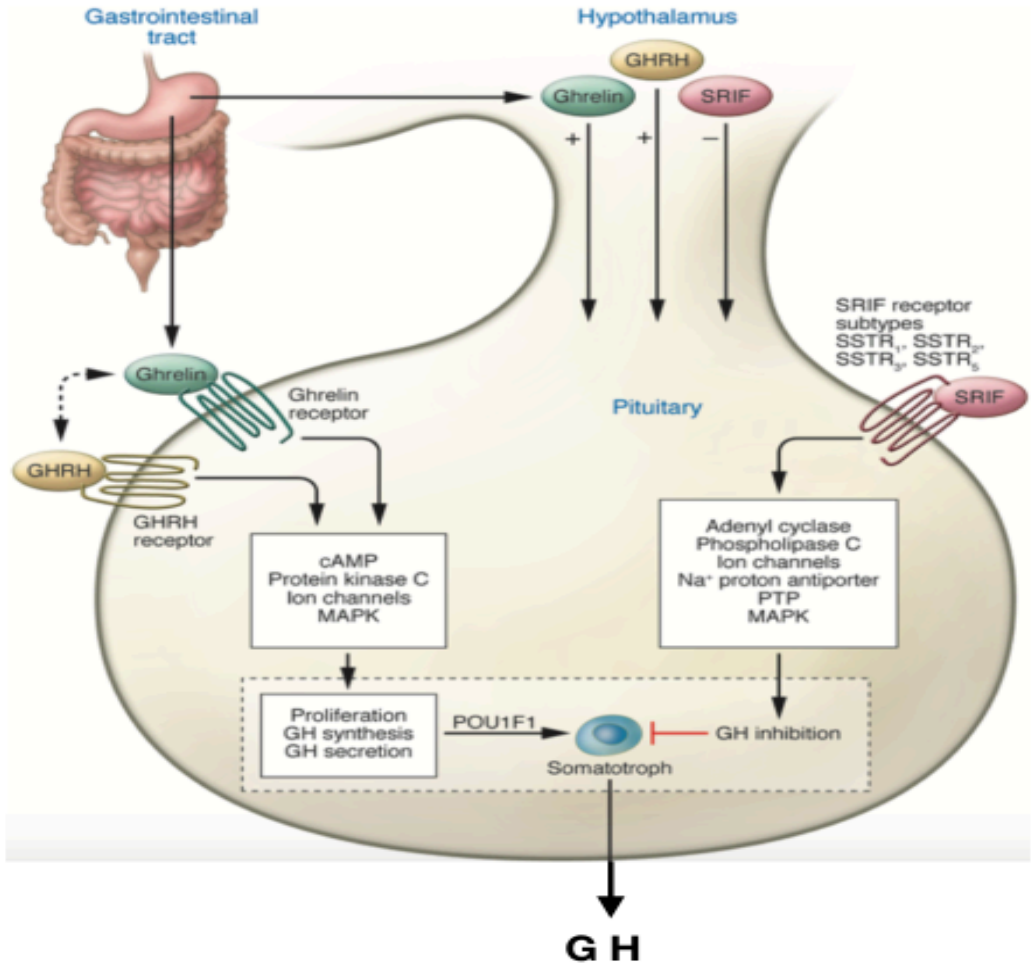
Malattie sistemiche: l'acromegalia

Inquadramento clinico

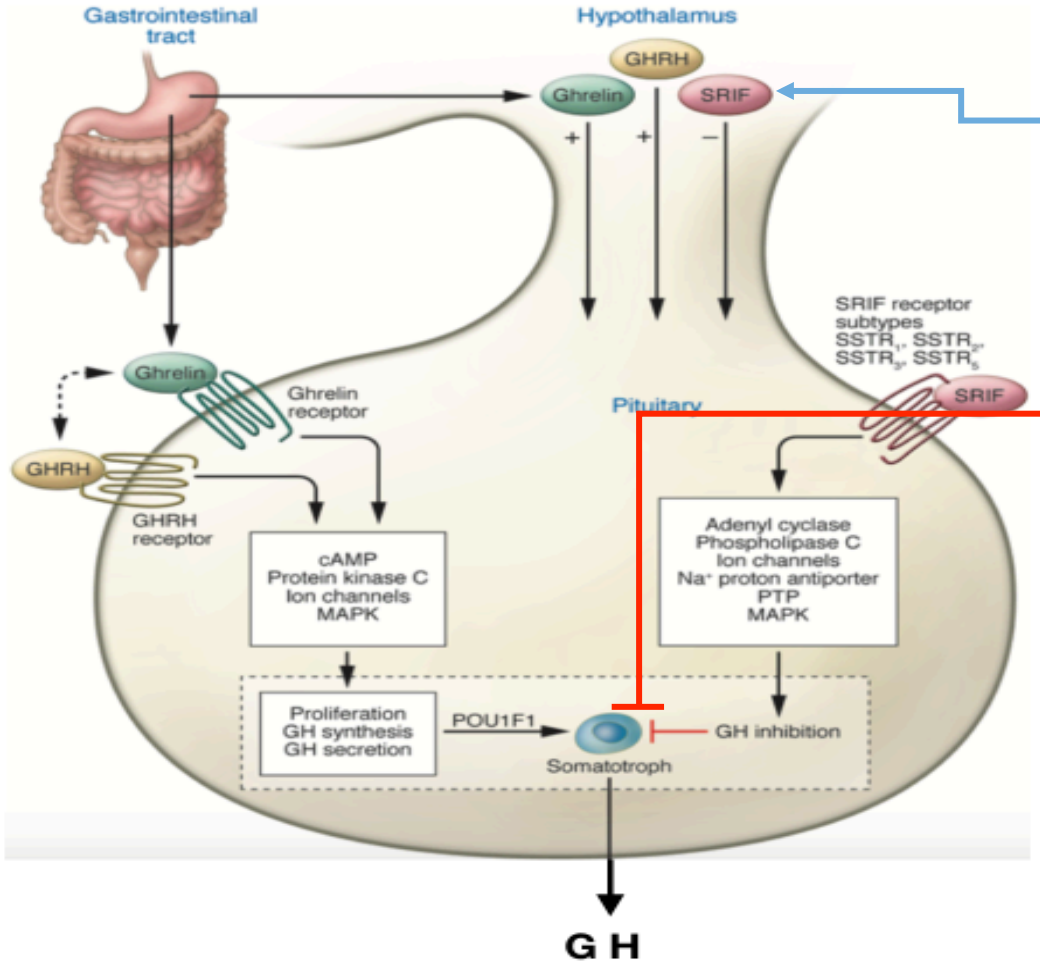
Dott. Giuseppe Citro

UOSD Diabetologia e Endocrinologia ASP Potenza

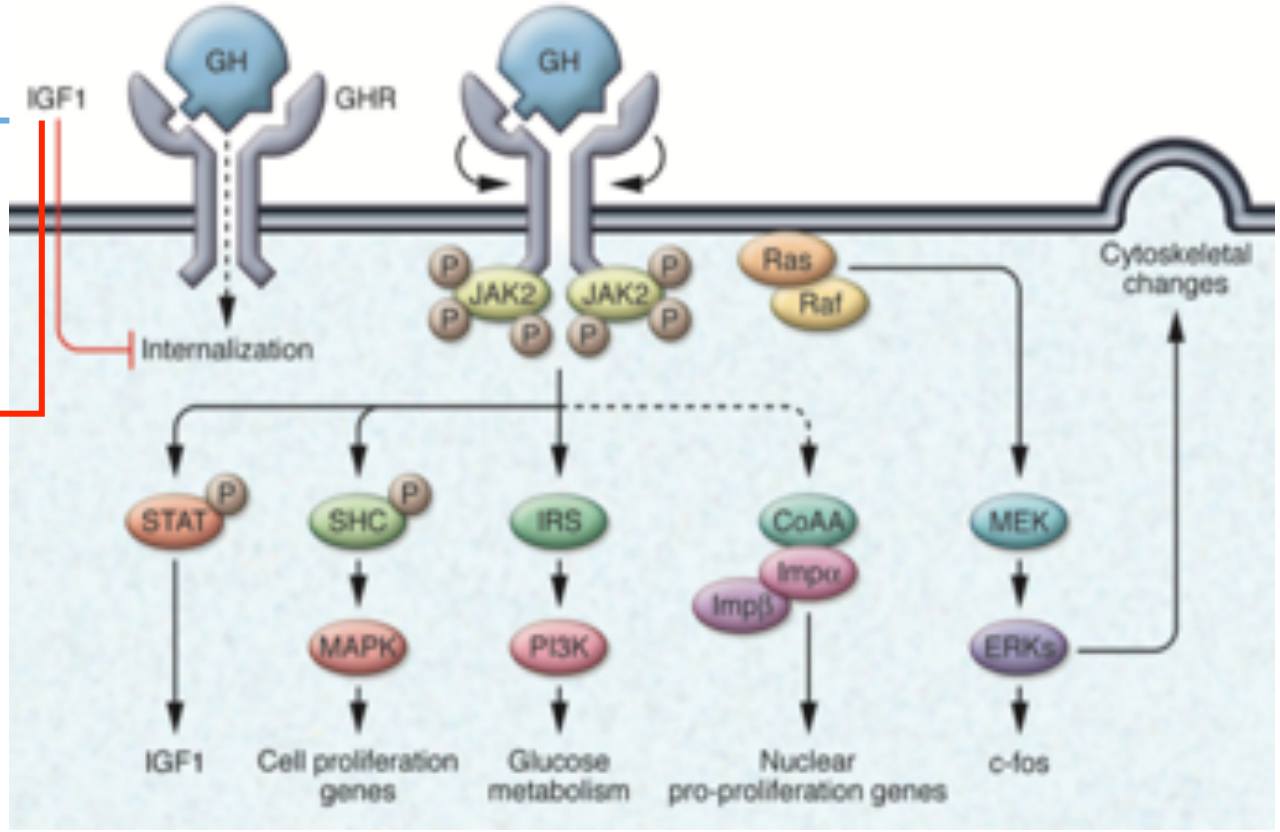
REGOLAZIONE SECREZIONE GH



REGOLAZIONE SECREZIONE GH



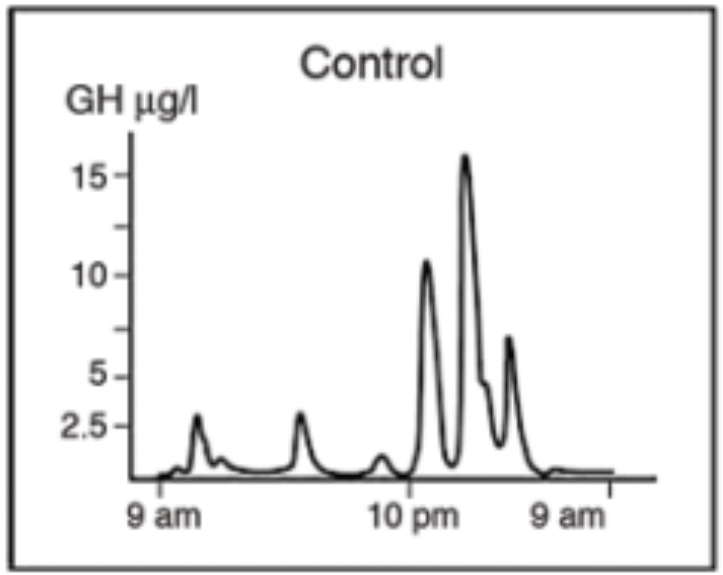
AZIONI DEL GH

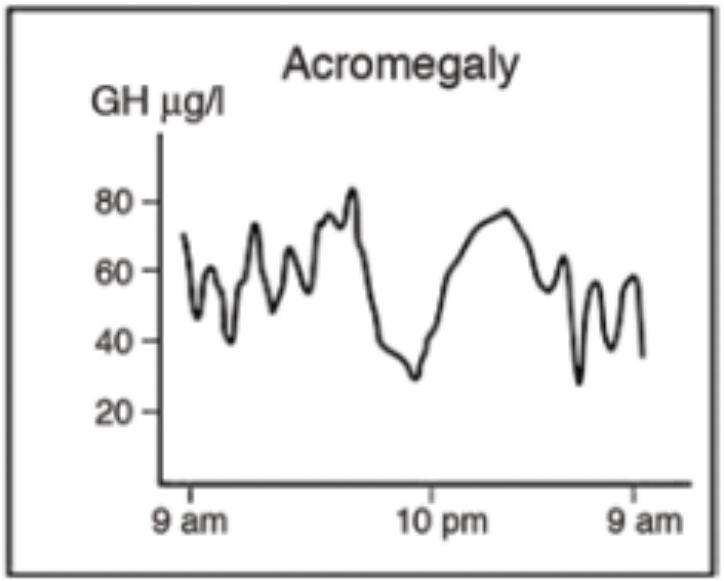


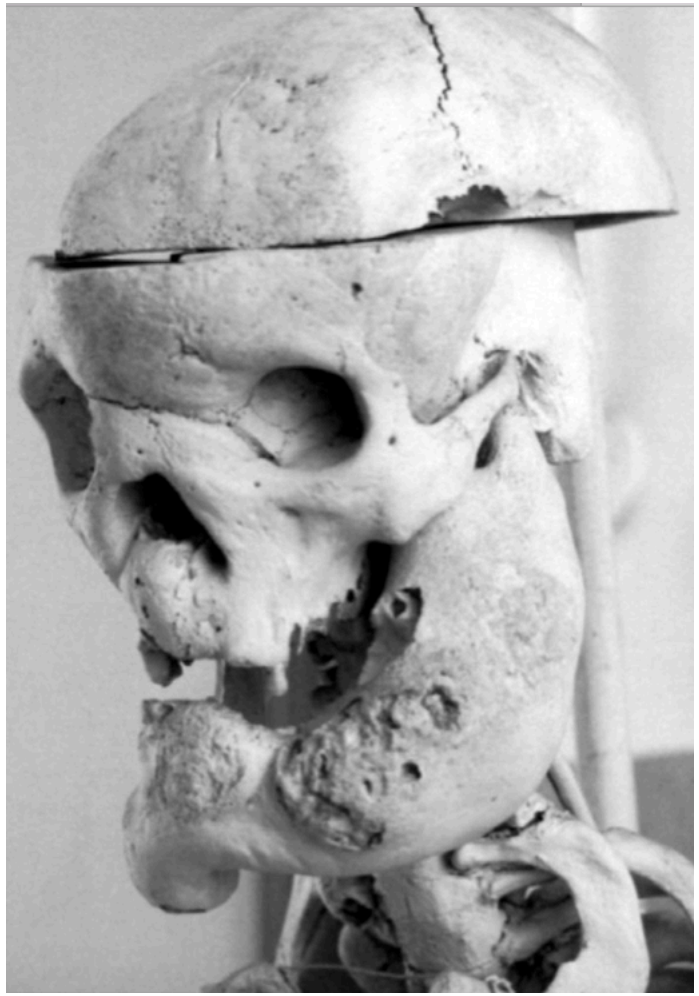
CAUSE DI IPERSECREZIONE GH

- **ADENOMA IPOFISARIO GH-SECERNENTE**
- **TUMORE IPOTALAMICO GHRH-SECERNENTE**
- **SECREZIONE ECTOPICA DI GH**

PATTERN DI SECREZIONE DEL GH







CARATTERISTICHE CLINICHE

Crescita ossea, in particolare crescita acrale
Bozze frontali, prognatismo, malocclusione mandibolare
Aumento di volume degli organi e ispessimento tissutale e cutaneo
Iperidrosi, parestesie, cefalea, difetti visivi
Segni di deficit di altre tropine ipofisarie

Features at diagnosis of 324 patients with acromegaly did not change from 1981 to 2006; Acromegaly remains underrecognized and under-diagnosed

Clin Endocrinol 2010 February ; 72(2): 203–208.

The main presenting complaints that brought the patients to medical attention

	(%)*
Change in face noted by patient	6.3
Change in face noted by other person	8.9
Enlarging hands/feet noted by patient	10.5
Enlarging hands/feet noted by other person	6.3
Concurrent changes in face & hands/feet noted by patient	6.3
Concurrent changes in face & hands/feet noted by other person	16.8
Visual or neurological complaint	18.1
Symptoms of gonadal dysfunction	8.6
Arthritis	5.1
Others	13

OTHERS: headaches , vision or visual field deficits, galactorrhea, gynecomastia, and infertility, snoring, sinus problems, hyperhidrosis, weight gain, fatigue, abnormal thyroid function tests and enlargement of the salivary glands

After the incidental discovery of an adenoma on brain imaging that was done for an unrelated complaint, such as after trauma,

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OTHERS: headaches , vision or visual field deficits, galactorrhea, gynecomastia, and infertility, snoring, sinus problems, hyperhidrosis, weight gain, fatigue, abnormal thyroid function tests and enlargement of the salivary glands
After the incidental discovery of an adenoma on brain imaging that was done for an unrelated complaint, such as after trauma,

The delay in diagnosis was long, an average of 5.3 ± 4 yrs from symptom onset, with no change over time. In most prior studies mean times from symptoms to diagnosis are 4 to 8 years

In conclusion, the clinical characteristics at diagnosis of patients with acromegaly did not change from 1981–2006 suggesting that clinical recognition of acromegaly has not significantly improved over the last 25 years.

As the likelihood of successful therapy relates to tumor size and disease severity, earlier recognition and initiation of treatment is needed.

E P I D E M I O L O G I A

Prevalence, incidence and age at diagnosis of acromegaly in population studies

	Population covered	Prevalence (per 100,000)			Annual incidence (per 100,000)			Age at diagnosis (years) Median (range)		
		Total	Males	Females	Total	Males	Females	Total	Males	Females
Fernandez et al.	81,449	8.6	4.9	3.7	NA	NA	NA	47 (30–63)	48.5 (30–52)	45 (39–63)
Daly et al.	71,972	12.5	8.3	4.2	NA	NA	NA	47 (17–65)	41 (19–65)	56 (17–63)
Tjornstrand et al	1,590,640	3.3	1.7	1.6	0.4	0.4	0..4	NA	NA	NA
Agustsson et al.	321,857	13.7	9.0	4.7	NA	0.8	0.4	45 (4–83)	45.0 (15–83)	44 (4–75)
Hoskuldsdottir	316,075	13.3	NA	NA	0.8	NA	NA	44.5[a] (24.5–49.7)	NA	NA
Raappana et al.	722,000 – 733,000	NA	NA	NA	0.3	0.4	0.3	40.5 (12–69)	41	38
Dal et al.	5,534,738	8.5	NA	NA	0.4	NA	NA	48.7[a] (47.2–50.1)	NA	NA
Bex et al.	10,850,000	4	NA	NA	0.2	NA	NA	NA	42 (8–81)	46 (17–80)
Mestron et al.	Population of Spain in 2001	3.4	NA	NA	0.2	NA	NA	45[a]	NA	NA
Gruppetta et al	417,608	12.4	10.6	14.3	0.3	0.2	0.4	44 (19–69)	36.5 (19–69)	49.5 (28–68)
Burton et al	50,170,946	7.8	7.7	7.7	1.1	1.0	1.2	41[a]	NA	NA
Kwon et al.	48,456.369	2.8	1.3	1.5	0.4	NA	NA	44.1[a]	42.2[a]	45.5[a]

Pituitary (2017) 20:4–9

E P I D E M I O L O G I A

	Adenoma size			
	Macroadenoma (% of cases)		Microadenoma (% of cases)	
	Males	Females	Males	Females
Fernandez et al.	85.7		14.3	
Daly et al.	88.9[a]		0	
	100	66.7[a]	0	0[a]
Tjornstrand et al	78	77	22	23
Agustsson et al.	62.5	71.4	28.1	23.8
Raappana et al.	78		22	
Dal et al.	69		31	
Bex et al.	79[a]		16[a]	
Mestron et al.	69[a]		25.8[a]	
Gruppetta et al	73.1		26.9	
	68.2	76.7	31.8	23.3
Kwon et al.	82.9		17.1	

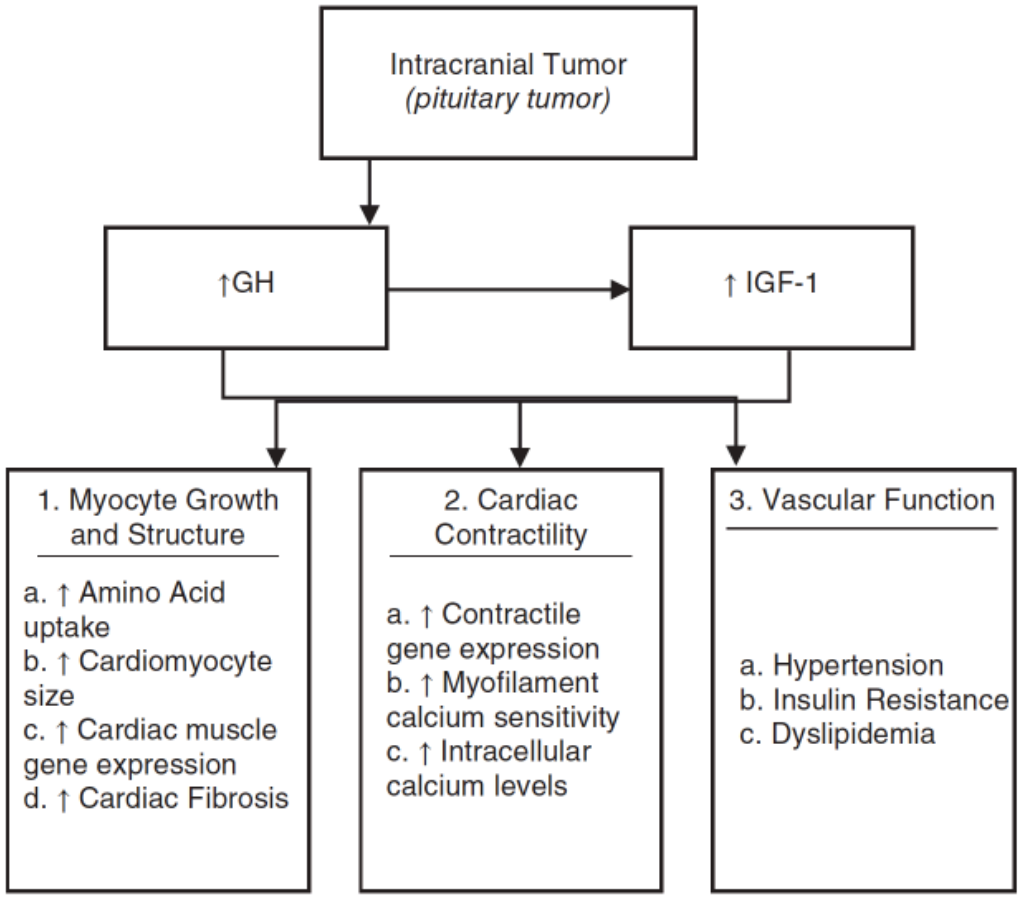
[a] *Percentages do not add up to 100 due to cases with unknown tumor size*

micro-adenomi (Ø < 1 cm)
macro-adenomi (Ø > 1 cm)

Frequency of macro and micro adenomas in patients with acromegaly as reported in population studies

Pituitary (2017) 20:4–9

CARATTERISTICHE CLINICHE - COMORBILITA': miocardiopatia



Clinical stages of acromegalic cardiomyopathy

Stage	Years of Active Disease	Characteristics
Early	<5 years	Enhanced contractility, decreased peripheral vascular resistance, increased cardiac output
Middle	>5 years	Biventricular hypertrophy, diastolic dysfunction, impaired cardiac performance
Late	>15 years	Systolic dysfunction, diastolic dysfunction (congestive heart failure), valvular disease, coronary artery disease, arrhythmias

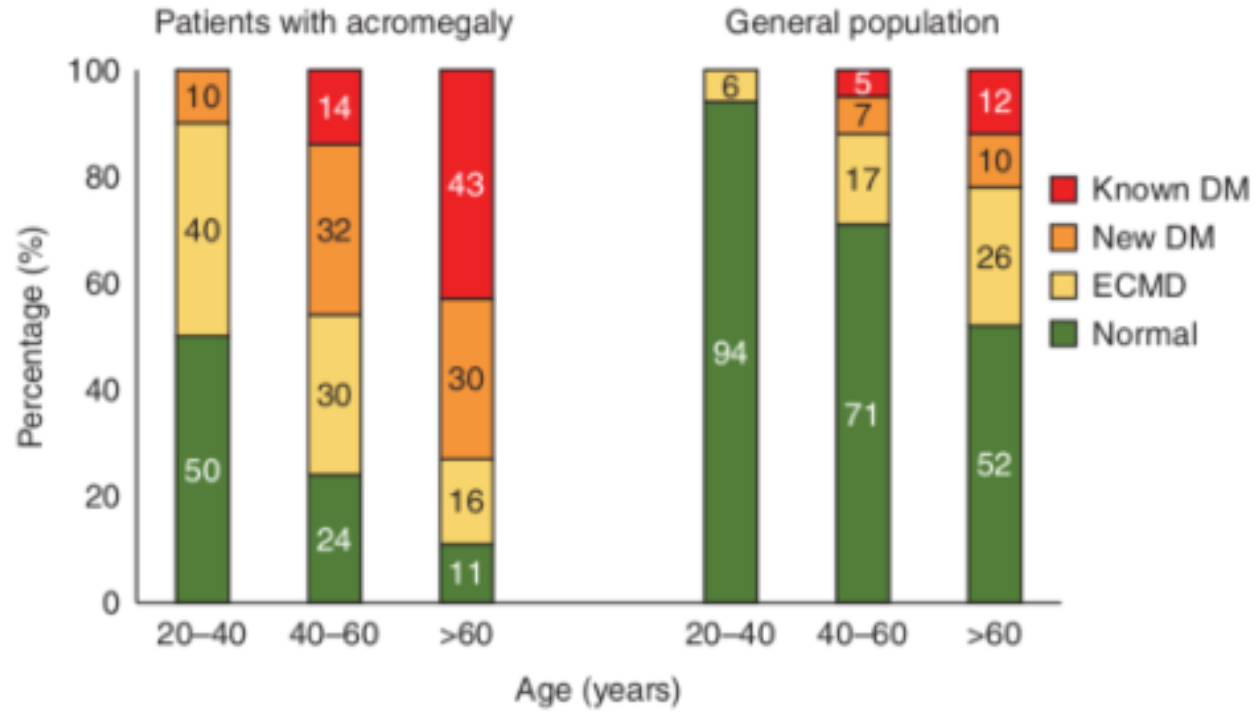
Clinical Cardiology. 2018;41:419–425

CARATTERISTICHE CLINICHE - COMORBILITA': diabete, IGT, IFG

Comparative characteristics of patients with acromegaly and matched participants from the general population

	Patients with acromegaly	General population
Number of patients/ participants	97	435
Male/female (%)	16/84	13/87
Age (years)	56 (47.5–64.5)	56 (47–64)
BMI (kg/m^2)	31.0 (27.7–34.2)	30.6 (27.2–34.1)
SBP (mmHg)	**138±20**	**140±24**
DBP (mmHg)	**86±13**	**86±12**
Known diabetes, *n* (%)	24 (24.7)	30 (6.9)
Newly diagnosed diabetes, *n* (%)	27 (27.8)	32 (7.4)
Total diabetes, *n* (%)	51 (52.5)	62 (14.3)
Isolated IFG, *n* (%)	10 (10.3)	45 (10.3)
Isolated IGT, *n* (%)	4 (4.1)	14 (3.2)
Combination of IFG+IGT, *n* (%)	11 (11.3)	23 (5.3)
ECMDs, *n* (%)	25 (25.8)	82 (18.8)
Normoglycaemia, *n* (%)	21 (21.6)	291 (66.9)

Prevalence of carbohydrate metabolism disturbance according to age in patients with acromegaly and the general adult population



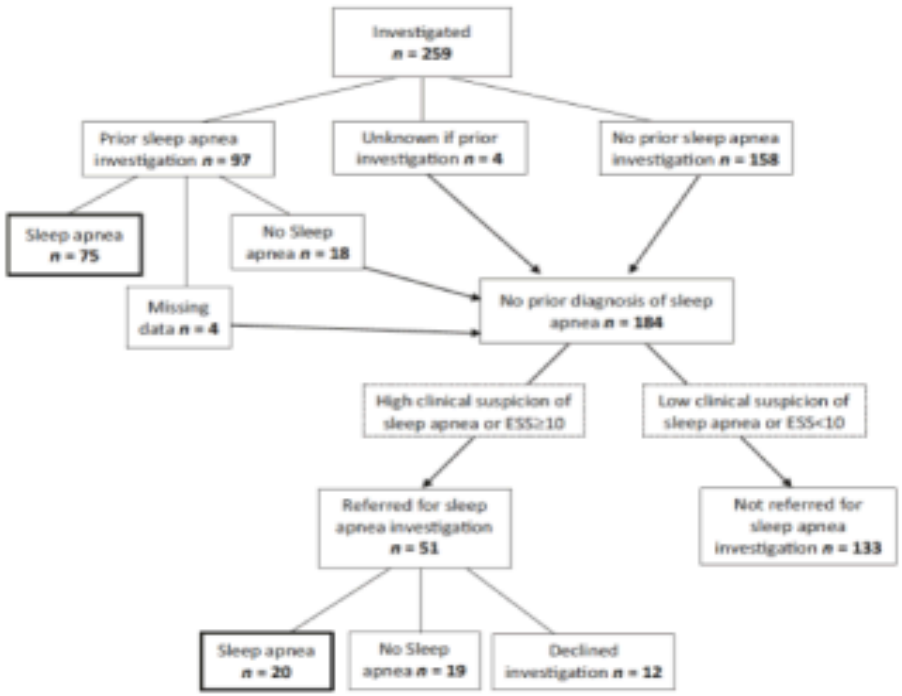
Endocrine Connections 2014; 3: 93-98

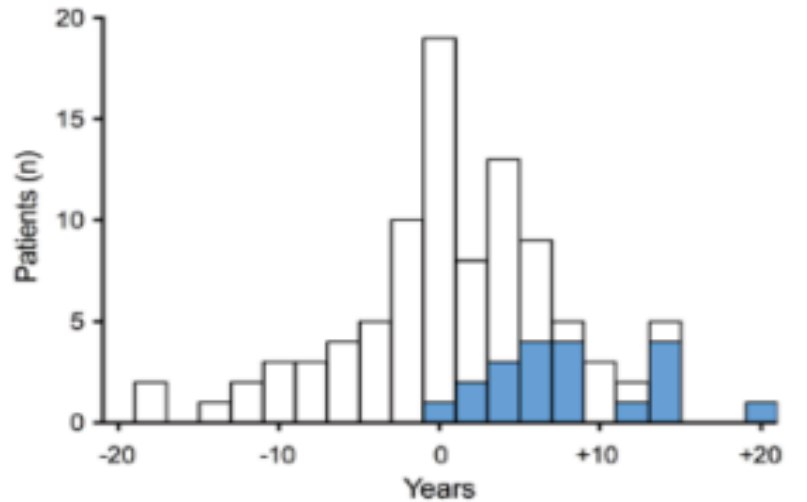
CARATTERISTICHE CLINICHE - COMORBILITA': apnee notturne

Temporal relationship of sleep apnea and acromegaly: a nationwide study

Cross-sectional multi center study of 259 Swedish patients with acromegaly.

Endocrine - July 2018





Diagnosis of sleep apnea in relation to the diagnosis of acromegaly (0 years). White bars ▫ represent the 75 patients with sleep apnea diagnosed prior to study Blue bars represent the 20 patients with sleep apnea identified in the study

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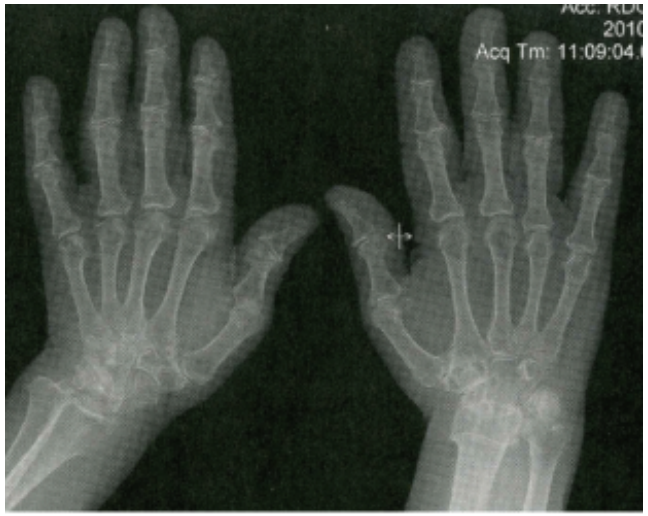
Characteristics of acromegaly- patients with, and without previously or newly diagnosed sleep apnea

	Sleep apnea ($n = 95$)	No sleep apnea ($n = 164$)	p value
Age in years[a]	59 (53–67)	58 (45–68)	0.14
Years since acromegaly diagnosis[a]	6.5 (2.9–12.5)	8.4 (4.0–14.7)	0.072
Men[b] (%)	55	49	0.36
Current smokers[b], valid %, $n = 255$	15	17	0.65
Current or previous smokers[2], valid %, $n = 255$	51	46	0.45
Snoring[b], valid %, $n = 253$	62	43	0.009
Partner-observed apneas during sleep[b], valid %, $n = 257$	44	15	<0.001
BMI[a] (kg/m^2)	30 (27–34)	26 (24–30)	<0.001
Waist circumference[a] (cm)	104 (92–113)	95 (86–104)	<0.001
Index finger circumference[a] (mm)	75 (69–81)	71 (68–79)	0.006
S-IGF-1 in the highest quartile[b]	33	20	0.021
Hypertension, current treatment[b] (%)	53	46	0.28
Diabetes, current treatment[b] (%)	8.4	8.5	0.97
Stroke or TIA[b] (%)	3.2	6.7	0.22

[a]Data are presented as median (25th–75th percentile) and compared by Mann–Whitney test

[b]Data are presented as percentage and compared by chi square test

CARATTERISTICHE CLINICHE - COMORBILITA': artropatia



Segni radiologici dell'artropatia acromegalica

Incremento dello spazio articolare
Riduzione dello spazio articolare (forme avanzate)
Entesopatia
Deformità articolari
Formazione di osteofiti
Calcificazioni delle superfici articolari
Eburneazione
Formazione di cisti subcondrali
Aumento di volume dei corpi vertebrali

CARATTERISTICHE CLINICHE - COMORBILITA': osteoporosi e fratture

Prevalence of osteoporosis and vertebral fractures in acromegalic patients

Clinical Cases in Mineral and Bone Metabolism 2011; 8(3): 37-43

Frequency and type of fractures in acromegalic patients.

	Tot. (18)*	F (10)*	M (8)
Pt with fractures	7 (39%)	3 (30%)	4 (50%)
Kind of fracture:			
▸ single	2 (29%)	2 (67%)	--
▸ multiple	5 (71%)	1 (33%)	4 (100%)
▸ mild	2 (29%)	1 (33%)	1 (25%)
▸ moderate	3 (42%)	2 (67%)	1 (25%)
▸ severe	2 (29%)	--	2 (50%)

**2 women did not perform x-ray examinations of the spine.*

CARATTERISTICHE CLINICHE - COMORBILITA': osteoporosi e fratture

Increased Prevalence of Radiological Spinal Deformities in Active Acromegaly: A Cross-Sectional Study in Postmenopausal Women

DEMOGRAPHICAL AND CLINICAL DATA OF ACROMEGALIC POSTMENOPAUSAL WOMEN WITH CONTROLLED (21 CASES) OR ACTIVE DISEASE (15 CASES)

	Postmenopausal acromegaly		
	Controlled disease	*Active disease*	*p*
Cases	21	15	
Age (years)	56 (44–79)	64 (49–74)	0.09
Duration of postmenopausal period (years)	10 (1–30)	12 (1–26)	0.86
Duration of disease (years)	7 (2–25)	6 (2–25)	0.63
Serum IGF-I (ng/ml)	185 (43–242)	303 (212–950)	<0.001
Urinary Dpd (μmol/M Cr)	8.1 (5.7–21.5)	9.8 (7.5–17.9)	0.09
Serum BSALP (U/liter)	47.0 (11.0–77.0)	57.0 (33.0–87.0)	0.07
Serum 25OH vitamin D (ng/ml)	19.0 (12.0–38.0)	18.0 (10.0–37.0)	0.36
Serum PTH (pg/ml)	39.0 (25.0–66.0)	42.0 (23.0–73.0)	0.95
T score (SD)	−1.2 (−4.1 to +1.3)	−1.4 (−2.9 to +1.2)	0.84
Spinal deformities rate (%)	33.0%	80.0%	0.006
Number of spinal deformities (%)			
Single	0	50%	0.04
Multiple	100%	50%	
Degree of spinal deformities (%)			
Mild	71.4%	83.3%	0.4
Moderate	14.3%	16.7%	
Severe	14.3%	0	

The data were compared using χ^2 test and Mann-Whitney test.

Conclusions: This cross-sectional study shows that high numbers of postmenopausal women with acromegaly develop vertebral fractures in relation to the activity of disease. Furthermore, our study shows that, in patientswith active acromegaly, vertebral fractures occur even in the presence of normal BMD, whereas in patients with controlled acromegaly, vertebral fractures are always accompanied by a pathological BMD. ***J Bone Miner Res 2005;20:1837–1844***

CARATTERISTICHE CLINICHE - COMORBILITA': osteoporosi e fratture

Vertebral Fractures in Patients With Acromegaly: A 3-Year Prospective Study

G. Mazziotti, A. Bianchi, T. Porcelli, M. Mormando, F. Maffezzoni, A. Cristiano, A. Giampietro, L. De Marinis, and A. Giustina

J Clin Endocrinol Metab 98: 3402–3410, 2013

Table 1. Skeletal Features of 88 Patients With Acromegaly at Study Entry and After a 3-Year Follow-Up in Comparison With 106 Control Subjects Followed Up for the Same Period of Time

	Acromegaly Patients (n = 88)			Control Subjects (n = 106)		
Variables	**Baseline**	**3 Years**	***P* Value**	**Baseline**	**3 Years**	***P* Value**
BMD Z-score at lumbar spine	−0.6 (range −3.0 to +3.7)	−0.5 (range −2.7 to +3.5)	.06	−0.5 (range −1.8 to +3.1)[a]	−0.2 (range −1.9 to +3.5)[a]	.36
BMD Z-score at femoral neck	+0.1 (range −2.5 to +3.6)	−0.2 (range −2.3 to +2.4)	.005	−0.3 (range −1.6 to +2.0)[a]	−0.5 (range −1.7 to +2.8)[a]	.66
Prevalent VF (cases)	34 (38.6%)[b]	53 (60.2%)[b]	<.001	0	4 (3.8%)	.12
Incident VF (cases)		37 (42.0%)[b]			4 (3.8%)	

Abbreviation: VF, vertebral fractures. Data are presented as median and range and comparisons were performed by nonparametric tests.

[a] BMD at the lumbar spine and femoral neck was measured in 62 of 106 control subjects.

[b] $P < .001$, acromegaly patients vs control subjects at the same time point.

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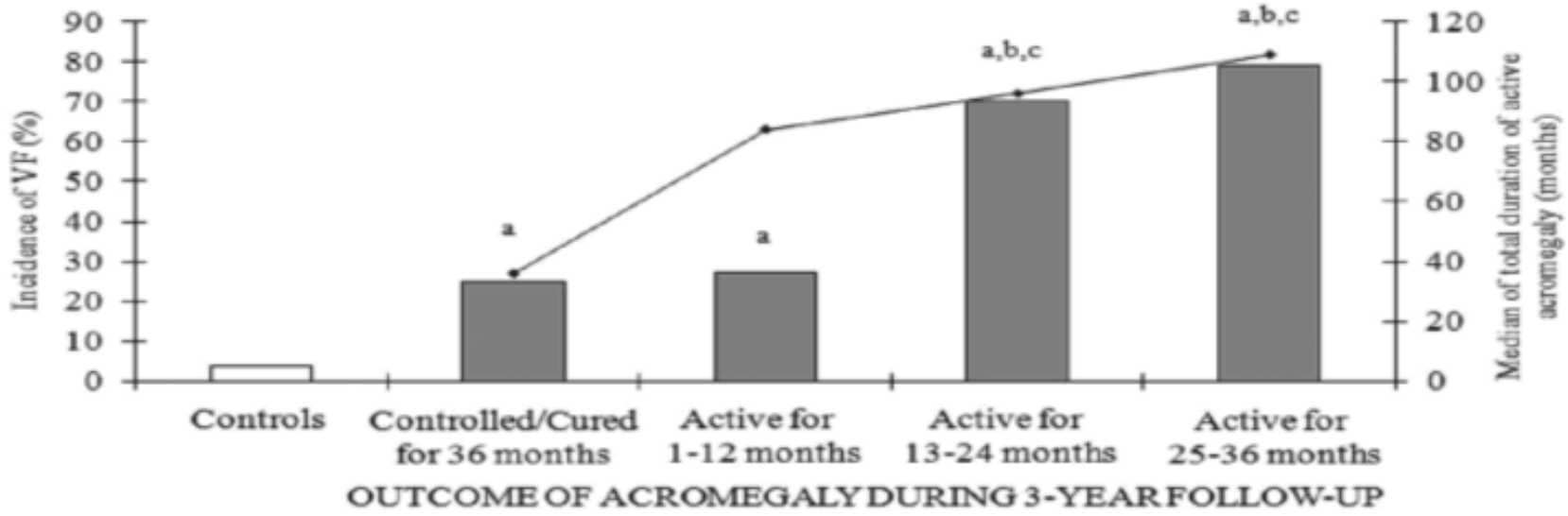


Figure 1. Incidence of vertebral fractures (VF) in patients with acromegaly, stratified according to the outcome of disease during a 3-year follow-up. The solid line shows the median of total duration of active acromegaly in the different groups of acromegaly patients, calculated on the basis of clinical history and the duration of uncontrolled disease during medical treatments (before and during the study period). a, $P < .05$ vs control subjects; b, $P < .05$ vs controlled/cured disease; c, $P < .05$ vs active disease for 1–12 months.

CARATTERISTICHE CLINICHE - COMORBILITA': osteoporosi e fratture

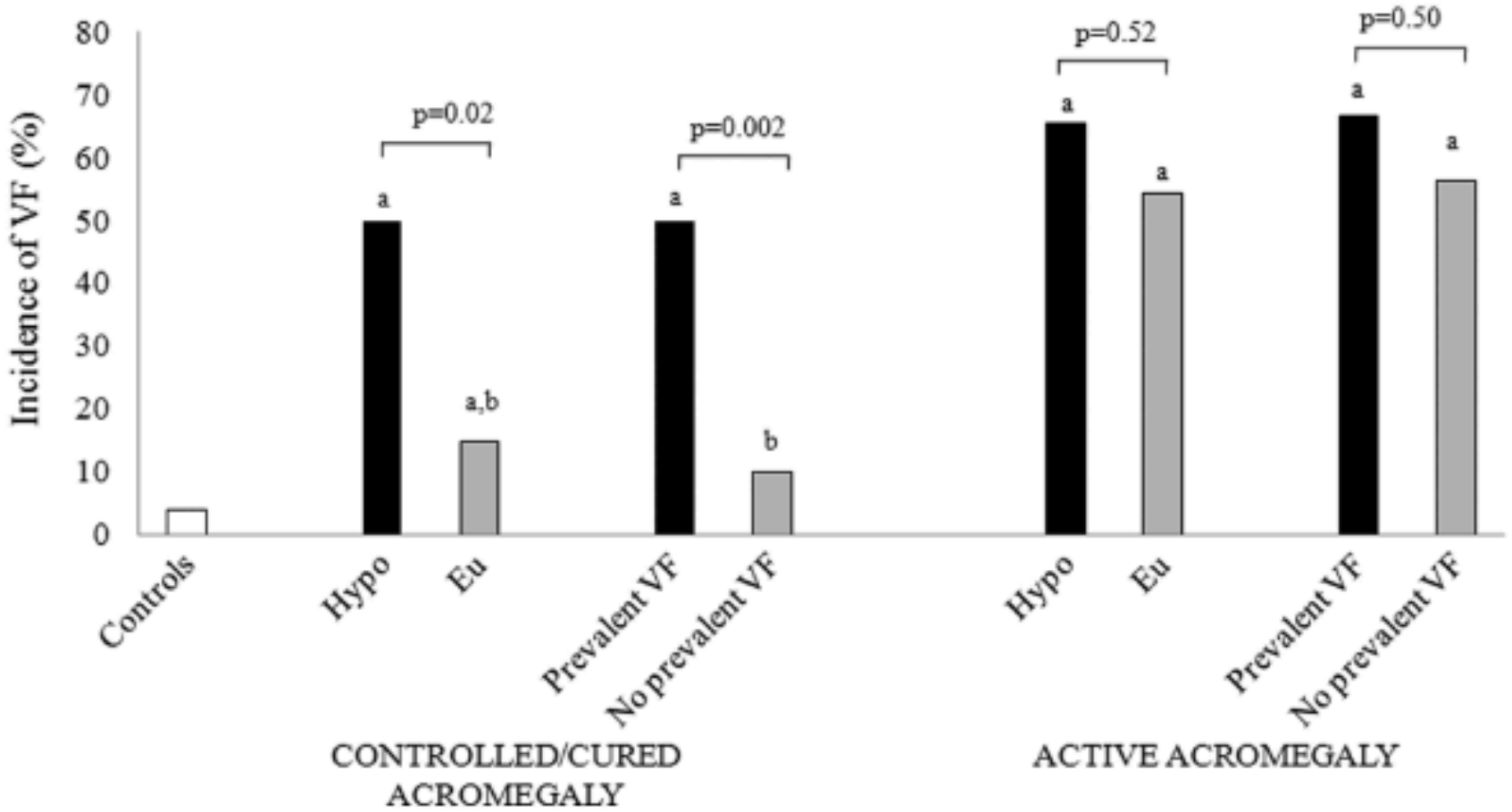


Figure 2. Incidence of vertebral fractures (VF) in patients with acromegaly stratified according to activity of disease, gonadal status and prevalent VF, in comparison with control subjects without acromegaly who were with normal gonadal function and without prevalent VF. Eu, eugonadism; Hypo, hypogonadism. a, $P < .05$ vs control subjects; b, $P < .05$ vs active acromegaly.

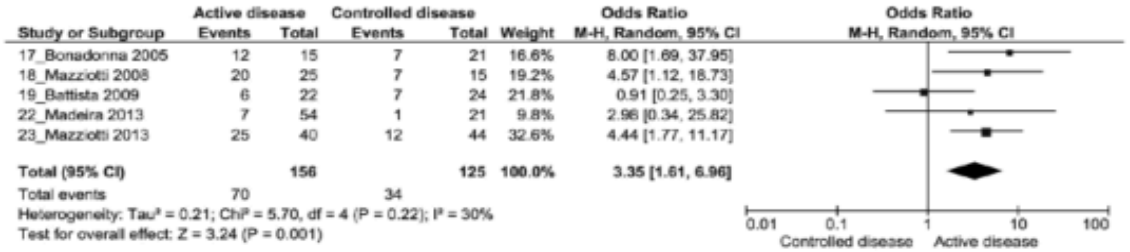
CARATTERISTICHE CLINICHE - COMORBILITA': osteoporosi e fratture

Bone Turnover, Bone Mineral Density, and Fracture Risk in Acromegaly: A Meta-Analysis

Gherardo Mazziotti, Elena Biagioli, Filippo Maffezzoni, Maurizio Spinello, Vincenza Serra, Roberto Maroldi, Irene Floriani, and Andrea Giustina

J Clin Endocrinol Metab100: 384–394, 2015

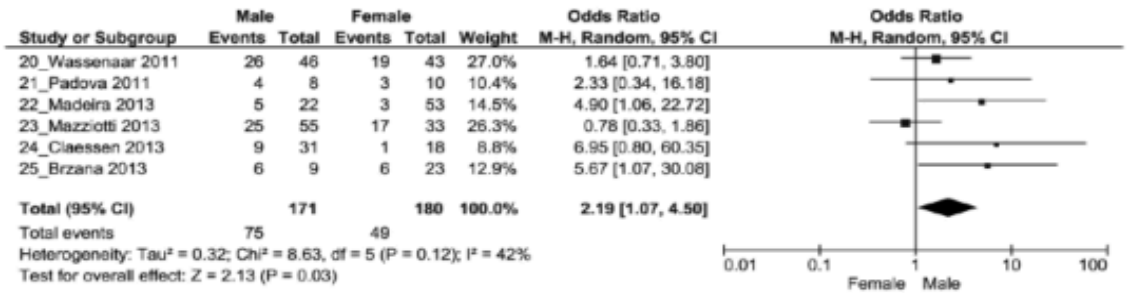
Forty-one studies fulfilled eligibility criteria and were therefore selected for data extraction and analysis. A total of 1935 patients were included



Study or Subgroup	Active disease Events	Total	Controlled disease Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
17_Bonadonna 2005	12	15	7	21	16.6%	8.00 [1.69, 37.95]
18_Mazziotti 2008	20	25	7	15	19.2%	4.57 [1.12, 18.73]
19_Battista 2009	6	22	7	24	21.8%	0.91 [0.25, 3.30]
22_Madeira 2013	7	54	1	21	9.8%	2.96 [0.34, 25.82]
23_Mazziotti 2013	25	40	12	44	32.6%	4.44 [1.77, 11.17]
Total (95% CI)		**156**		**125**	**100.0%**	**3.35 [1.61, 6.96]**
Total events	70		34			

Heterogeneity: Tau² = 0.21; Chi² = 5.70, df = 4 (P = 0.22); I² = 30%
Test for overall effect: Z = 3.24 (P = 0.001)

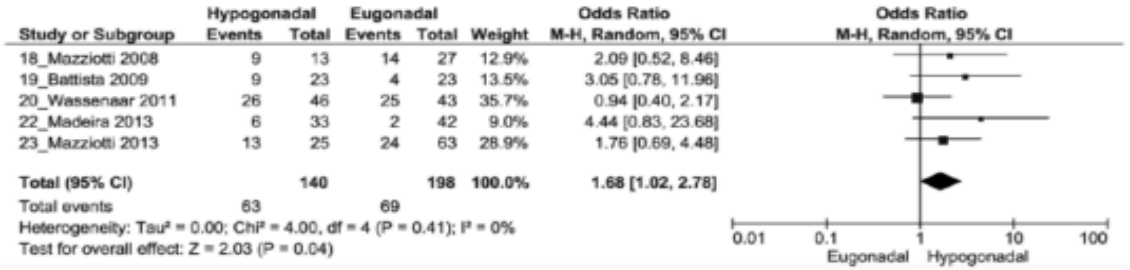
Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Controlled disease Active disease



Study or Subgroup	Male Events	Total	Female Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
20_Wassenaar 2011	26	46	19	43	27.0%	1.64 [0.71, 3.80]
21_Padova 2011	4	8	3	10	10.4%	2.33 [0.34, 16.18]
22_Madeira 2013	5	22	3	53	14.5%	4.90 [1.06, 22.72]
23_Mazziotti 2013	25	55	17	33	26.3%	0.78 [0.33, 1.86]
24_Claessen 2013	9	31	1	18	8.8%	6.95 [0.80, 60.35]
25_Brzana 2013	6	9	6	23	12.9%	5.67 [1.07, 30.08]
Total (95% CI)		**171**		**180**	**100.0%**	**2.19 [1.07, 4.50]**
Total events	75		49			

Heterogeneity: Tau² = 0.32; Chi² = 8.63, df = 5 (P = 0.12); I² = 42%
Test for overall effect: Z = 2.13 (P = 0.03)

Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Female Male



Study or Subgroup	Hypogonadal Events	Total	Eugonadal Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
18_Mazziotti 2008	9	13	14	27	12.9%	2.09 [0.52, 8.46]
19_Battista 2009	9	23	4	23	13.5%	3.05 [0.78, 11.96]
20_Wassenaar 2011	26	46	25	43	35.7%	0.94 [0.40, 2.17]
22_Madeira 2013	6	33	2	42	9.0%	4.44 [0.83, 23.68]
23_Mazziotti 2013	13	25	24	63	28.9%	1.76 [0.69, 4.48]
Total (95% CI)		**140**		**198**	**100.0%**	**1.68 [1.02, 2.78]**
Total events	63		69			

Heterogeneity: Tau² = 0.00; Chi² = 4.00, df = 4 (P = 0.41); I² = 0%
Test for overall effect: Z = 2.03 (P = 0.04)

Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Eugonadal Hypogonadal

Patients with acromegaly had high frequency of vertebral fractures (odds ratio, 8.26; 95% CI, 2.91–23.39; (p <.0001), in close relationship with male gender, hypogonadism, and active acromegaly.

CARATTERISTICHE CLINICHE - COMORBILITA': osteoporosi e fratture

High prevalence of vertebral fractures despite normal bone mineral density in patients with long-term controlled acromegaly

M J E Wassenaar, N R Biermasz, N A T Hamdy, M C Zillikens[1], J B J van Meurs[1,2], F Rivadeneira[1,2], A Hofman[2], A G Uitterlinden[1,2], M P M Stokkel[3], F Roelfsema, M Kloppenburg[4], H M Kroon[5], J A Romijn and A M Pereira

European Journal of Endocrinology (2011) **164** 475–483

Design: Case–control study.

Patients and measurements: Eighty-nine patients (46% male, mean age: 58 years) were included. We studied VFs and non-VFs, bone mineral density (BMD), and markers of bone turnover. In 48 patients, BMD assessment was also obtained 7 years prior to the current study. To compare VF prevalence, data from a sample of the Dutch population ($n=3469$) were used.

Prevalence of vertebral fractures by age category in acromegaly patients compared with a Dutch epidemiological control cohort.

	Subjects		Vertebral fracture cases				
Age category	Acromegaly ($n=89$)	Controls ($n=3469$)	Acromegaly (n (%))	Controls (n (%))	**Odds ratio**	**95% CI**	***P* value**
<55	19	–	11 (59%)	–	–	–	–
56–60	25	826	13 (53%)	25 (3%)	3.7	1.3–10.9	0.01
61–65	18	955	8 (44%)	48 (5%)	6.5	3.4–12.4	<0.001
66–70	15	796	10 (67%)	72 (9%)	4.4	2.4–8.2	<0.001
71–75	8	560	7 (88%)	73 (13%)	2.4	1.3–4.3	<0.01
>76	4	332	3 (75%)	37 (11%)	2.3	1.3–3.6	<0.01

CARATTERISTICHE CLINICHE - COMORBILITA': osteoporosi e fratture

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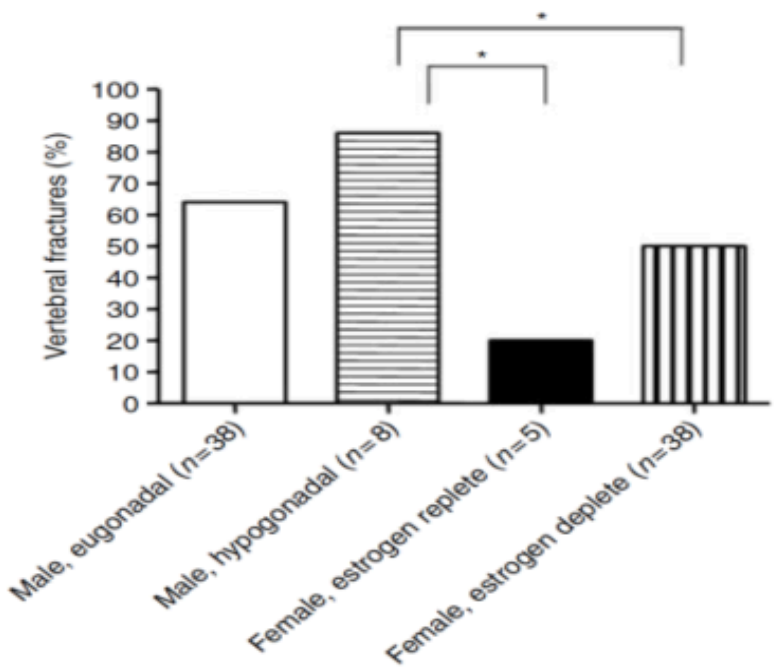

Prevalence of vertebral fractures in male- and female-cured acromegalic patients, grouped according to gonadal status. *$P<0.05$. Data were analyzed by binary logistic regression analysis with adjustments for age, gender, and BMI.

CARATTERISTICHE CLINICHE - COMORBILITA': osteoporosi e fratture

High prevalence of vertebral fractures despite normal bone mineral density in patients with long-term controlled acromegaly

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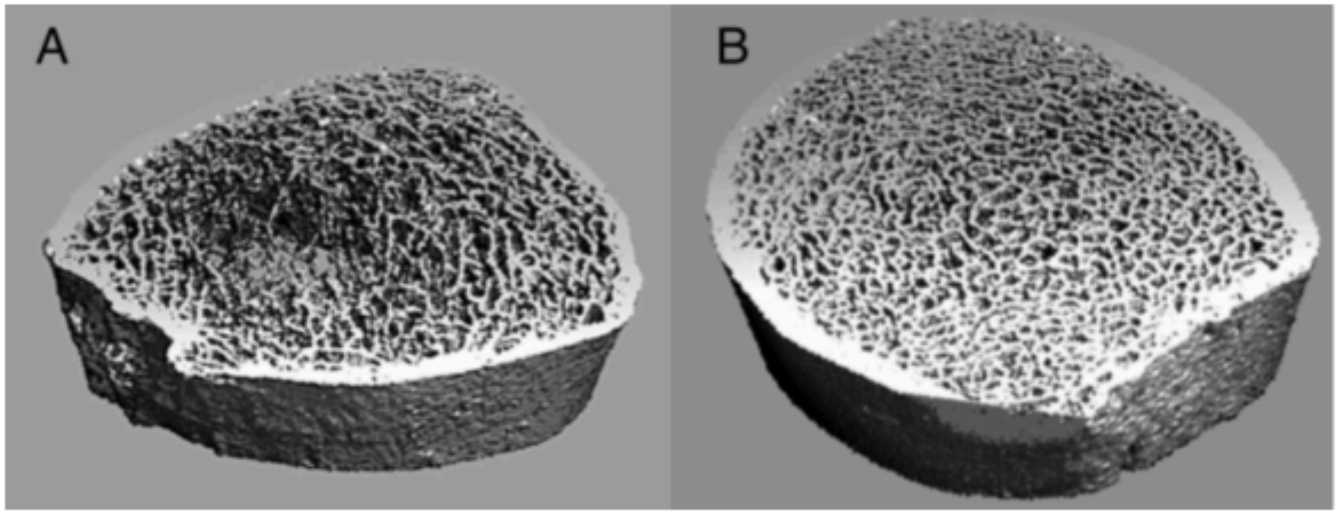
BMD (g/cm^2), *T*- and *Z*-scores of the lumbar spine at baseline and follow-up in patients with and without VF. Data are shown as mean (S.E.M.) unless mentioned otherwise.

	Vertebral fractures (VF)			
	No VF ($n=15$ (34%))	VF ($n=27$ (66%))	**Difference** (95% CI)	***P* value**
BMD lumbar spine				
Baseline	1.06 (0.04)	1.00 (0.03)	−0.06 (−0.18–0.06)	0.29
Follow-up	1.01 (0.04)	1.00 (0.03)	0.01 (−0.10–0.11)	0.90
Delta	−0.01 (0.02)	0.00 (0.01)	0.02 (−0.02–0.06)	0.26
T-score lumbar spine				
Baseline	−0.19 (0.35)	−0.53 (0.27)	−0.23 (−1.23–0.82)	0.66
Follow-up	−0.50 (0.35)	−0.69 (0.26)	0.32 (−0.94–1.00)	0.95
Delta	−0.06 (0.25)	−0.10 (0.17)	−0.37 (−1.02–0.27)	0.25
Z-score lumbar spine				
Baseline	0.74 (0.42)	0.12 (0.27)	−0.49 (−1.50–0.53)	0.34
Follow-up	0.56 (0.41)	0.40 (0.26)	−0.01 (−0.95–0.93)	0.96
Delta	0.04 (0.16)	0.24 (0.96)	−0.46 (−3.39–2.47)	0.75

Data were analyzed by analysis of covariance with adjustments for age, gender, and BMI. Delta was calculated as follows: (follow-up value − baseline value)/baseline value. CI, confidence interval; *n*, number; BMD, bone mineral density; BMI, body mass index.

CARATTERISTICHE CLINICHE - COMORBILITA': osteoporosi e fratture

	Acromegalic Patients (n = 82)
Demographic data	
Age, y	50.9 ± 13.8
Ethnicity (Caucasian/non-Caucasian)	44/38
Sex (male/female)	32/50
BMI (kg/m^2)	30.6 ± 5.6
Diagnosis of T2DM, %	35.4
Hypogonadism, %	45.1
Hypothyroidism on hormone replacement, %	31.7
Hypocortisolism on hormone replacement, %	35.4
Disease data	
Age at diagnosis, y	43.3 ± 14.1
Estimated period without treatment, y	6.8 ± 5.8
Tumor size (micro-/macroadenoma)	12/70
Patients submitted to surgery	61
Patients submitted to radiotherapy	22



Differences in trabecular bone in the distal tibia between acromegalic and control patient. A, Acromegalic patient. B, Healthy control.

Conclusions: Acromegaly appears to have a deleterious effect on trabecular bone microarchitecture, and in this specific population, the gonadal status might be more important than T2DM or acromegaly activity in determining bone health. High-resolution peripheral quantitative computed tomography seems promising for evaluating acromegalic bone properties and for addressing the limitations posed by dual-energy x-ray absorptiometry. ***(J Clin Endocrinol Metab 98: 1734 –1741, 2013)***

CARATTERISTICHE CLINICHE - COMORBILITA': osteoporosi e fratture

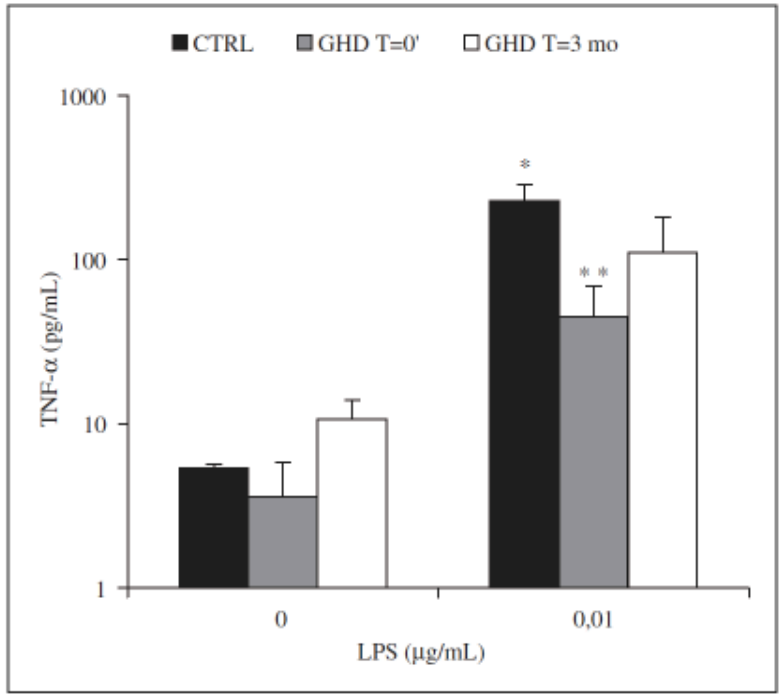


Figure 1

Effect of GH therapy on *in vitro* production of TNF-α by unstimulated and LPS-stimulated PBMC of GHD children before (shaded bars) and after 3 months of treatment (open bars) in comparison with healthy controls (CTRL, solid bars).
Results are represented as mean + SEM.
* T=0 *versus* corresponding CTRLs p<0.05 (Mann-Whitney U test).
** 3 months *versus* corresponding T=0' p<0.05 (Wilcoxon test).
° 3 months *versus* corresponding CTRLs p<0.05 (Mann-Whitney U test).

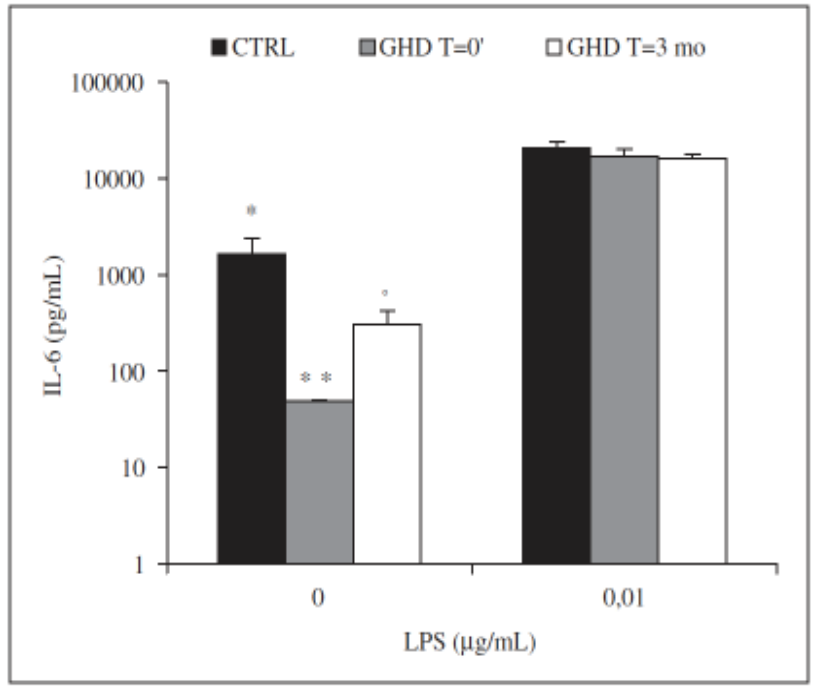


Figure 2

Effect of GH therapy on *in vitro* production of IL-6 by unstimulated and LPS-stimulated PBMC of GHD children before (shaded bars) and after 3 months of treatment (open bars) in comparison with healthy controls (CTRL, solid bars).
Results are represented as mean + SEM.
* T=0 *versus* corresponding controls p<0.05 (Mann-Whitney U test).
** 3 months *versus* corresponding T=0' p<0.05 (Wilcoxon test).
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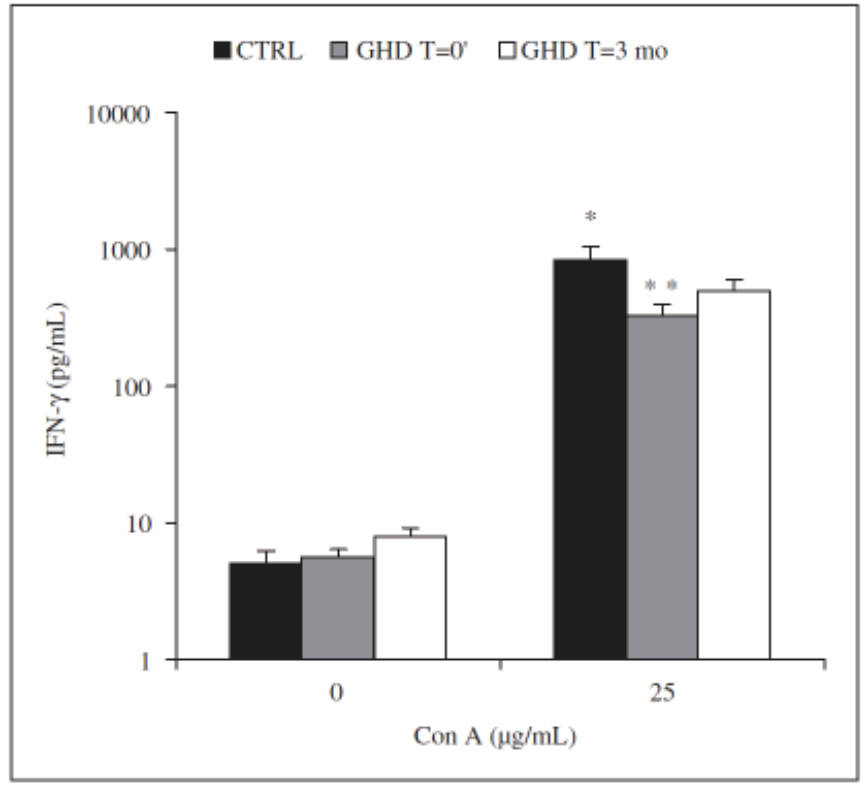


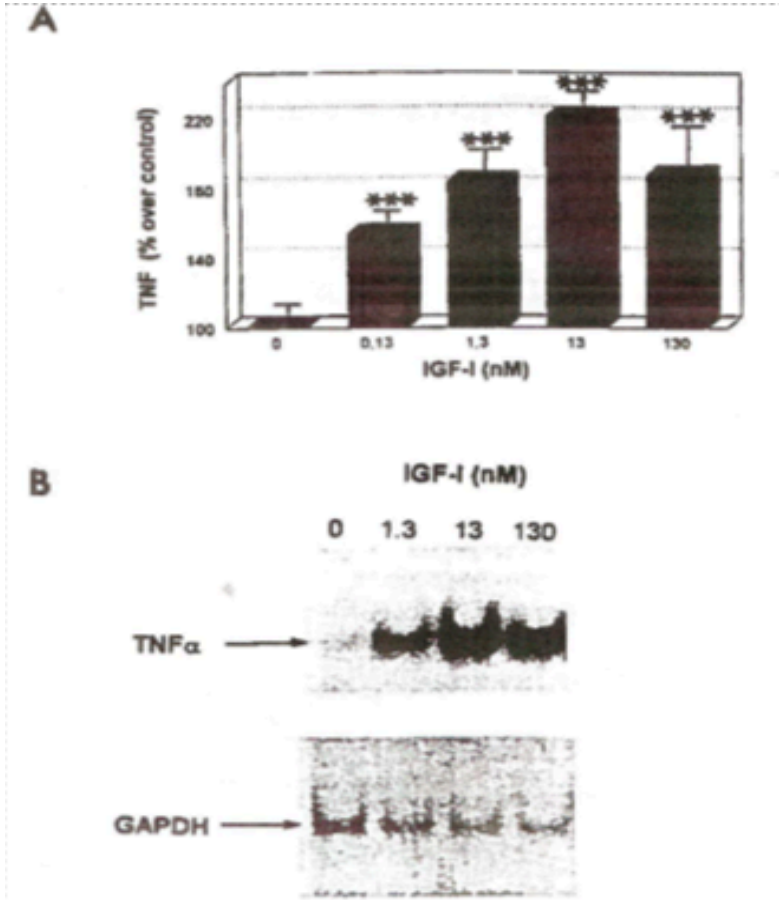
Figure 3

Effect of GH therapy on *in vitro* production of IFN-γ by unstimulated and Con A-stimulated PBMC of GHD children before (shaded bars) and after 3 months of treatment (open bars) in comparison with healthy controls (CTRL, solid bars).
Results are represented as mean + SEM.
* T=0 *versus* corresponding controls p<0.05 (Mann-Whitney U test).
** 3 months *versus* corresponding T=0' p<0.05 (Wilcoxon test).

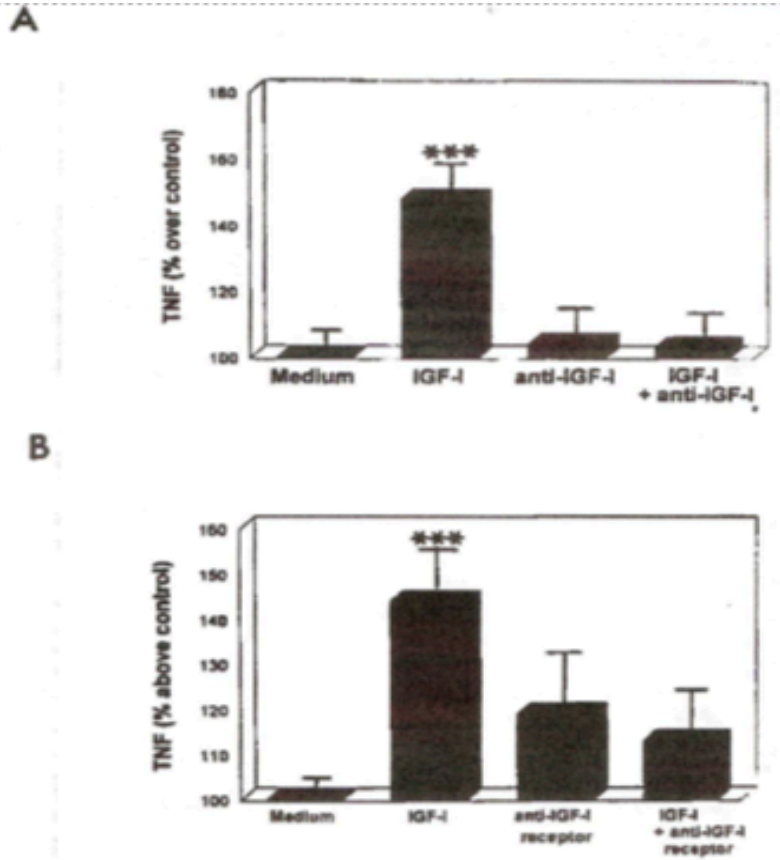
Eur. Cytokine Netw., Vol. 16 n° 1, *March 2005*, 65-9

Effect of growth hormone therapy on the proinflammatory cytokine profile in growth hormone-deficient children

CARATTERISTICHE CLINICHE - COMORBILITA': osteoporosi e fratture



A, IGF-I increases human monocyte TNFα production. Human monocytes were cultured for 24 h in presence of increasing concentrations of IGF-I (0.13–130 nM). At the end of the incubation period, supernatants were collected and assayed for TNFα content. Data represent mean ± SEM of five experiments. ***, $P < 0.001$ *vs.* samples incubated with medium alone. B, IGF-I up-regulates human monocyte TNFα mRNA levels. Autoradiograph (5-h exposure) illustrating effect of IGF-I on macrophage TNFα mRNA levels. ANA-1 cells were exposed to increasing concentrations of IGF-I (1.3–130 nM) for 3 h. At the end of the incubation period, total cytoplasmic RNA was analyzed for TNFα and GAPDH mRNA levels as described in *Materials and Methods*.



Monoclonal antibodies against IGF-I and IGF-I receptor abolish stimulation of basal TNFα production in IGF-I treated macrophages. ANA-1 cells were pretreated for 1 h with an anti-IGF-I antibody (1/10000) (A) or with saturating amounts (1 μg/ml) of an antibody against the IGF-I receptor (B) before addition of 13 nM IGF-I. After 24 h, supernatants were harvested and assayed for TNFα content. Data represent mean ± SEM of four experiments. ***, $P < 0.001$ *vs.* untreated samples.

CARATTERISTICHE CLINICHE - COMORBILITA': osteoporosi e fratture

Journal of Pathology
J Pathol 2002; **198**: 220–227.
Published online 1 August 2002 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/path.1190

Original Paper

Proinflammatory cytokine (TNFα/IL-1α) induction of human osteoclast formation

Osami Kudo,[1] Yosuke Fujikawa,[2] Ichiro Itonaga,[1] Afsie Sabokbar,[1] Takehiko Torisu[2] and Nicholas A Athanasou[1]*

[1] *Department of Pathology, University of Oxford, Oxford, UK*
[2] *Department of Orthopaedic Surgery, Oita Medical University, Oita, Japan*

**Correspondence to:*
Nicholas A Athanasou,
Department of Pathology,
Nuffield Orthopaedic Centre,
Windmill Road, Headington,
Oxford OX3 7LD, UK.
E-mail:
nick.athanasou@ndos.ox.ac.uk

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Abstract

TNFα and IL-1α are potent stimulators of bone resorption *in vivo* and *in vitro*. Recently, it has been demonstrated that these two cytokines directly induce osteoclastogenesis in mouse marrow cultures. This study determined whether TNFα (± IL-1α) is also capable of inducing human osteoclastogenesis. The $CD14^+$ monocyte fraction of human peripheral mononuclear cells was cultured with TNFα ± IL-1α in the presence of M-CSF. TNFα induced the formation of multinucleated cells (MNCs) which were positive for TRAP, VNR and cathepsin K and showed evidence of resorption pit formation. IL-1α stimulated TNFα-induced lacunar resorption two- to four-fold. Osteoprotegerin, the decoy receptor for RANKL, did not inhibit this process. Anti-human IL-1α neutralizing antibodies significantly inhibited resorption without inhibiting the formation of $TRAP^+/VNR^+$ MNCs. These results suggest that, in the presence of M-CSF, TNFα is sufficient for inducing human osteoclast differentiation from circulating precursors by a process which is distinct from the RANK/RANKL signalling pathway.

Keywords: **osteoclast; bone resorption; TNFα; IL-1α; inflammatory cytokine; monocytes**

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 12, Number 4, 1997
Blackwell Science, Inc.

CARATTERISTICHE CLINICHE - COMORBILITA': osteoporosi e fratture

Identification and Characterization of the Insulin-like Growth Factor I Receptor in Mature Rabbit Osteoclasts

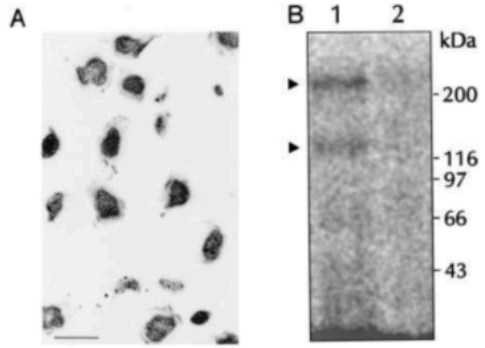
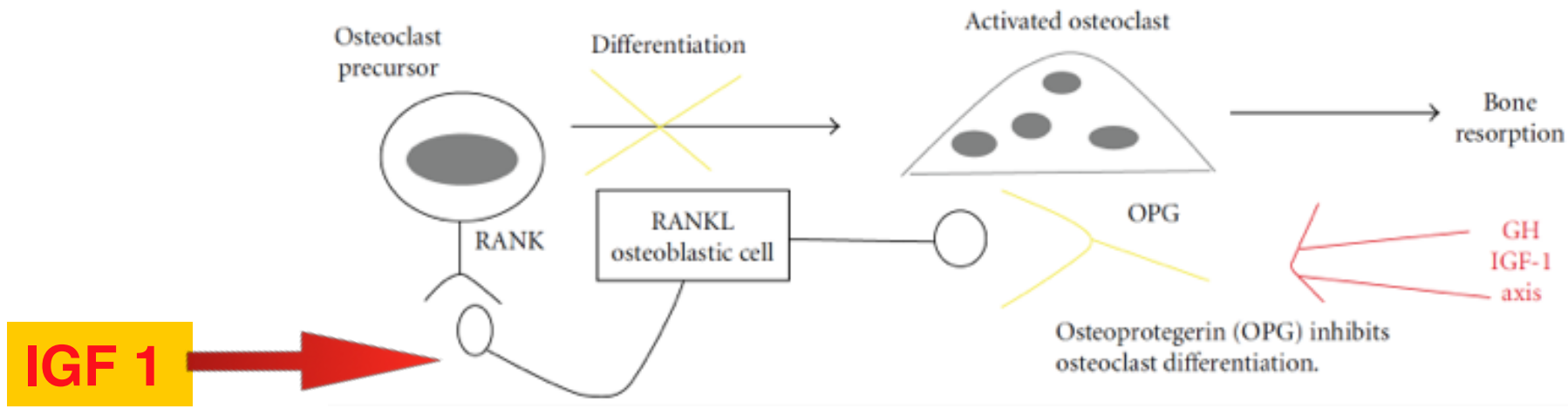


FIG. 3. TRAP staining of purified osteoclasts and affinity cross-linking of ^{125}I-IGF-I to its binding sites on purified osteoclasts. (A) Isolated mature osteoclasts from rabbit long bone stained for TRAP. Bar, 50 μm. (B) The purified osteoclasts were incubated with 0.1 nM ^{125}I-IGF-I for 4 h at 4°C in the absence (lane 1) or presence (lane 2) of a 200-fold molar excess unlabeled IGF-I. The ^{125}I-IGF-I in cross-linked complexes was visualized by automatic phosphorimaging. The arrow heads indicate the two cross-linked complexes with apparent molecular masses of 230 and 130 kD, respectively.



IGF 1

CARATTERISTICHE CLINICHE - COMORBILITA': osteoporosi e fratture

- GH e IGF 1 svolgono un ruolo importante nel fisiologico turn over osseo e insieme agli ormoni gonadici determinano la corretta acquisizione della massa ossea
- L'eccesso di GH − IGF 1, soprattutto se associato a ipogonadismo, altera la struttura dell'osso, determinando un significativo aumento del rischio fratturativo

CARATTERISTICHE CLINICHE - COMORBILITA': neoplasie

The Incidence of Cancer Among Acromegaly Patients: Results From the German Acromegaly Registry

J Clin Endocrinol Metab 100: 3894–3902, 2015

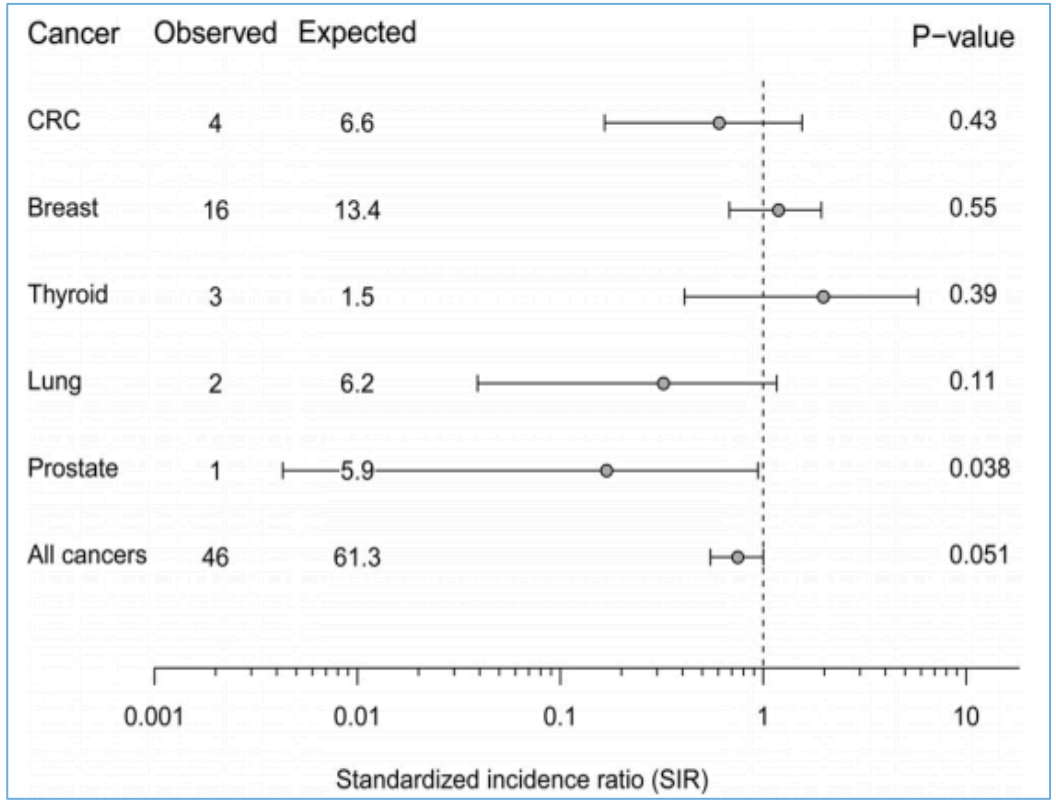
	Patients With Cancer	Patients Without Cancer	All Patients	*P* Value
n	42	403	445	
Women	30 (71.4)	217 (53.8)	247 (55.5)	.029
Age, y	65.2 ± 11.3	57.7 ± 14.2	58.4 ± 14.1	<.001
Age at first diagnosis, y	49.5 ± 14.4	45.3 ± 14.1	45.7 ± 14.2	.081
Height, cm	169.5 ± 9.1	173.2 ± 11.4	172.9 ± 11.2	.045
Weight, kg	80.4 ± 15.7	85.5 ± 16.6	85.0 ± 16.5	.093
BMI, kg/m^2	27.9 ± 4.2	28.6 ± 4.7	28.5 ± 4.6	.41
Received operation	37 (88.1)	366 (93.1)	403 (92.6)	.22
On acromegaly medication	22 (52.4)	175 (44.1)	197 (44.9)	.30
Received radiation therapy	12 (29.3)	85 (22.0)	97 (22.7)	.29
Random GH, ng/mL (n = 27; 237)	0.90 [0.25, 1.85]	0.92 [0.40, 2.33]	0.91 [0.39, 2.31]	.61
≥2.5 ng/mL	6 (22.2)	55 (23.2)	61 (23.1)	.91
≥1.0 ng/mL	12 (44.4)	117 (49.4)	129 (48.9)	.63
IGF-1, ng/mL (n = 42; 390)	178 [128, 257]	184 [137, 254]	183 [134, 255]	.51
IGF-1 normal	31 (73.8)	281 (72.1)	312 (72.2)	.81
Random GH and IGF-1 (n = 27; 232)				.74
GH normal/IGF-1 normal	12 (44.4)	104 (44.8)	116 (44.8)	
GH elevated/IGF-1 normal	7 (25.9)	58 (25.0)	65 (25.1)	
GH normal/IGF-1 elevated	3 (11.1)	15 (6.5)	18 (6.9)	
GH elevated/IGF-1 elevated	5 (18.5)	55 (23.7)	60 (23.2)	
Pegvisomant: IGF-1 normal (n = 7; 48)	5 (71.4)	33 (68.8)	38 (69.1)	1.00
Acromegaly uncontrolled (n = 41; 382)	7 (17.1)	78 (20.4)	85 (20.1)	.61

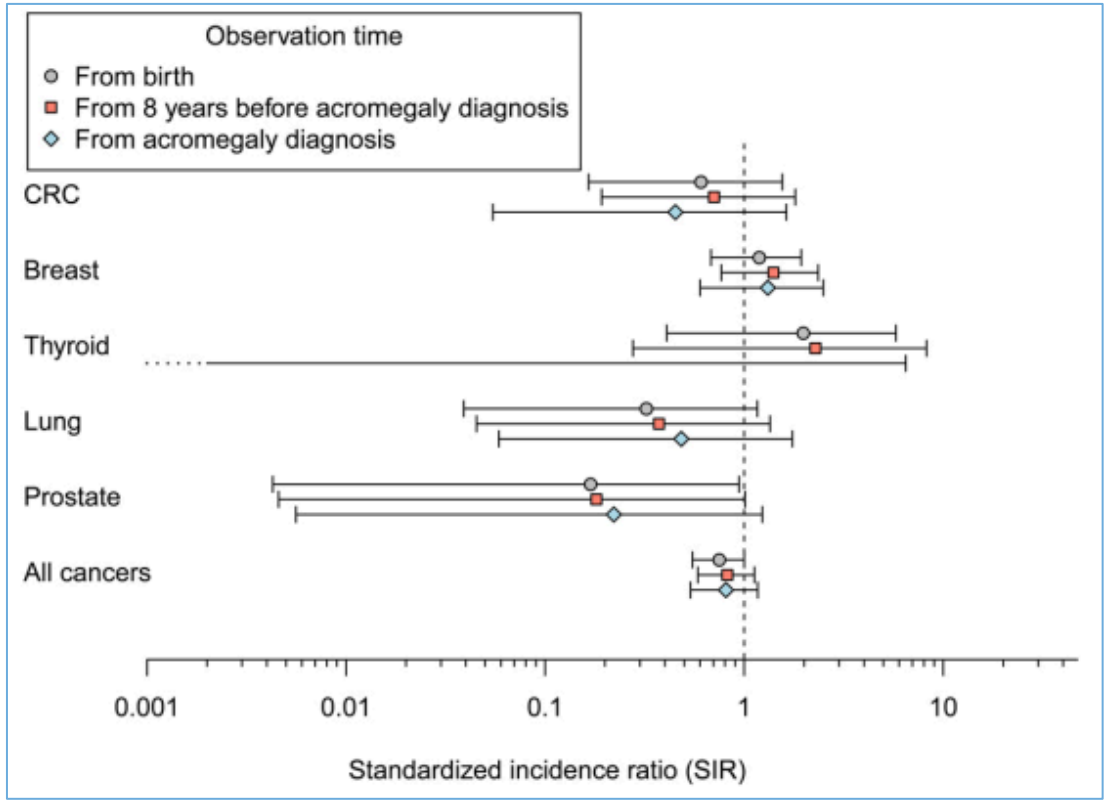
Abbreviation: BMI, body mass index. Data are expressed as number (percentage), means ± SD, or median [interquartile range]. GH values were only used for those not known to be on pegvisomant, and values at the last visit are reported. The number of data available is provided for those with and without cancer. *P* values refer to the comparison between those with and without cancer. GH elevated (ie, ≥1 ng/mL for random GH, or ≥0.4 ng/mL for oral glucose tolerance test values), IGF-1 normal (ie, < upper limit of center specific, age, and gender-matched reference range). "Uncontrolled" is defined as elevated GH and elevated IFG-1 if not using pegvisomant, or simply elevated IGF-1 if using pegvisomant.

CARATTERISTICHE CLINICHE - COMORBILITA': neoplasie

The Incidence of Cancer Among Acromegaly Patients: Results From the German Acromegaly Registry

J Clin Endocrinol Metab 100: 3894–3902, 2015





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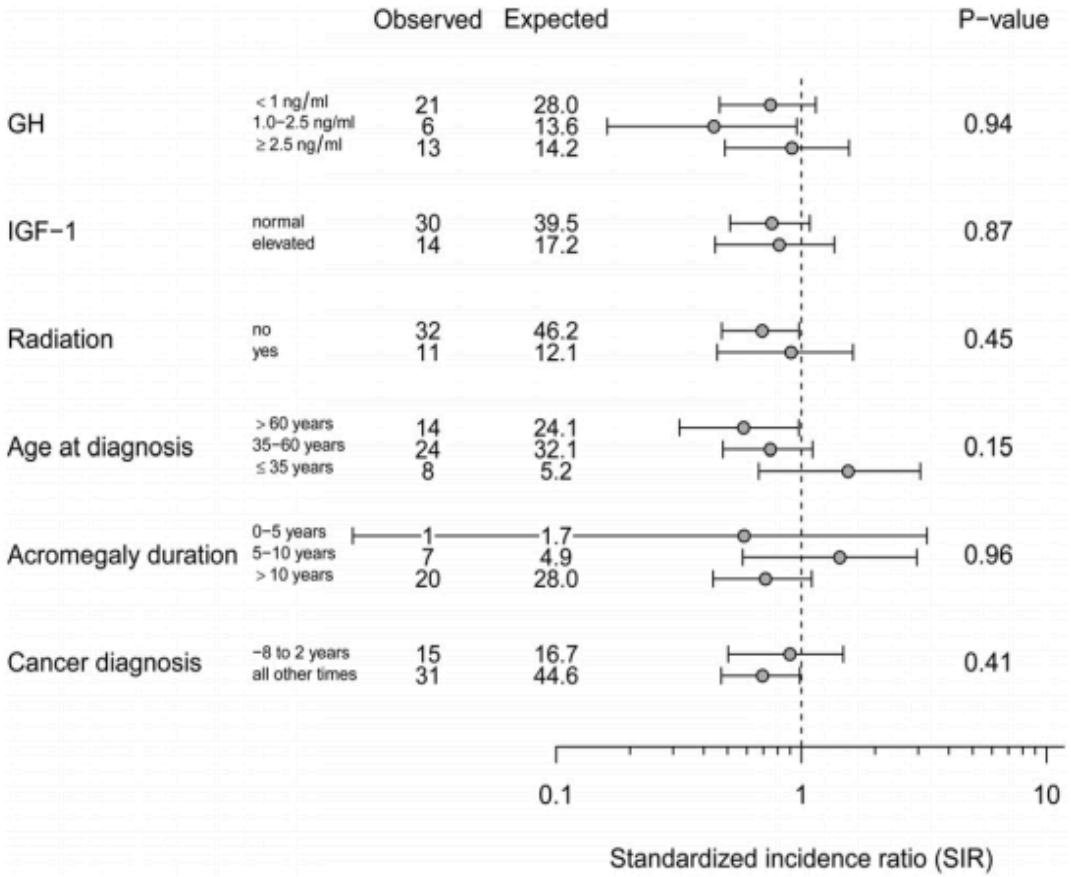


I dati suggeriscono che pazienti trattati adeguatamente presso centri specializzati non presentano una maggiore incidenza di neoplasie rispetto alla popolazione generale

CARATTERISTICHE CLINICHE - COMORBILITA': neoplasie

Cancer Incidence Among Patients With Acromegaly in Denmark, Excluding the First Year After Acromegaly Diagnosis

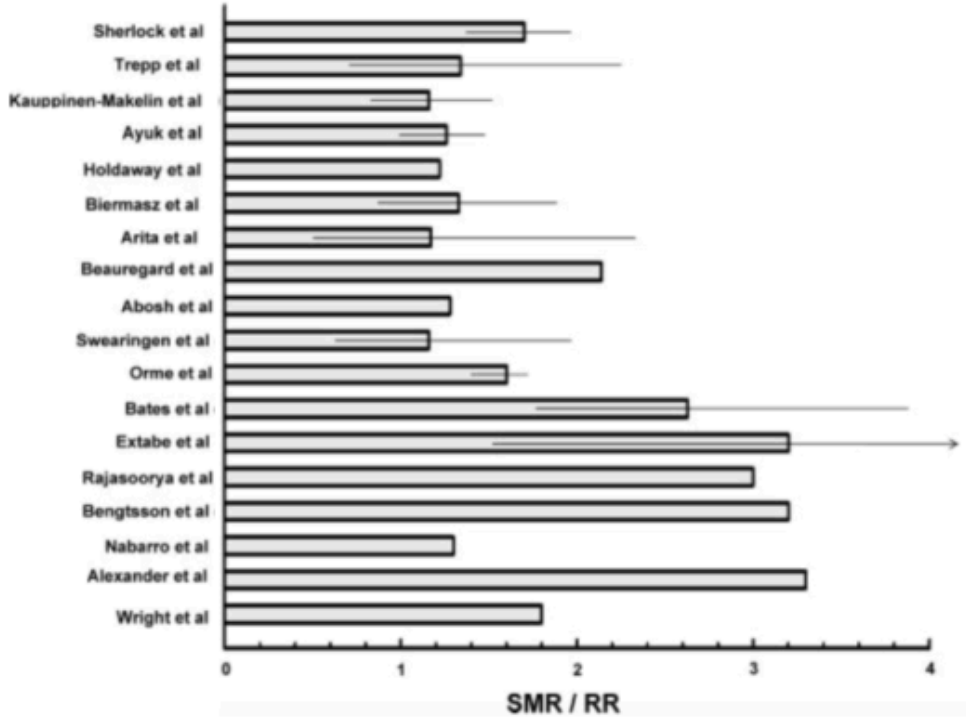
J Clin Endocrinol Metab 103: 2182–2188, 2018

	Observed	Expected	SIR (95% CI)
Overall, cancer	81	72.7	1.1 (0.9–1.4)
Localized cancer	43	36.6	1.2 (0.9–1.6)
Nonlocalized cancer	25	22.0	1.1 (0.7–1.7)
Colorectal cancer	10	7.1	1.4 (0.7–2.6)
Localized	5	2.7	1.9 (0.6–4.3)
Nonlocalized	5	3.6	1.4 (0.5–3.3)
Breast cancer	9	8.1	1.1 (0.5–2.1)
Localized	4	4.0	N/A
Nonlocalized	5	3.6	1.4 (0.5–3.2)
Lung cancer	4	7.9	NA
Localized	0	1.5	NA
Nonlocalized	4	5.8	NA
Thyroid cancer	1	0.3	NA
Gastric cancer	4	1.1	NA
Prostate cancer	9	6.6	1.4 (0.6–2.6)
Urinary tract cancers	5	4.9	1.0 (0.3–2.4)
Hematological cancers	5	3.9	1.3 (0.4–3.0)

Abbreviation: NA, <5 cancers observed, so SIRs are not reported.

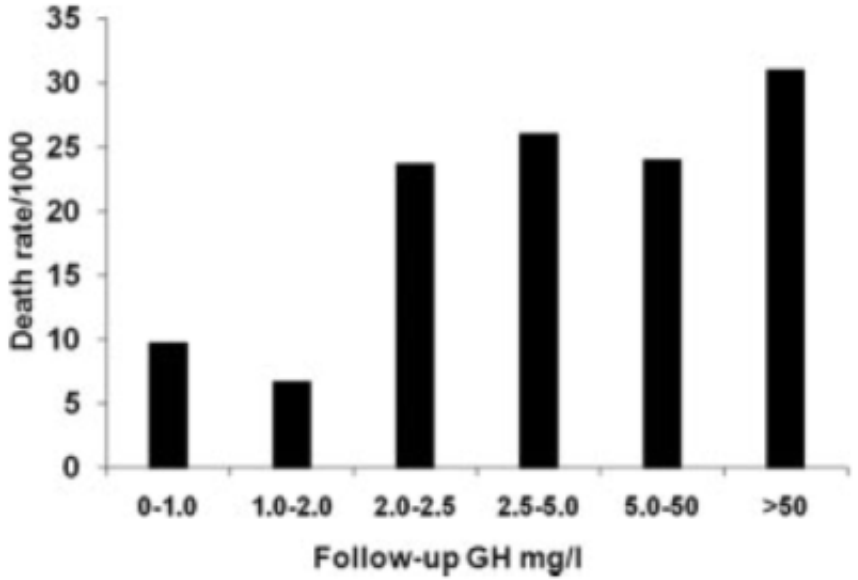
M O R T A L I T A’

Summary of studies assessing mortality rates in patients with acromegaly. *(Bars 95% CI)*



Endocrine Reviews 31: 301–342, 2010

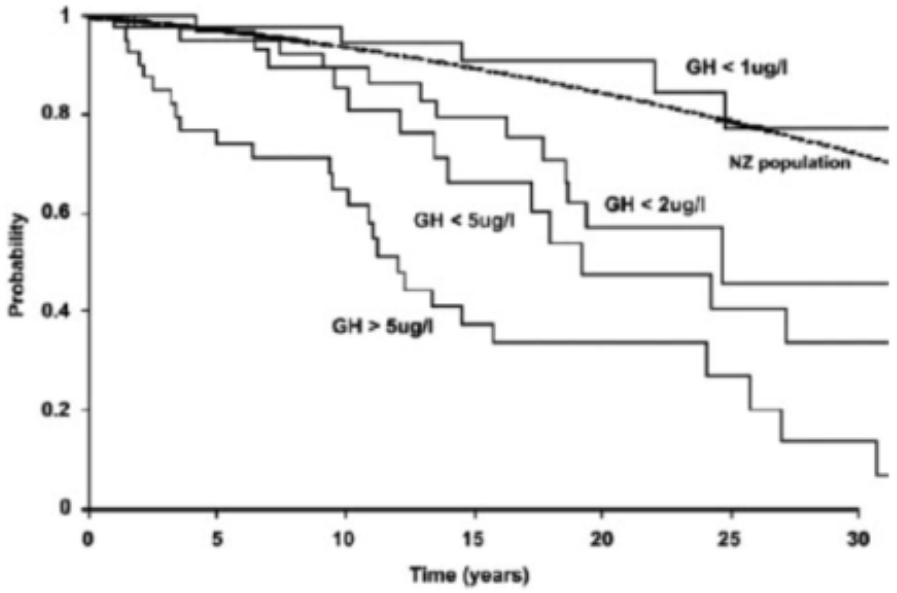
Crude death rates per 1000 in patients with acromegaly related to posttreatment GH levels.



Endocrine Reviews 31: 301–342, 2010

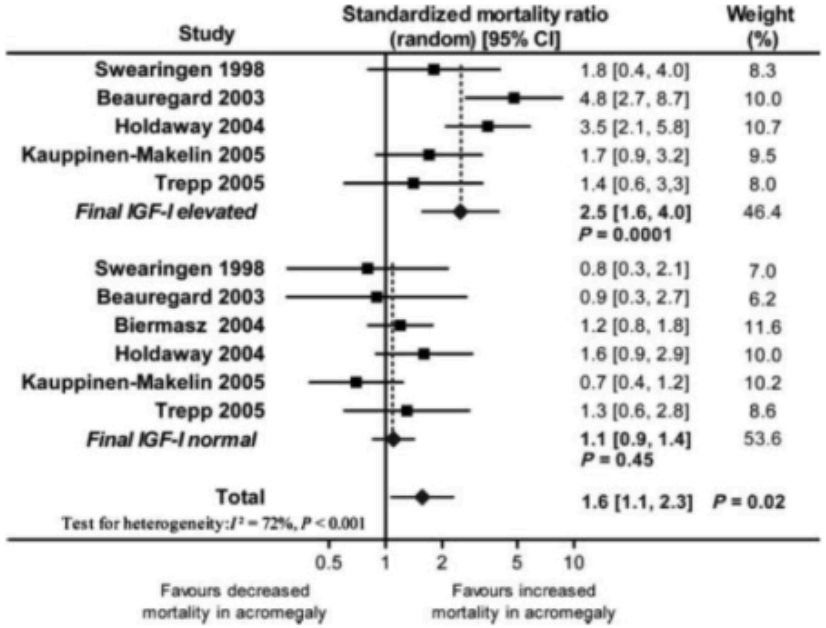
M O R T A L I T A’

Probability of survival in acromegaly according to serum GH concentrations at last review after treatment



Endocrine Reviews 31: 301–342, 2010

Pooled SMRs in studies of acromegaly grouped according to IGF-I level at final follow-up. Data are SMR (95% CI).



Endocrine Reviews 31: 301–342, 2010

M O R T A L I T A’

Studies assessing disease-specific mortality rates in patients with acromegaly

	No. of patients	No. of deaths	Mortality cause
Wright, 1970	194	55	Total group SMR, 1.8; cause-specific: vascular, 38.5%; respiratory, 18%; malignant, 18%
Alexander, 1980	164	45	Total group SMR, 3.3 (male 24/5, SMR = 4.8; female 21/8.1, SMR = 2.6); cause-specific: vascular, 60%; respiratory, 15.5%; malignant, 15.5%
Nabarro, 1987	256	47	Total group SMR, 1.3 (<55 yr, 10/5.3, SMR = 1.9; female 23/13.7, SMR = 1.7); cause-specific: cardio/cerebrovascular 47/37.2, SMR = 1.3 N/S; vascular, 55%; respiratory, 6%; malignant, 23%
Bengtsson, 1988	166	62	Total group SMR, 3.2; cause-specific: vascular deaths 32/9, SMR = 3.6; cancer deaths 15/5.6, SMR = 2.7
Rajasoorya, 1994	151	32	Total group SMR, 3.0; cause-specific: cardiovascular SMR 3; cerebrovascular SMR 3; malignancy SMR 1
Extabe, 1993	74	10	Total group SMR, 3.2 (1.55–5.93) [male, SMR 7 (2.81–14.4), female, SMR 1.4 (0.29–4.17)]; cause-specific: vascular, 10 (0.25–55.7); malignancy, 7.1 (2.31–16.6)
Bates, 1993	79	28	Total group SMR, 2.63 (1.8–3.9); cause-specific: vascular, 57%; respiratory, 25%; malignant, 11%
Orme, 1998	1362	366	Total group SMR, 1.60 (1.44–1.77); cause-specific: vascular, SMR 1.76 (1.47–2.07), $P < 0.001$; cerebrovascular, SMR 2.06 (1.5–2.76), $P < 0.001$; respiratory, SMR 1.85 (0.92–1.44), $P < 0.001$; malignant, SMR 1.16 (0.92–1.44), $P = 0.1$
Swearingen, 1998	149	12	Total group SMR, 1.16 (0.66–2.0); cause-specific: vascular, 5/12; respiratory, 1/12; malignant, 4/12
Abosch, 1998	254	29	Total group SMR, 1.28; cause-specific, not available in majority of 20 deaths
Beauregard, 2003	103	18	Total group SMR, 2.14; cause-specific: vascular, 5/18; malignant, 9/18
Arita, 2003	154	11	Total group SMR, 1.17 (0.54–2.38); cause-specific: vascular, 4/11; respiratory, 2/11; malignant, 2/11
Biermasz, 2004	164	28	Total group SMR, 1.33 (0.87, 1.87); cause-specific: vascular, 7/28; malignant, 13/28
Holdaway, 2004	208	72	Total group SMR, 1.22; cause-specific: vascular, 36/72 (50%); respiratory, 2/76; malignant, 17/72 (24%)
Ayuk, 2004	419	95	Total group SMR, 1.26 (1.03–1.54), $P = 0.045$; cause-specific: cardiovascular, SMR 1.37 (0.98–1.9), $P = 0.111$; cerebrovascular, SMR 2.68 (1.73–4.15), $P = 0.007$; respiratory, SMR 1.52 (0.88–2.61), $P = 0.219$; malignant, SMR 0.91 (0.59–1.39), $P = 0.65$
Mestron, 2004	219	56	Total group SMR, not available; SMR 1.3 (0.52–2.67) for remission group and 1.38 (0.51–3.0) in persistent disease group; cause-specific: cardiovascular, 26.8%; cerebrovascular, 8.9%; respiratory, 5.4%; malignant, 16.1%
Kauppinen-Makelin, 2005	334	56	Total group SMR, 1.16 (0.85–1.54); cause-specific: cardiovascular, 23.2% (coronary artery disease); other cardiovascular diseases, (16.1%); cerebrovascular, 14.3%; malignant, 21.4%
Trepp, 2005	94	13	Total group SMR, 1.34 (0.71–2.29); cause-specific: cardiovascular, 6/13; malignant, 4/13
Sherlock, 2009	501	162	Total group SMR, 1.7 (1.4–2.0), $P < 0.001$; cause-specific: cardiovascular, SMR 1.9 (1.6–2.4), $P > 0.001$; cerebrovascular, SMR 2.7 (1.9–4.1), $P < 0.001$; respiratory, SMR 1.8 (1.1–2.8), $P = 0.01$; malignant, SMR 1.2 (0.9, 1.7), $P = 0.26$

Endocrine Reviews, June 2010, 31(3):301–342

D I A G N O S I

Acromegaly: An Endocrine Society Clinical Practice Guidelines

J Clin Endocrinol Metab 99: 3933–3951, 2014

- ***MISURARE I LIVELLI DI IGF-1 IN TUTTI I PAZIENTI CON LE CARATTERISTICHE FENOTIPICHE DELL'ACROMEGALIA***
- ***MISURARE I LIVELLI DI IGF-1 NEI PAZIENTI SENZA LE CARATTERISTICHE FENOTIPICHE DELL'ACROMEGALIA MA CON DIVERSE COMORBILITA' (apnee notturne, diabete tipo 2, artrosi, tunnel carpale, iperidrosi, ipertensione)***
- ***MISURARE I LIVELLI DI IGF-1 IN TUTTI I PAZIENTI CON MASSE IPOFISARIE***
- ***IN PAZIENTI CON LIVELLI ELEVATI O DUBBI DI IGF-1, DIMOSTRARE LA MANCATA SOPPRESSIONE DEL GH AL DI SOTTO DI 1 mcrg/l MEDIANTE OGTT***

D I A G N O S I

Acromegaly: An Endocrine Society Clinical Practice Guidelines

J Clin Endocrinol Metab 99: 3933–3951, 2014

- ***NON E' RACCOMANDATO IL DOSAGGIO DEL GH RANDOM NELLA DIAGNOSI DI ACROMEGALIA***
- ***DOPO DIAGNOSI BIOCHIMICA, VA EFFETTUATA RMN IPOTALAMO IPOFISARIA PER EVIDENZIARE IL TUMORE E VALUTARNE L'ESTENSIONE PARASELLARE, SOSTITUITA DALLA TAC IN CASO DI IMPOSSIBILITA' AD ESEGUIRE RMN***
- ***E' RACCOMANDATO LO STUDIO DEL CAMPO VISIVO SE IL TUMORE INTERESSA IL CHIASMA OTTICO***

D I A G N O S I

Problemi legati al dosaggio dell'IGF-1

I livelli sono alti in
- Pubertà
- Periodo post-puberale
- Ragazzi/e alti/e
- Gravidanza

I livelli sono bassi in
- Malattie acute intercorrenti
- Malattie sistemiche
- Insufficienza epatica o renale
- Diabete mellito tipo 1
- Terapia con Estrogeni per os
- Digiuno
- Malnutrizione

Problemi metodologici
- Definizione dei range di normalità per età
- Interferenza di proteine leganti
- Antisieri che non consentono misure precise e riproducibili
- Assenza di standard di riferimento

GH RANDOM

Sicuramente positivo se > 40 ng/ml

Sicuramente negativo se < 0,4 ng/ml

D I A G N O S I

Problemi legati all'OGTT per GH

Livelli alti si trovano in

- **Condizioni fisiologiche**
  - Picchi secretori
  - Digiuno
  - Esercizio
  - Stress
  - Sonno
  - Ragazzi alti
- **Condizioni patologiche**
  - Diabete mellito tipo 1
  - Epatopatia
  - Insufficienza renale cronica
  - Depressione
  - Malnutrizione
  - Disturbi del comportamento alimentare
  - Ipertiroidismo

MANCATA SOPPRESSIONE DEL GH DOPO OGTT (falsi positivi)

- Ragazzi/e alti/e
- Adolescenza
- Diabete mellito
- Insufficienza epatica o renale
- Malnutrizione
- Anoressia nervosa
- Depressione
- Tossicodipendenza da eroina

D I A G N O S I

Cause di discrepanza GH/IGF-I in acromegalia

IGF-I di norma e GH > 1 ng/ml	IGF-I patologiche e GH < 1 ng/ml
Anoressia nervosa	Pregressa RT
Malnutrizione	Problemi di dosaggio GH
Cirrosi epatica	Scarso numero di prelievi GH
Traumi	
Stress chirurgico	
Insufficienza respiratoria	
Neoplasie	
Insufficienza renale	
Diabete mellito tipo 1 scompensato	
Terapia estrogenica	

RT: radioterapia

D I A G N O S I

Acromegaly: An Endocrine Society Clinical Practice Guidelines

J Clin Endocrinol Metab 99: 3933–3951, 2014

Fatta la diagnosi di ipersecrezione di GH è raccomandato:

- Indagare sulla presenza di eventuali comorbilità (ipertensione, diabete, cardiopatie, apnee notturne)
- Ricercare eventuale neoplasia del colon
- Indagare l'eventuale presenza di gozzo
- Indagare l'eventuale ipopituitarismo associato

INQUADRAMENTO CLINICO

QJM: An International Journal of Medicine, 2017, 411–420

Complicanza	Alla diagnosi	Follow-up
Alterazione del metabolismo glucidico	Glicemia a digiuno e/o OGTT 75 gr per glicemia 0' e 120' HbA1c	6-12 MESI o SECONDO CLINICA 6-12 MESI o SECONDO CLINICA
Alterazioni del metabolismo lipidico	Quadro lipidico	12 MESI o SECONDO CLINICA
Alterazioni cardiovascolari	ECG Ecocardiogramma	ANNUALE ANNUALE Se patologico alla diagnosi o cattivo compenso ormonale
Alterazioni polmonari	Spirometria	SECONDO CLINICA
Poliposi colon	Colonscopia (> 40aa)	OGNI 3 ANNI (Se patologica alla diagnosi o cattivo compenso ormonale) ALTRIMENTI 5-10 ANNI (7)
Neoplasia mammaria	Come popolazione generale	Come popolazione generale
Neoplasia prostatica	Come popolazione generale	Come popolazione generale
Complicanze osteoarticolari Sindrome tunnel carpale	DXA (se ipogonadismo) Rx scheletro (se sintomatologia per osteoartrite) EMG	2-3 ANNI SECONDO CLINICA SECONDO CLINICA
Alterazioni del sonno/OSAS	Polisonnografia (se Epworth score patologico)	ANNUALE (Se patologica alla diagnosi o cattivo compenso ormonale)
Ipertensione arteriosa	Valutazione PAO ambulatoriale o ABPM/24 h	AD OGNI VISITA ANNUALE
Ateromasia carotidea	EcoDoppler TSA	SECONDO CLINICA
Visceromaglia	ETG tiroide ETG addome superiore	1-2 ANNI (se struma) ANNUALE (in terapia con SSA) o SECONDO CLINICA
Qualità della vita	Questionario AcroQOL/PASQ	ANNUALE

INQUADRAMENTO CLINICO

AcroQol

Questionario:

1. Mi mancano le forze nelle gambe
2. Mi sento brutto/a
3. Mi sento depresso/a
4. Mi vedo orribile nelle foto
5. Limito le uscite con gli/le amici/amiche per colpa del mio aspetto
6. Cerco di evitare le relazioni sociali
7. Mi vedo diverso/a quando mi guardo allo specchio
8. Noto un rifiuto da parte della gente per colpa della mia malattia
9. Ho dei problemi per svolgere le mie attività abituali (per esempio lavorare, studiare, svolgere le faccende domestiche, attività familiari o attività durante il tempo libero)
10. La gente mi guarda a causa del mio aspetto
11. Vi sono parti del mio corpo (naso, piedi, mani...) che sono troppo grandi
12. Ho dei problemi per fare cose con le mani, per esempio cucire o maneggiare utensili
13. La malattia influenza il mio rendimento nel lavoro o nelle mie attività abituali
14. Mi fanno male le articolazioni
15. Mi sento stanco/a
16. Russo di notte
17. Trovo difficoltà ad articolare le parole per colpa delle dimensioni della mia lingua
18. Ho problemi a mantenere delle relazioni sessuali
19. Mi sento una persona malata
20. I cambi fisici dovuti alla mia malattia condizionano la mia vita
21. Ho poco desiderio sessuale
22. Mi sento debole

Per ogni domanda esistono 5 possibili risposte a cui attribuire un punteggio, la cui somma va poi riportata.
Se la risposta alla singola domanda è:

- sempre/completamente d'accordo = 1
- la maggior parte del tempo/abbastanza d'accordo = 2
- qualche volta/nè d'accordo né in disaccordo = 3
- raramente/abbastanza in disaccordo = 4
- mai/completamente in disaccordo = 5

Malattie sistemiche: l'acromegalia

t e r a p i a

Dott. Giuseppe Citro

UOSD Diabetologia e Endocrinologia ASP Potenza

T E R A P I A

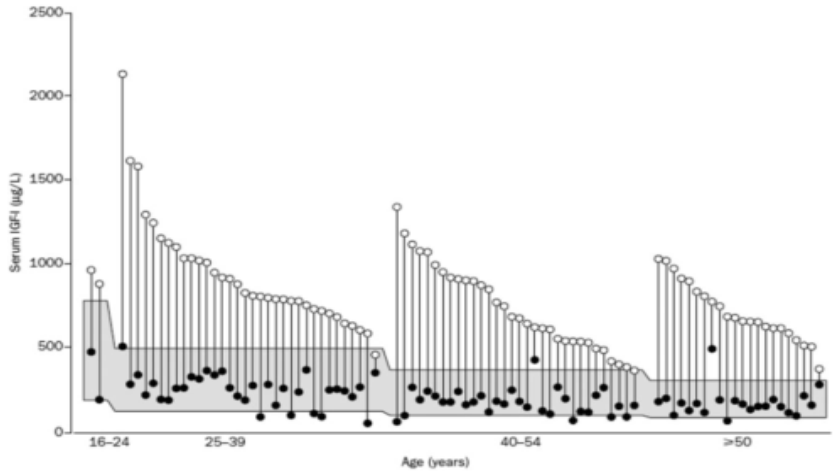
Obiettivi terapeutici

- Controllo biochimico della malattia
- Riduzione della massa tumorale
- Miglioramento della sintomatologia

T E R A P I A

Obiettivi terapeutici: controllo biochimico della malattia

- Normalizzazione dell'IGF-1 (?)
  variabilità tra differenti assays, fattori confondenti preanalitici e analitici, differenti range di riferimento

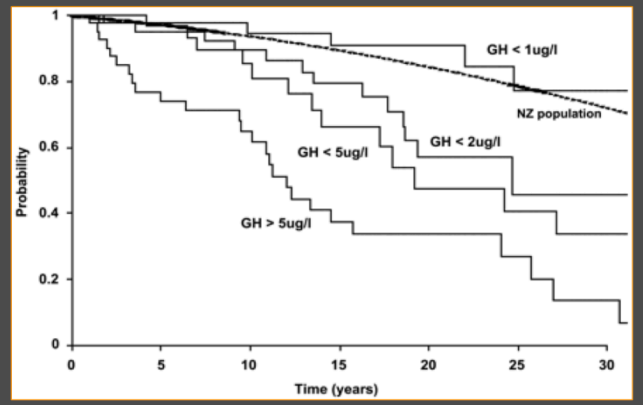


Baseline and lowest values of individual serum insulin-like growth factor-1 concentrations achieved in 90 patients treated for 12 months or more with daily pegvisomant
The shaded area represents the age-adjusted normal range for insulin-like growth factor-1

QJM: An International Journal of Medicine, 2017, 411–420

- Soppressione dei livelli di GH
  nadir del GH dopo OGTT < 1 mcrg/L o < 0,4 mcrg/L con metodi ultrasensibili

Probability of survival in acromegaly according to serum GH concentration at last review after treatment (curves different at *P* < 0.0001, by log rank). The *dotted line* represents the probability of survival for the New Zealand population.



Holdaway et al., *J Clin Endocrinol Metab* 2004

Obiettivi terapeutici: riduzione della massa tumorale

- Significativa se si riduce del 20 − 25 %

VOLUME ?
Differenti tecniche di misurazione
Forma del tumore
Variabilità legata all'operatore

SINGOLO DIAMETRO ?
Più semplice da misurare
Minore variabilità intra e interoperatore

T E R A P I A

Obiettivi terapeutici: controllo clinico della malattia

Le principali cause di mortalità sono rappresentate dalle comorbilità cardiovascolari e respiratorie, cui dà un importante contributo l'anomalo metabolismo dei carboidrati

Pertanto è raccomandato gestire aggressivamente l'ipertensione, l'ipertrofia cardiaca, il diabete, le apnee notturne e l'osteopatia, per prevenire l'eccesso di mortalità nell'acromegalico

T E R A P I A

Acromegaly treatment outcomes

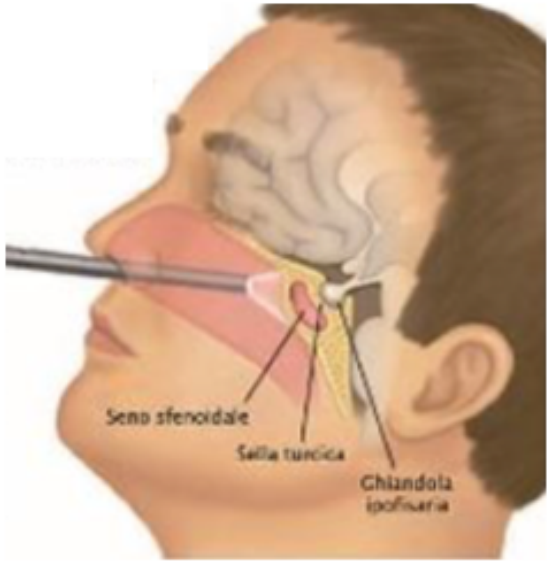
Outcome	Criteria[a]	Management
Active disease	Random GH >1 μg/liter and nadir GH after OGTT ≥0.4 μg/liter	Periodic MRI
	Elevated IGF-I	Monitor and actively treat comorbidities
	Clinically active	Actively treat or change treatment
Controlled disease	Random GH <1 μg/liter or nadir GH after OGTT <0.4 μg/liter	Periodic but less frequent MRI[b]
	Age-sex normalized IGF-I	No change to current treatment; consider reducing SRL dose

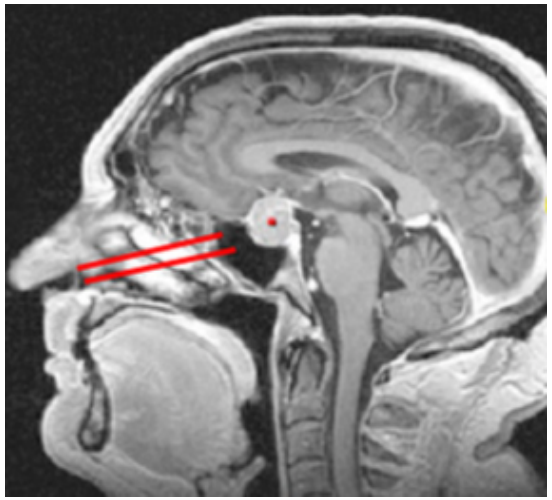
MRI, Magnetic resonance imaging.

[a] Strong recommendations: assessment of GH during an OGTT and total IGF-I after surgery; random GH for patients on SRLs; if discrepant biochemical results, GH sampling three to five times over 2 h; always use reliable standardized assays and ultrasensitive assay for IGF-I and GH measurement.

[b] For example, every 2–3 yr.

T E R A P I A
Chirurgia





Congestione nasale
Sinusite
Epistassi

Emorragia
Rinoliquorrea
Meningite
Ictus
Disturbi visivi
Diabete insipido
Ipopituitarismo

Mortalità operatoria < 0,5 %

Horm Res 2000; 53:71–5.

FATTORI ASSOCIATI ALL'INSUCCESSO CHIRURGICO:
Dimensioni del tumore
Estensione extra-sellare
Elevati livelli pre-operatori di GH

Clinical follow-up and outcome data of 57 patients with surgically treated GH-secreting pituitary adenomas

Follow-up state (12–88 months postop)		
Remission[a]	40/57	70.2
Persistence[b]	14/57	24.6
Recurrence	1/42	2.4
Adjuvant treatment		
Medical therapy	13/16	
Dopamine agonist	4/13	
Somatostatin analog	8/13	
Both	1/13	
Focused radiotherapy (γ-knife)	10/16	

[a] Two patients not cured by surgery alone achieved remission after γ-knife radiosurgery, so that ultimately 42 of 57 (73.7%) were in remission.
[b] After surgery, 16 patients had persistent acromegaly; 2 subsequently achieved remission after γ-knife radiosurgery.

Surgical Management of GH-Secreting Pituitary Adenomas: An Outcome Study Using Modern Remission Criteria
J Clin Endocrinol Metab 86: 4072–4077, 2001

T E R A P I A
Medica

La terapia medica ha un ruolo importante come trattamento adiuvante in caso di chirurgia non risolutiva

È di prima scelta quando la chirurgia non è praticabile

ANALOGHI RECETTORIALI DELLA SOMASTOSTATINA

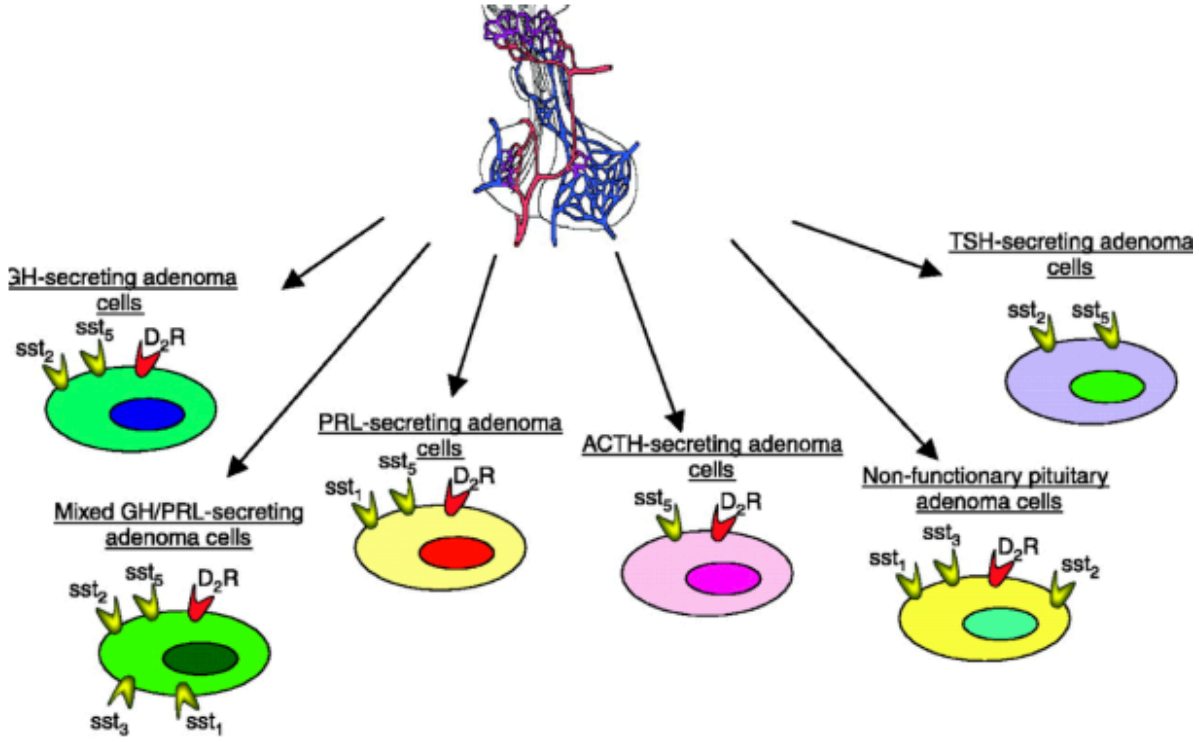
ANTAGONISTI RECETTORIALI DEL GH

DOPAMINO-AGONISTI

T E R A P I A
Medica: analoghi recettoriali della somatostatina

Tissue-specific expression of somatostatin receptor genes

	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Brain					
Cortex	++++	++++	++	++	++
Striatum	±	+	++	+	++
Hippocampus	++	++	++	++	++
Amygdala	+++++	++	+++	+	++
Olfactory bulb	++	++	++	++	++
Thalamus	++	+	+	±	++
Hypothalamus	++	++	+	±	+++++
POA	+	+	+	+	+++++
Cerebellum	±	±	+++++	–	–
Midbarin	+	+	+	±	++
Pons	+	+	+	±	–
Periphery					
Pituitary	++	+++	++	+	++++
Pancreas	–	+	–	–	–
Islets	++	++++	+	++	+
Stomach	+	+	+	+	–
Small intestine	++	–	+	+	++
Liver	–	–	++	–	–
Lung	–	–	–	++	–
Kidney	–	+	+	+	–
Heart	+	–	+	++++	–
Spleen	++	+	++++	+	+
Adrenals	+	++++	+	–	–

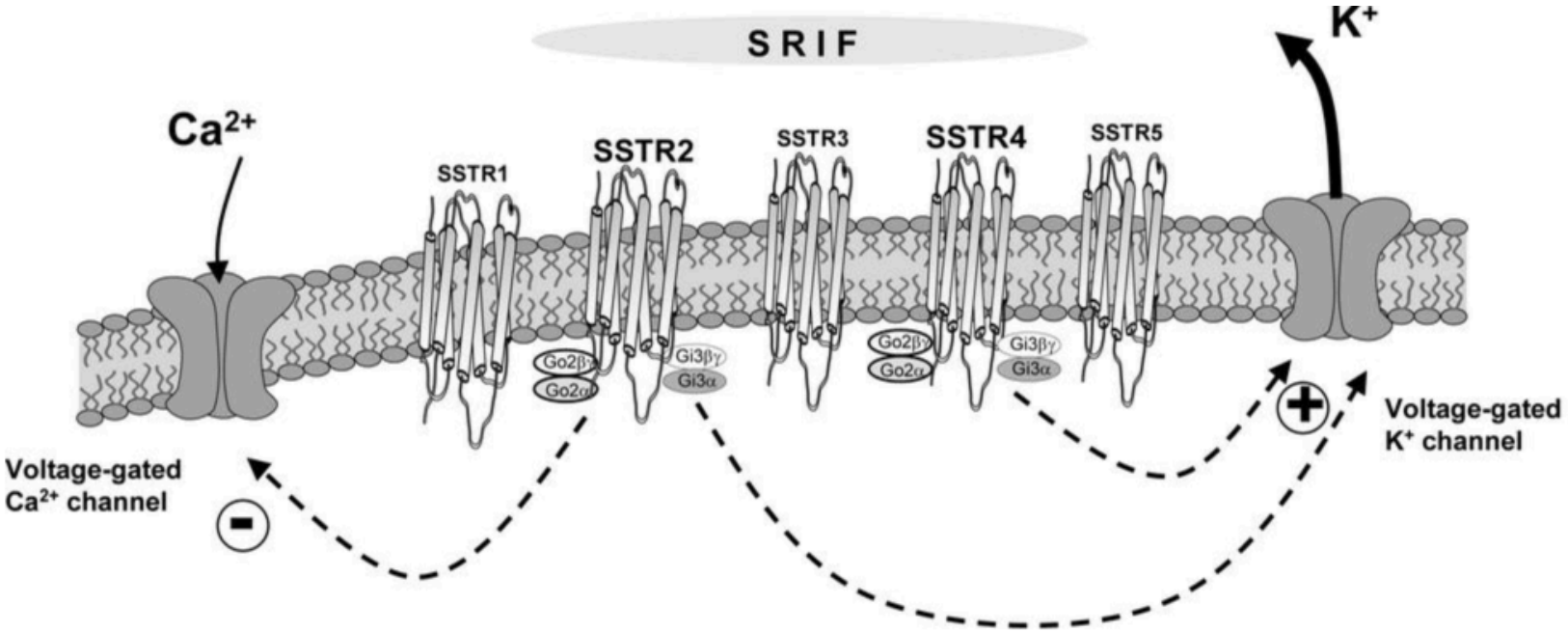


Distribution of somatostatin and D_2 dopamine receptors in the different type of pituitary adenomas.

Journal of molecular endocrinology 2009; 42: 361-370

T E R A P I A

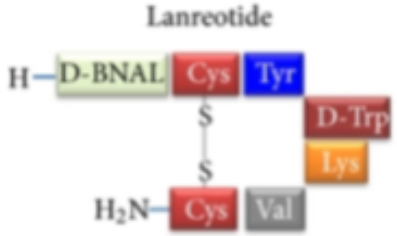
Medica: analoghi recettoriali della somatostatina

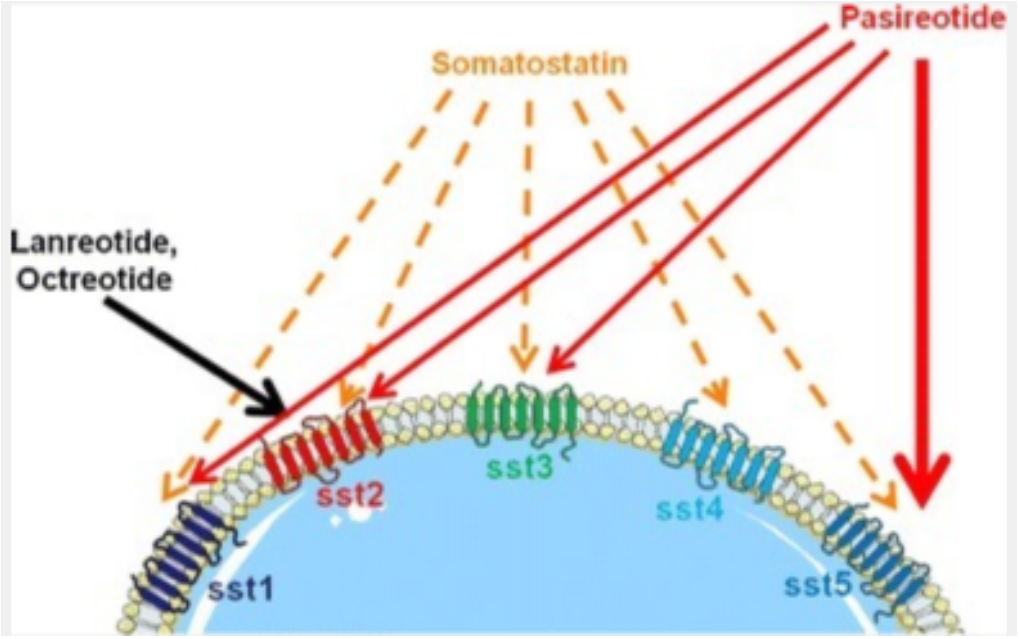


Signalling pathways employed by SRIF via *SSTRs on voltage-gated Ca^{2+} and K^{+} channels. When SRIF binds to SSTRs, SSTR2 and 4 activate voltage-gated K^{+} channels and only SSTR2 inactivates voltage-gated Ca^{2+} channels to increase K^{+} outflow and decrease Ca^{2+} influx, which subsequently leads to inhibition of GH secretion*.

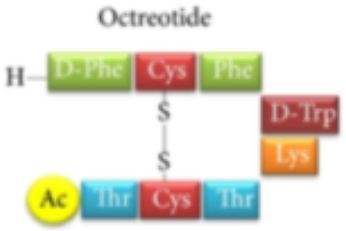
T E R A P I A

Medica: analoghi recettoriali della somatostatina

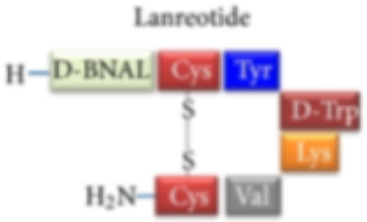




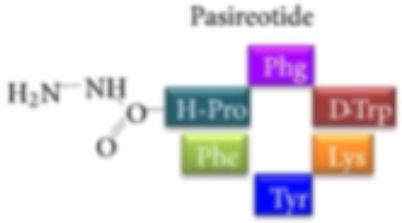
T E R A P I A
Medica: analoghi recettoriali della somatostatina



OCTREOTIDE LAR: intramuscolo ogni 28 giorni
iniziando da 20 mg e aumentando, se necessario,
fino a 40 mg



LANREOTIDE: Microsfere depot intramuscolo ogni 7 − 14 giorni
oppure soluzione acquosa (Autogel) sottocute ogni 4 − 6 settimane
La dose iniziale è di 90 mg/mese aumentabili fino a 120 mg/mese

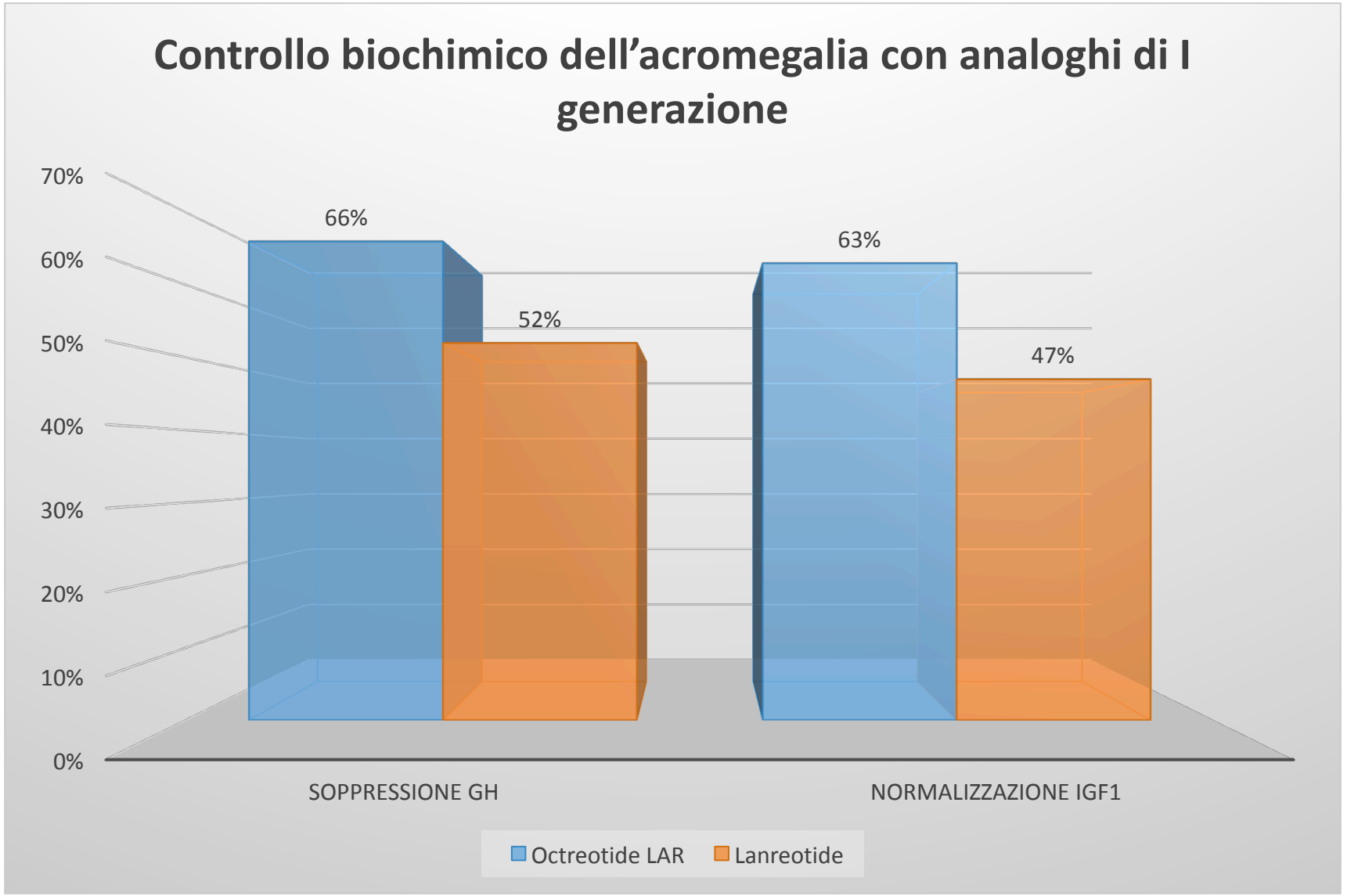


PASIREOTIDE: intramuscolo ogni 4 settimane
iniziando da 40 mg e aumentando, se necessario, fino a 60 mg

T E R A P I A

Medica: analoghi recettoriali della somatostatina

controllo biochimico



T E R A P I A

Medica: analoghi recettoriali della somatostatina

controllo biochimico

	% of subjects meeting efficacy criteria		Mean GH levels		Mean IGF-I levels	
	GH	IGF-I normalization	Pretherapy	On therapy	Pretherapy	On therapy
Octreotide LAR						
Unselected (n = 126)	54 ± 0.002[a]	63 ± 0.002[b]	15.8 ± 2.9	4.1 ± 0.8	601 ± 35	330 ± 75
Preselected (n = 486)	58 ± 0.003	68 ± 0.003	10.2 ± 2.3	2.3 ± 1.1	735 ± 48	313 ± 35
All subjects (n = 612)	57 ± 0.05[c]	67 ± 0.05[d]	12.6 ± 3.9	3.2 ± 1.53	644 ± 66	327 ± 30.5
Lanreotide SR						
Unselected (n = 609)	48 ± 0.002	42 ± 0.002	15.1 ± 6.0	5.3 ± 2.4	689 ± 95	432 ± 97
Preselected (n = 305)	50 ± 0.005	56 ± 0.003	19.7 ± 4.0	3.5 ± 0.5	735 ± 48	321 ± 24
All subjects (n = 914)	48 ± 0.04	47 ± 0.03	16.9 ± 3.2	5.9 ± 1.3	741 ± 51	442 ± 30
Octreotide (sc) (primary therapy only)						
All subjects (n = 266) (unselected, n = 252, preselected, n = 14)	53 ± 0.05	54 ± 0.05	40.8 ± 4.3	8.76 ± 1.0	693 ± 66	288 ± 41

Data represent mean ± SE. Unselected, Subjects who had not been selected for somatostatin analog responsiveness before study entry; Preselected, subjects who were selected for somatostatin analog responsiveness before study entry. Units for mean GH are micrograms per liter and for mean IGF-I are nanograms per milliliter.

[a] $P = 0.016$ *vs.* lanreotide SR.

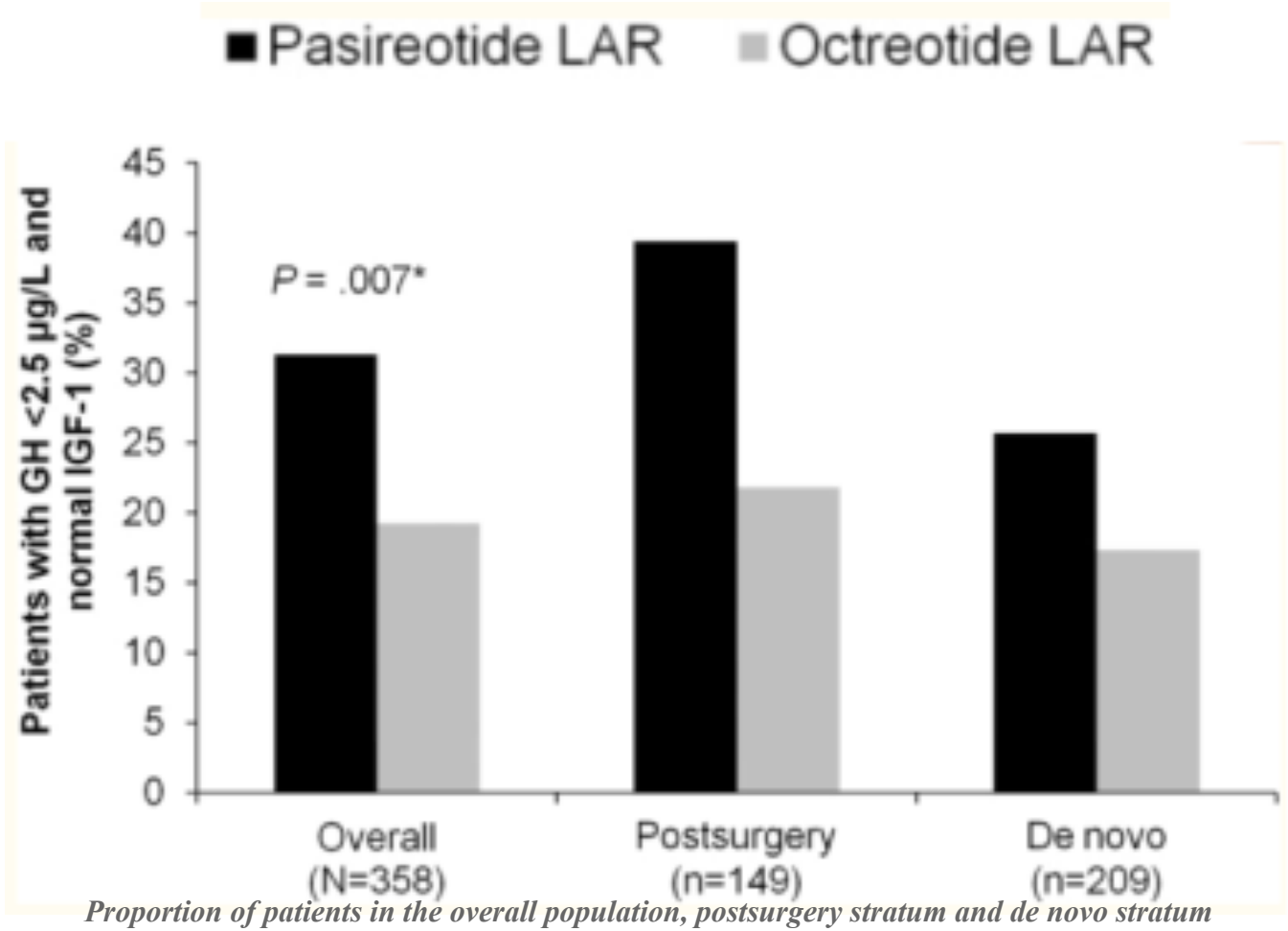
[b] $P = 0.007$ *vs.* lanreotide SR.

[c] $P = 0.01$ *vs.* lanreotide SR.

[d] $P = 0.0009$ *vs.* lanreotide SR.

J Clin Endocrinol Metab, August 2005, 90(8):4465–4473

T E R A P I A
Medica: analoghi recettoriali della somatostatina
controllo biochimico



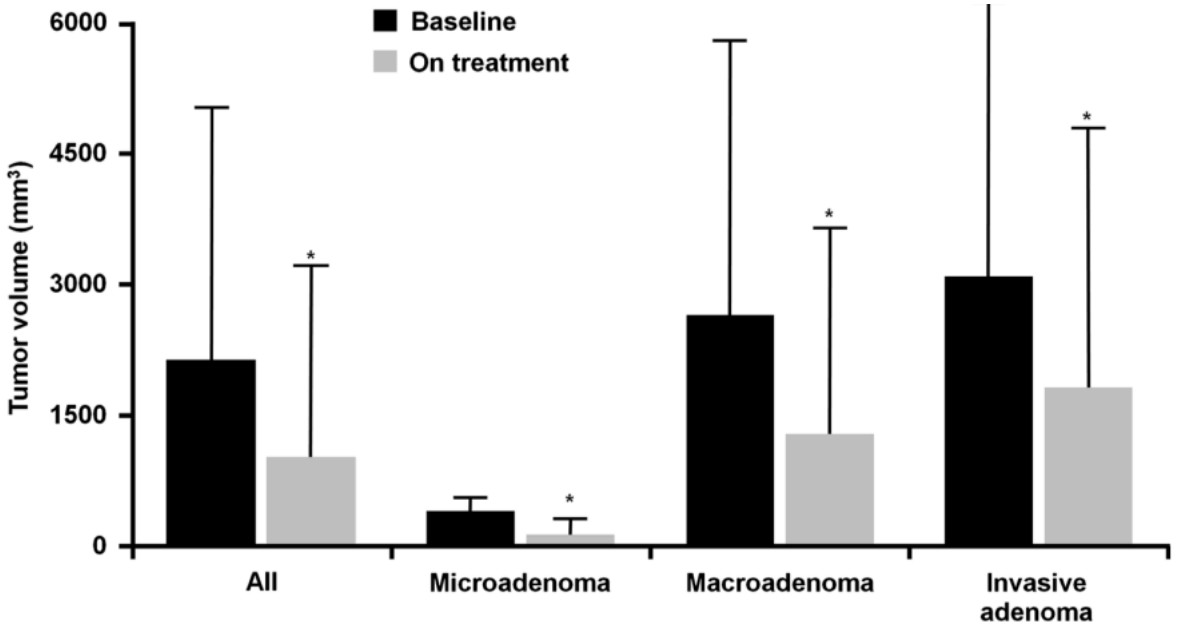
*Proportion of patients in the overall population, postsurgery stratum and de novo stratum with GH <2.5 µg/L and normal IGF-1 after 12 months of treatment with pasireotide LAR or octreotide LAR. *, P = .007 pasireotide LAR vs octreotide LAR in the overall population*

Pasireotide Versus Octreotide in Acromegaly: A Head-to-Head Superiority Study

JCEM 2014 Mar; 99(3): 791–799

T E R A P I A

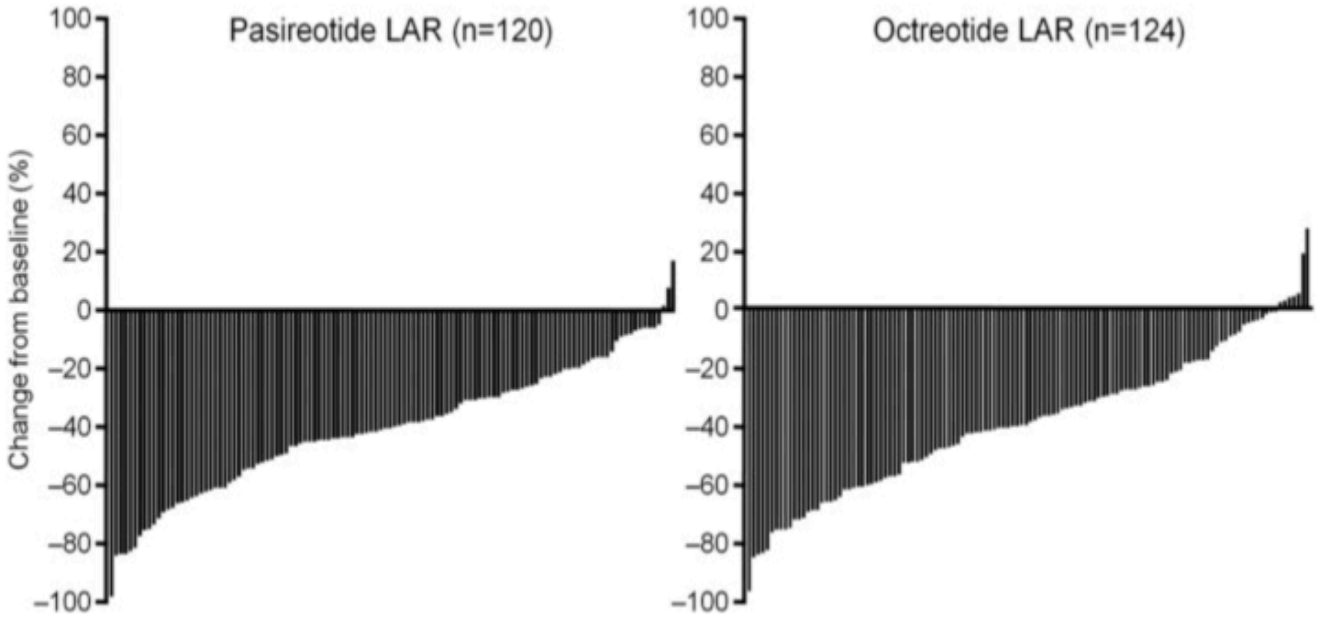
Medica: analoghi recettoriali della somatostatina riduzione della massa tumorale



Tumor size before and during first-line octreotide LAR treatment, evaluated in the whole series and according to tumor type

Colao AM, Auriemma RS, Pivonello R. The effects of somatostatin analogue therapy on pituitary tumor volume in patients with acromegaly. Pituitary 2016; 19:210–21.

T E R A P I A
Medica: analoghi recettoriali della somatostatina
riduzione della massa tumorale

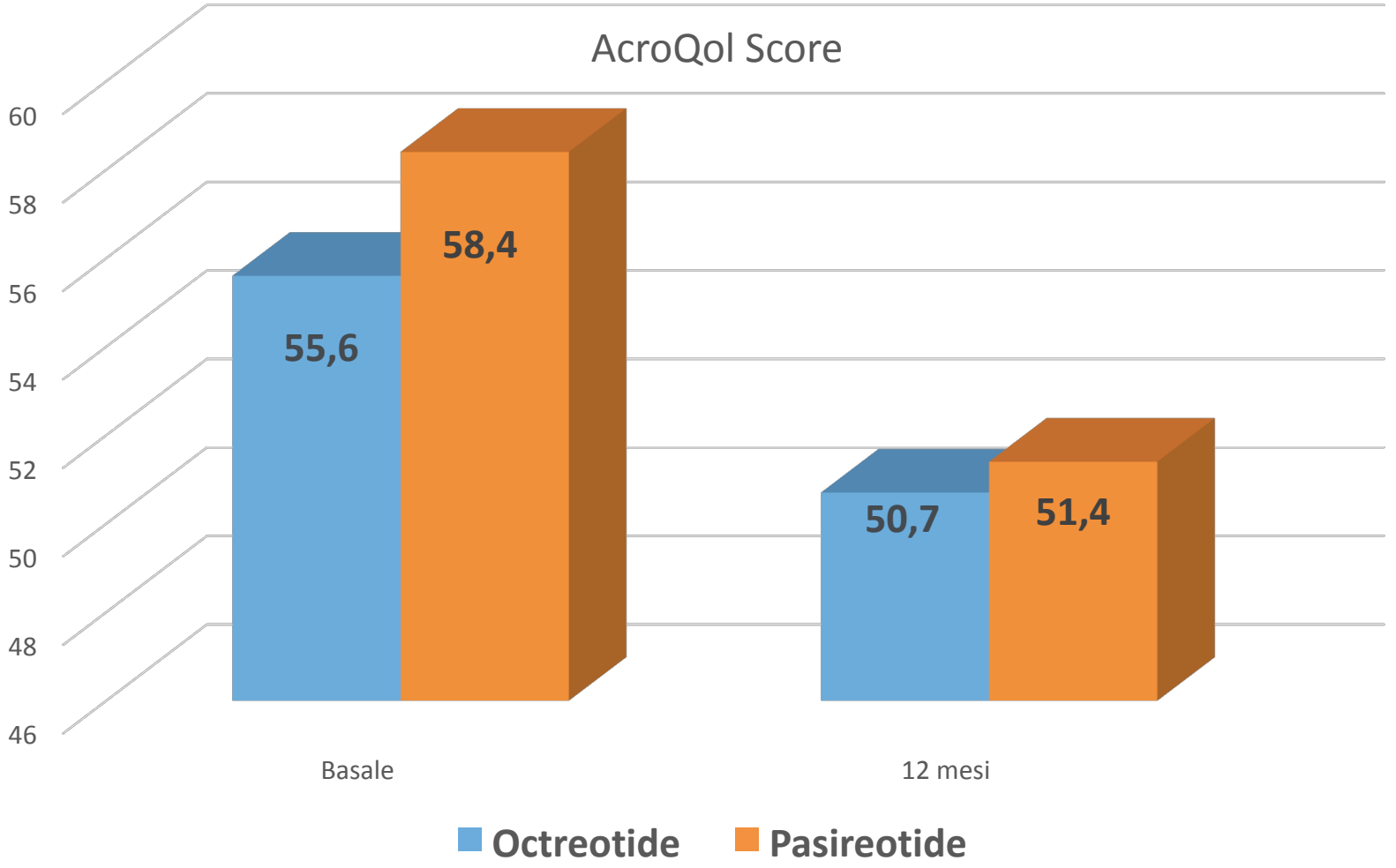


Riduzione significativa (> 20%) del volume tumorale si ottiene nell'81% del gruppo pasireotide e nel 75% del gruppo octreotide. Risultati simili si hanno sia nei soggetti trattati dopo la chirurgia che in quelli de novo.

Pasireotide Versus Octreotide in Acromegaly: A Head-to-Head Superiority Study

J Clin Endocrinol Metab. 2014 Mar; 99(3): 791–799.

T E R A P I A
Medica: analoghi recettoriali della somatostatina
sintomatologia



Pasireotide Versus Octreotide in Acromegaly: A Head-to-Head Superiority Study

J Clin Endocrinol Metab. 2014 Mar; 99(3): 791–799

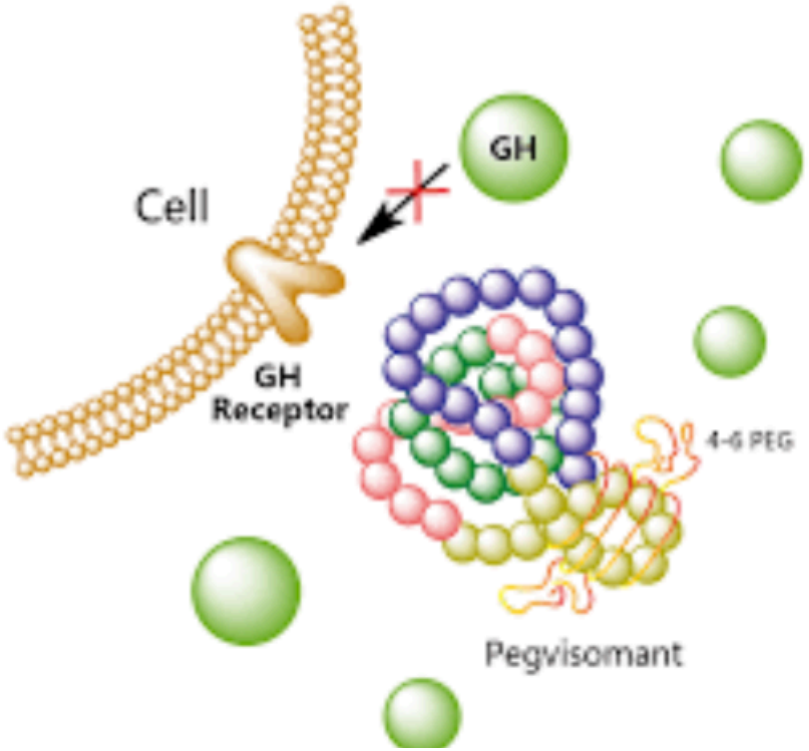
T E R A P I A

Medica: analoghi recettoriali della somatostatina

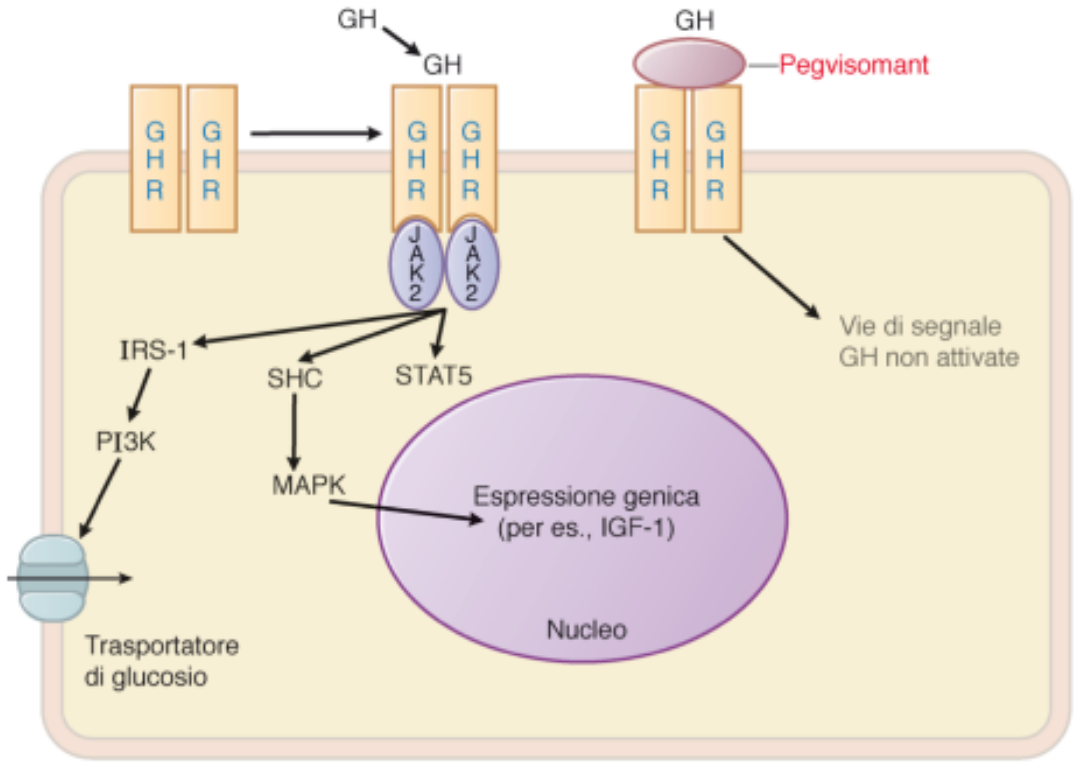
effetti collaterali

	Pasireotide LAR, n = 178	Octreotide LAR, n = 180
Diarrhea	70 (39.3)	81 (45.0)
Hyperglycemia	51 (28.7)	15 (8.3)
Cholelithiasis	46 (25.8)	64 (35.6)
Diabetes mellitus	34 (19.1)	7 (3.9)
Headache	33 (18.5)	46 (25.6)
Abdominal pain	32 (18.0)	40 (22.2)
Alopecia	32 (18.0)	35 (19.4)
Nasopharyngitis	28 (15.7)	28 (15.6)
Nausea	24 (13.5)	39 (21.7)
Increased blood creatine phosphokinase	23 (12.9)	21 (11.7)
Abdominal distension	21 (11.8)	21 (11.7)
Arthralgia	17 (9.6)	22 (12.2)
Fatigue	17 (9.6)	18 (10.0)
Dizziness	17 (9.6)	19 (10.6)
Back pain	14 (7.9)	20 (11.1)

T E R A P I A
Medica: pegvisomant

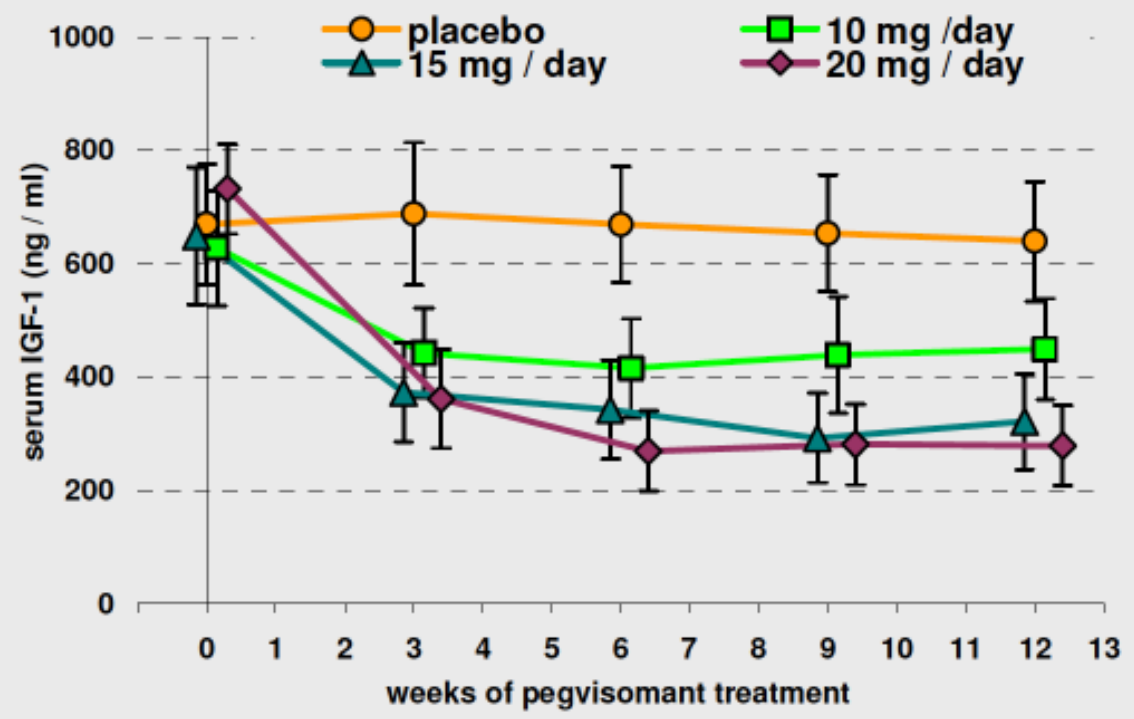


Analogo del GH in cui la pegylazione ne riduce la clearance renale, mentre le differenze aminoacidiche ne aumentano l'affinità recettoriale, che impedisce la dimerizzazione del recettore e la trasduzione del segnale



Una iniezione sottocute al giorno
10 – 30 mg / die

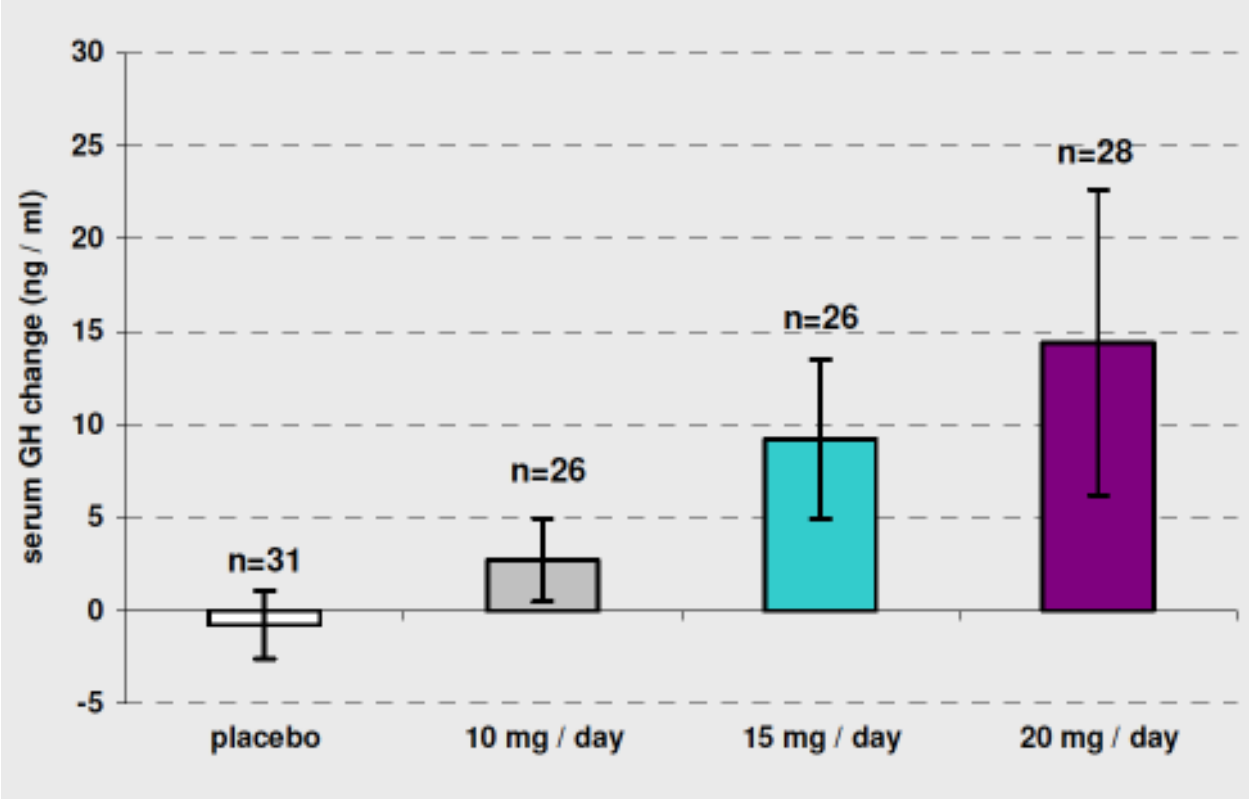
T E R A P I A
Medica: pegvisomant
controllo biochimico



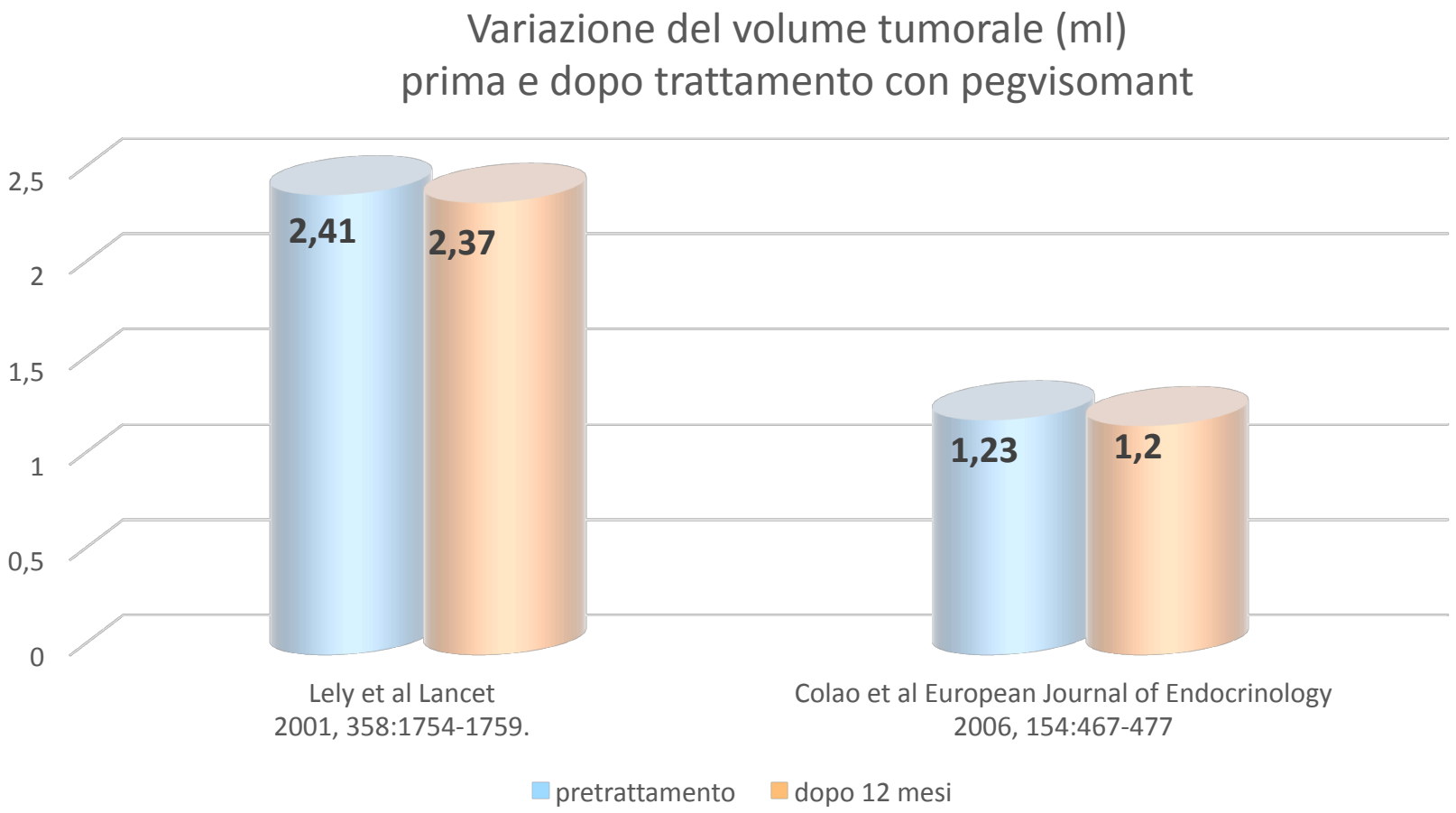
A 12 settimane di trattamento si ottiene la normalizzazione dei livelli di IGF 1 nel 10% - 38% - 75% - 82% rispettivamente nel gruppo placebo − pegvisomant 10 mg − 15 mg e 20 mg

Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant.
The New England Journal of Medicine 2000, 342:1171-1177

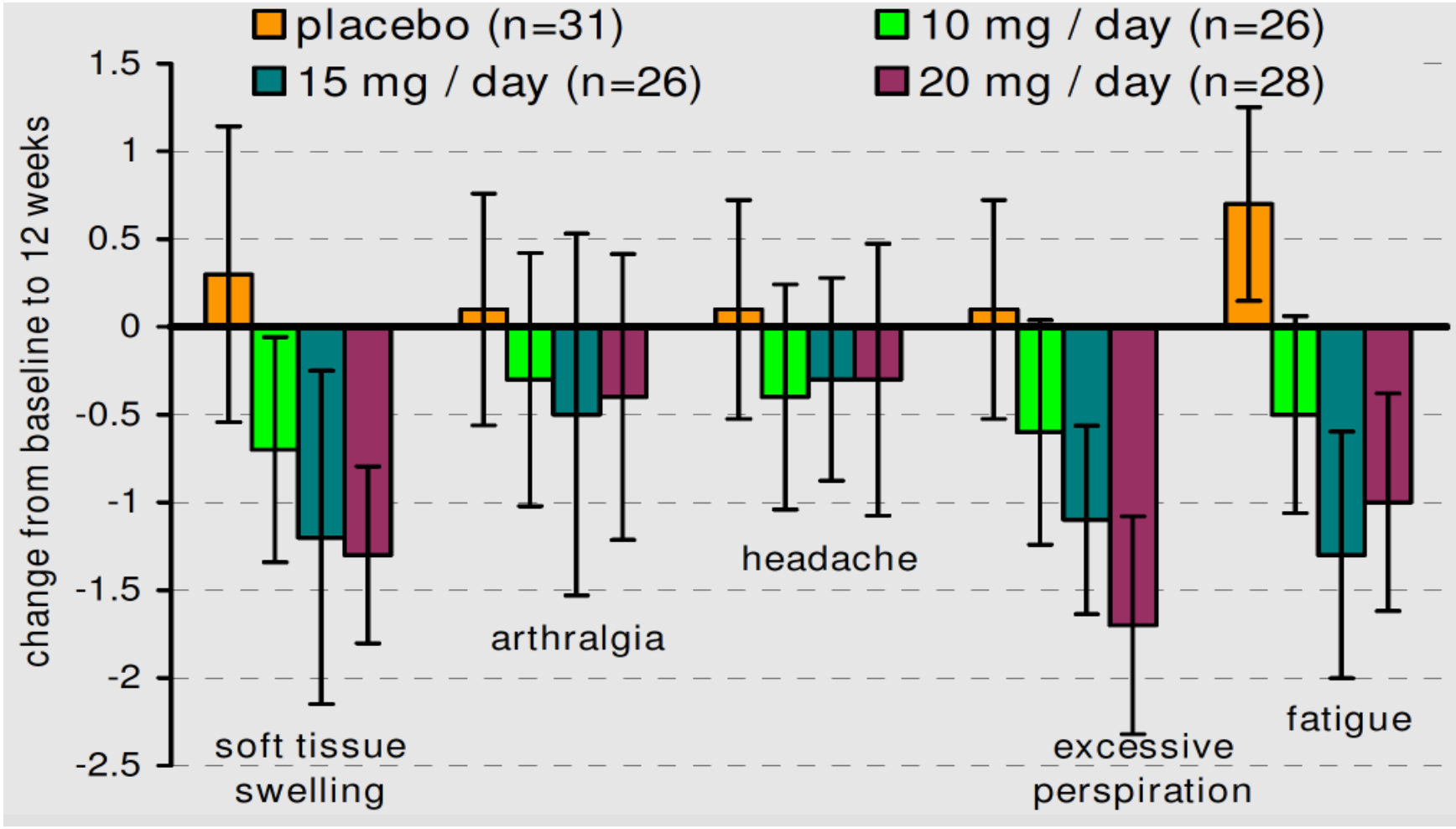
T E R A P I A
Medica: pegvisomant
controllo biochimico



T E R A P I A
Medica: pegvisomant
massa tumorale



T E R A P I A
Medica: pegvisomant
sintomatologia



Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant.

The New England Journal of Medicine 2000, 342:1171-1177

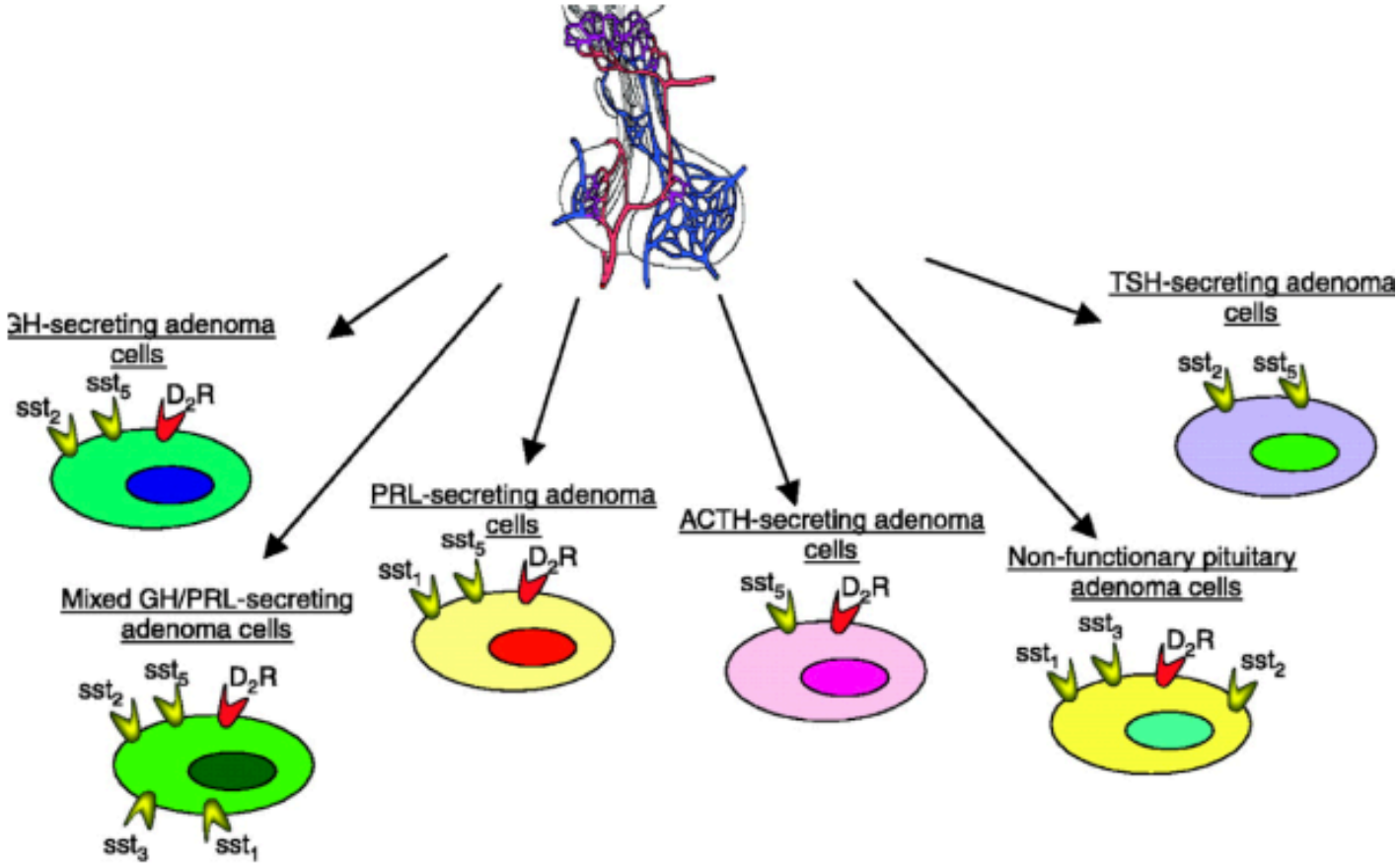
T E R A P I A
Medica: pegvisomant
effetti collaterali

Adverse event	Trainer 2000[7] Placebo n = 32	Trainer 2000[7] PEG 10mg/d n = 26	Trainer 2000[7] PEG 15mg/d n = 26	Trainer 2000[7] PEG 20mg/d n = 28
Infections	5* (16%)	5* (19%)	4* (15%)	5* (18%)
Headache	4 (12%)	3 (12%)	2 (8%)	3 (11%)
Injection-site reaction	0 (0%)	2 (8%)	1 (4%)	3 (11%)
Pain	2 (6%)	2 (8%)	1 (4%)	4 (14%)
Diarrhoea	1 (3%)	1 (4%)	0 (0%)	4 (14%)
Nausea	1 (3%)	0 (0%)	2 (8%)	4 (14%)
Flatulence	0 (0%)	0 (0%)	1 (4%)	3 (11%)

Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant.

The New England Journal of Medicine 2000, 342:1171-1177

T E R A P I A
Medica: dopamino-agonisti



Distribution of somatostatin and D_2 dopamine receptors in the different type of pituitary adenomas.

Journal of molecular endocrinology 2009; 42: 361-370

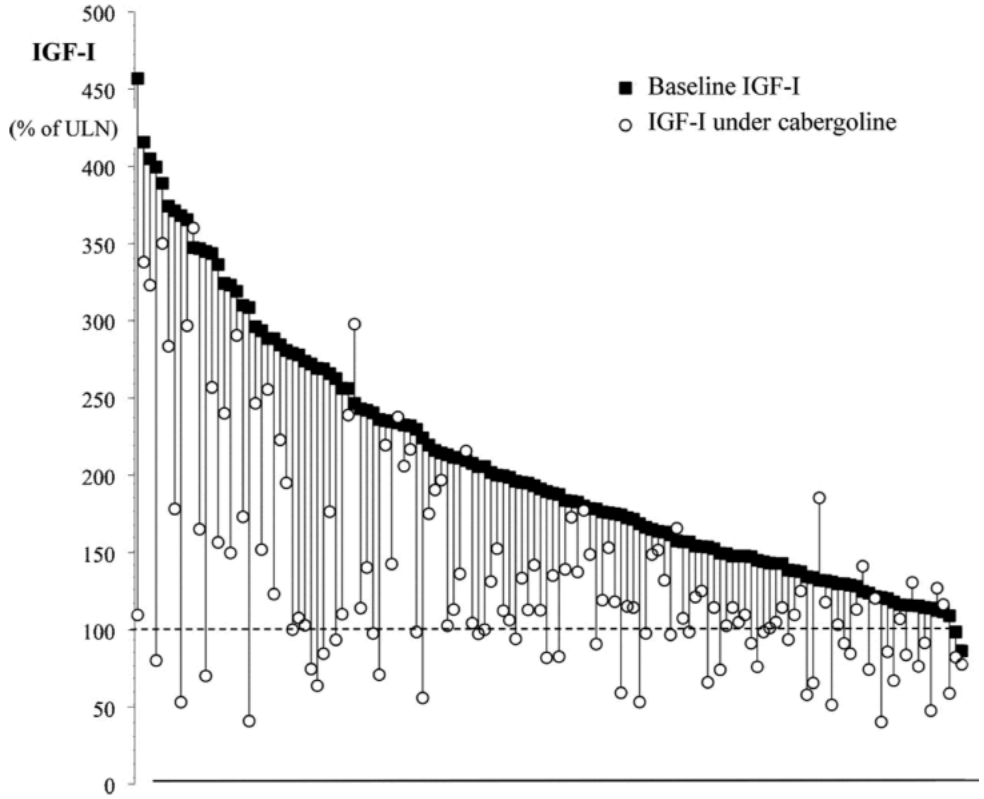
T E R A P I A
Medica: dopamino-agonisti
bromocriptina

Uso limitato per la frequenza di effetti collaterali: sintomi gastrointestinali − letargia − ipotensione ortostatica

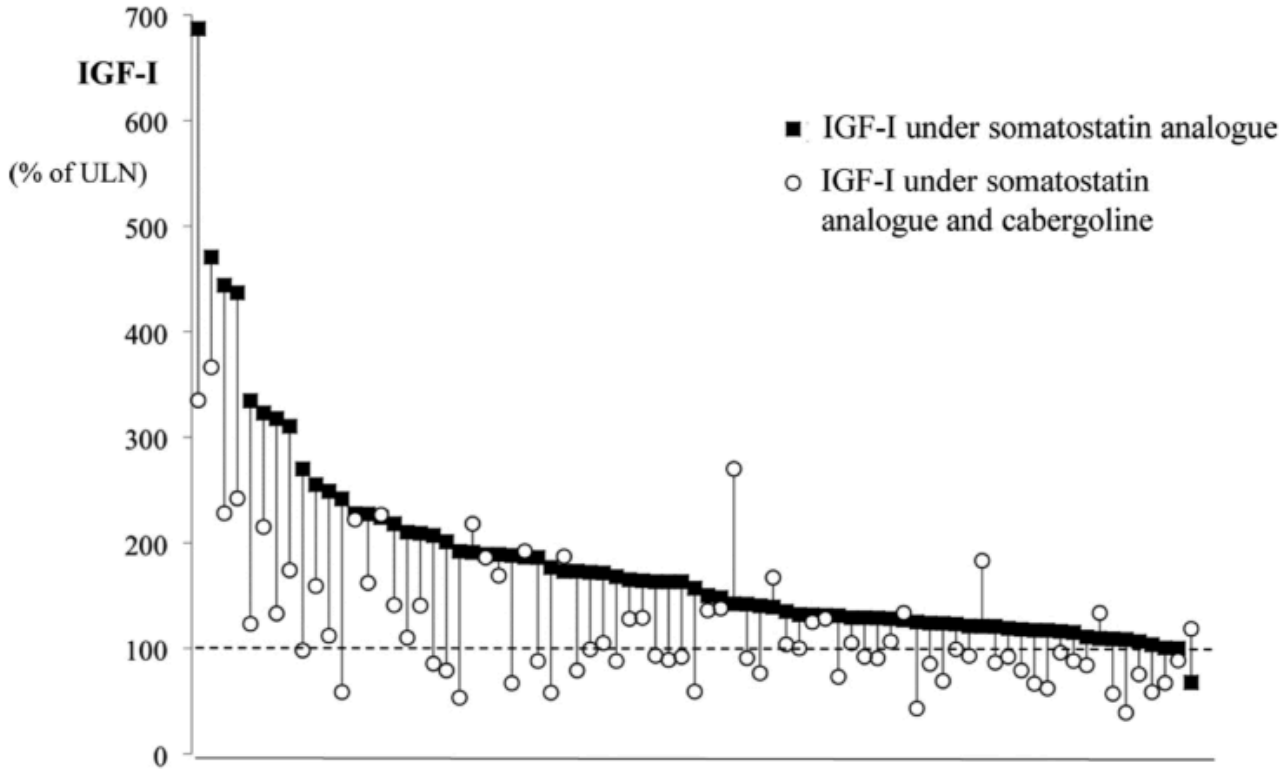
Normalizza il GH e l'IGF1 in solo il 10% dei casi di adenoma GH-secernente

Treatment of acromegaly with dopamine agonists
Endocrinol Metab Clin North Am 1992; 21:713–35

T E R A P I A
Medica: dopamino-agonisti
cabergolina



Individual IGF-I levels, expressed as a percentage of the age-adjusted ULN range before (*black squares*) and after treatment with cabergoline (*open circles*) in patients with acromegaly



Individual IGF-I levels, expressed as a percentage of the age-adjusted ULN range during treatment with somatostatin analogs alone (*black squares*) and after cabergoline adjunction (*open circles*) in patients with acromegaly.

Place of Cabergoline in Acromegaly: A Meta-Analysis

J Clin Endocrinol Metab 96: 1327–1335, 2011

T E R A P I A

Medica: dopamino-agonisti

cabergolina

POSSIBILI EFFETTI COLLATERALI

Nausea

Cefalea

Disturbi dell'umore

Vertigini

Congestione nasale

Valvulopatie cardiache, descritte in pazienti trattati con alte dosi (Parkinson), non si manifestano con i dosaggi usati nella terapia dell'acromegalia (1 – 3,5 mg/settimana)

T E R A P I A

Medica: dopamino-agonisti

cabergolina

Acromegaly: An Endocrine Society Clinical Practice Guideline

J Clin Endocrinol Metab 99: 3933–3951, 2014

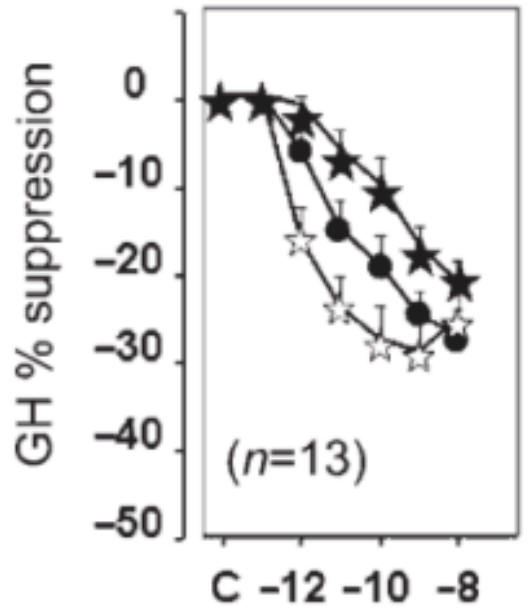
In a patient with only modest elevations of serum IGF-1 and mild signs and symptoms of GH excess, we suggest a trial of a dopamine agonist, usually cabergoline, as the initial adjuvant medical therapy.

T E R A P I A

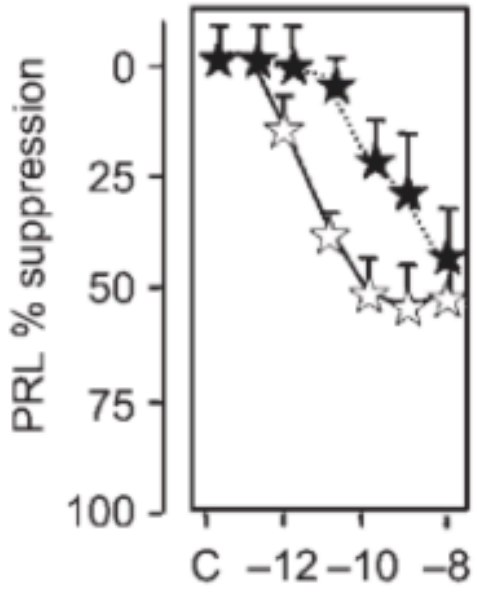
Medica: molecole chimeriche (dopastatin)

Efficacy of chimeric molecules directed towards multiple somatostatin and dopamine receptors on inhibition of GH and prolactin secretion from GH-secreting pituitary adenomas classified as partially responsive to somatostatin analog therapy

European Journal of Endocrinology (2005) **153** 135–141



★ Octreotide ● BIM - 23244 ☆ BIM - 23A387



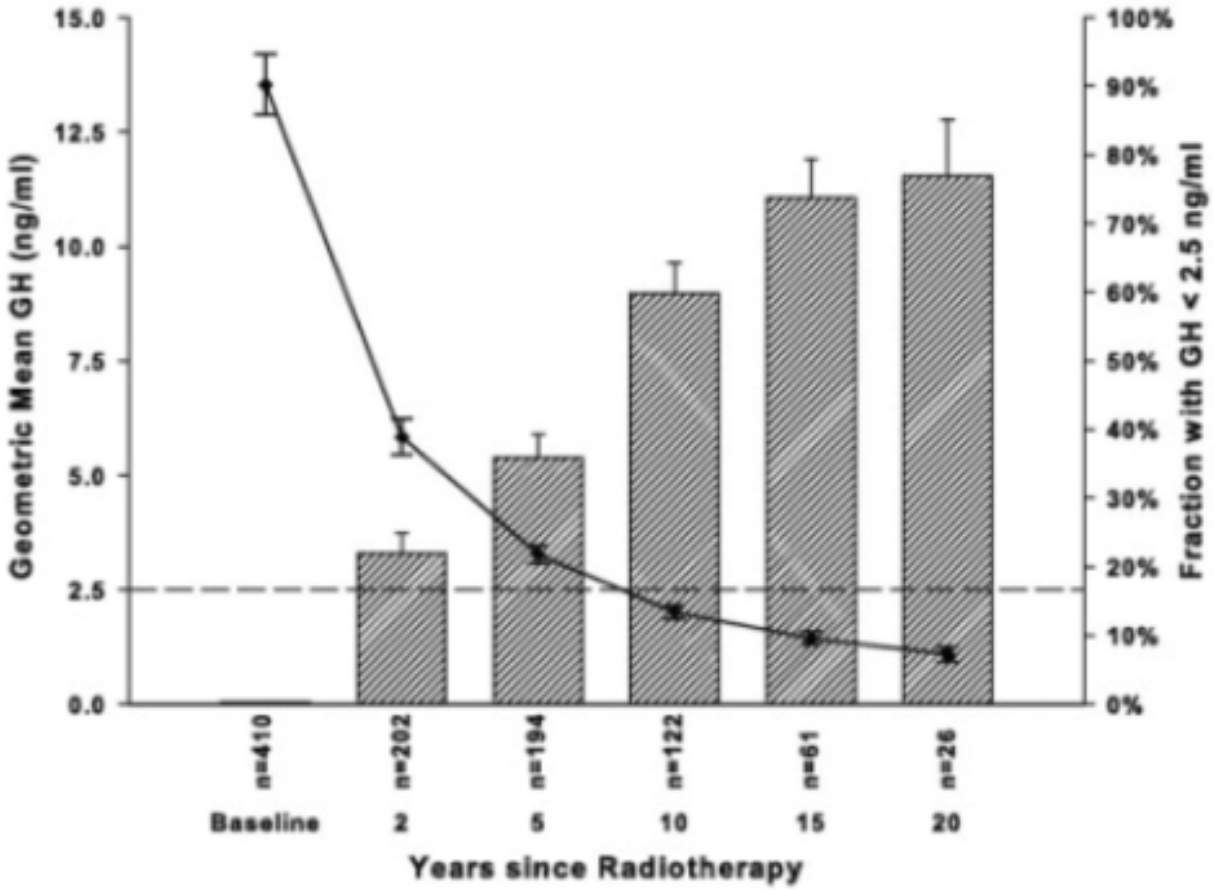
★ Octreotide ☆ BIM - 23A387

T E R A P I A

Radioterapia

È usata come terapia adiuvante in caso di malattia persistente dopo trattamento chirurgico e medico, oppure se tali trattamenti non sono tollerati

T E R A P I A
Radioterapia
controllo biochimico



J Clin Endocrinol Metab 2006; 91:1239–45.

I livelli di GH si riducono da 13,5 a 5,3 ng/ml dopo 2 anni, per scendere a 2 ng/ml dopo 10 anni e a 1,1 ng/ml a 20 anni dalla terapia

T E R A P I A
Radioterapia
riduzione della massa tumorale

The role of stereotactic radiosurgery in the multimodal management of growth hormone–secreting pituitary adenomas

Neurosurg Focus 29 (4):E11, 2010

The authors reviewed the growing body of literature concerning the role of radiosurgical procedures in the treatment armamentarium of acromegaly, and identified more than 1350 patients across 45 case series.

the authors report that radiosurgery offers true hormonal normalization in 17% to 82% of patients and tumor growth control in 37% to 100% of cases across all series, while minimizing adverse complications.

GLI AUTORI ATTRIBUISCONO L'AMPIA VARIABILITA' DEI RISULTATI
ALL'USO DI DIFFERENTI SCHEMI DI TRATTAMENTO E DI DEFINIZIONE
DI REMISSIONE

T E R A P I A

Radioterapia

effetti collaterali

Long-Term Follow-Up Results of Postoperative Radiotherapy in 36 Patients with Acromegaly

J Clin Endocrinol Metab **85:** 2476–2482, 2000

Development of hypopituitarism in patients with acromegaly up to 139 ± 12 months after radiotherapy

Follow-up	TSH-axis substitution No. of patients[b]	ACTH-axis substitution No. of patients[b]	LH/FSH-axis substitution No. of male patients[b]	LH/FSH-axis deficiency No. of female patients[c]	GH-reserve (ITT) insufficient No. of patients	Substitution[a] No. of patients
Postoperative	2/36 (6%)	4/36 (11%)	1/23 (4%)	2/13 (15%)		4/36 (11%)
0–5 yr After radiotherapy	3/34 (9%)	5/32 (16%)	8/22 (36%)		8/36 (22%)	10/35 (29%)
6–10 yr After radiotherapy	9/27 (33%)	8/27 (30%)	9/17 (53%)		12/29 (41%)	15/28 (54%)
11–15 yr After radiotherapy	7/18 (39%)	6/18 (33%)	7/9 (78%)		9/19 (47%)	10/18 (56%)
>15 yr After radiotherapy	5/11 (45%)	5/11 (45%)	5/6 (83%)		7/13 (54%)	7/12 (58%)
Final follow-up	12/34 (35%)	10/32 (31%)	11/22 (50%)	4/8 (50%)	13/36 (36%)	18/35 (51%)

[a] Requirement of substitution for one or more pituitary deficiencies after radiotherapy. One patient substituted completely after surgery is excluded.

[b] Development of substitution after radiotherapy is analyzed after exclusion of patients with postoperative deficiency.

[c] Female LH/FSH deficiency is evaluated dependent on pre/postmenopausal status (see *Subjects and Methods*) and only assessed at the end of follow-up and postoperatively. Three female patients not evaluated because of use of contraceptive drugs.

T E R A P I A
Radioterapia
effetti collaterali

Long-Term Follow-Up Results of Postoperative Radiotherapy in 36 Patients with Acromegaly

J Clin Endocrinol Metab **85:** 2476–2482, 2000

Aumentato rischio di secondo tumore

Ictus

Neurite ottica

Deficit di nervi cranici

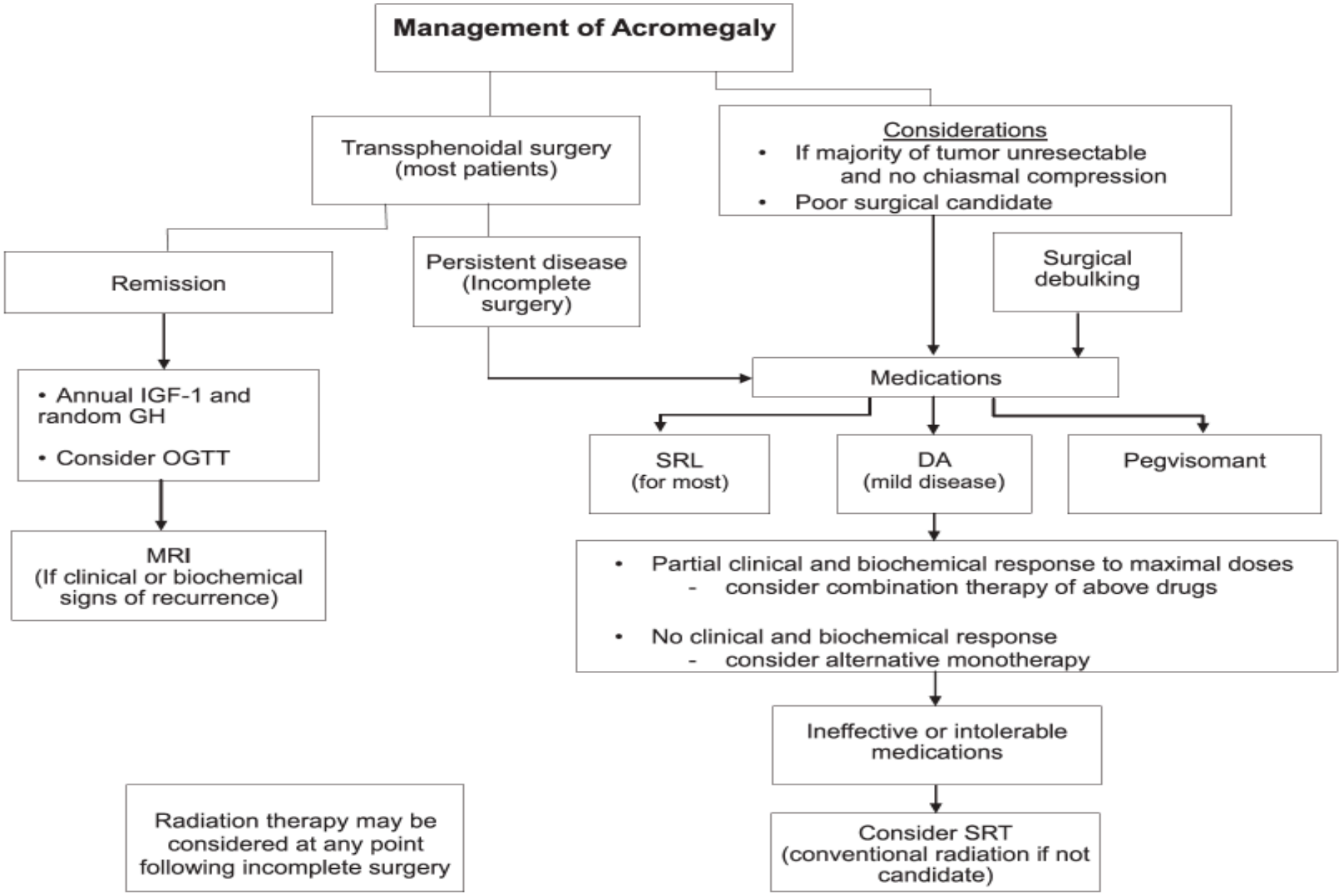
Radionecrosi

J Clin Endocrinol Metab 2005; 90:800–4

J Radiat Oncol Biol Phys 1999; 45:693–8

J Neurooncol 2004; 69:257–72

T E R A P I A


Management of Acromegaly
Transsphenoidal surgery (most patients)
Considerations
• If majority of tumor unresectable and no chiasmal compression
• Poor surgical candidate
Remission
Persistent disease (Incomplete surgery)
Surgical debulking
• Annual IGF-1 and random GH
• Consider OGTT
Medications
SRL (for most)
DA (mild disease)
Pegvisomant
MRI (If clinical or biochemical signs of recurrence)
• Partial clinical and biochemical response to maximal doses
- consider combination therapy of above drugs
• No clinical and biochemical response
- consider alternative monotherapy
Ineffective or intolerable medications
Radiation therapy may be considered at any point following incomplete surgery
Consider SRT (conventional radiation if not candidate)