glucose and HbA1c were lower in cured patients than in the two other groups.

• HOMA-S was not significantly different according to disease activity while HOMA-β was lower in controlled patients compared to cured patients.

Figure 2: Correlation between Δ IGF-I z-score and Δ glucose



• The change in fasting glucose was positively correlated with the change in IGF-I z-score

Table 3: Evolution of parameters according to the medical treatment at the last visit

	SSA (n=30)	SSA+PEG (n=6)
Δ Age (years)	+8.8 ± 7.1	+11.3 ± 8.2
Δ BMI (kg/m²)	+1.4 ± 2.8	+1.6 ± 2.2
Δ z-score IGF-I	-2.8 [-6.6 ; 0.1]	-3.4 [-8.3 ; -2.4]
Δ Fasting glucose (mg/dl)	+2.0 [-32.0 ; 79.0]	+5 [-14.0 ; 13.0]
Δ Fasting insulinemia (µU/ml)	-9.0 [-36.0 ; 10.0]	-12.0 [-28.2 ; -0.4]
Δ HbA1c (%) *	+0.3 ± 0.8	-1.7 ± 3.5
Δ HOMA-β (%)	-60.7 [-190.9 ; 106.5]	-85.4 [-127.7 ; -18.4]
Δ HOMA-S (%)	+44.5 [-95.8 ; 234.1]	+98.5 [-2.4 ; 133.5]

Values are shown as mean ± SD or median [min-max]. * p < 0.05

• HbA1c decreased in patients under SSA+PEG (-1.7%) but increased in patients with SSA alone (+0.3%)

Table 4 : Predictive factors for abnormal glucose tolerance after treatment of acromegaly according to univariate and multivariate analysis

	Univariate analysis			Multivariate analysis		
Variables	Odds ratio	95% IC	p	Odds ratio	95% IC	p
Age *	1.05	0.998-1.097	NS	1.03	0.963-1.092	NS
z-score IGF-I *	1.13	0.718-1.768	NS	0.75	0.412-1.369	NS
BMI *	0.99	0.885-1.115	NS			NS
Group at diagnosis §	3.50	1.158-10.578	<0.05	5.80	1.314-25.518	<0.05
Treatment with SSA *	7.50	2.235-25.165	<0.001	12.17	2.587-57.281	<0.05

* at last visit. §NGT or IFG/IGT and DM

CONCLUSIONS

• This study shows that more than 50% of acromegalic patients have still IGT or diabetes after treatment and at distance from diagnosis.

• Improvement of glucose metabolism is mainly observed in cured patients and in patients treated with pegvisomant.

• Risk factors for persistence or occurence of abnormal glucose tolerance after treatment of acromegaly are the glucose tolerance status at diagnosis of acromegaly and ongoing treatment with SSA.