Ruolo del GH nella sarcopenia/osteoporosi dell'anziano

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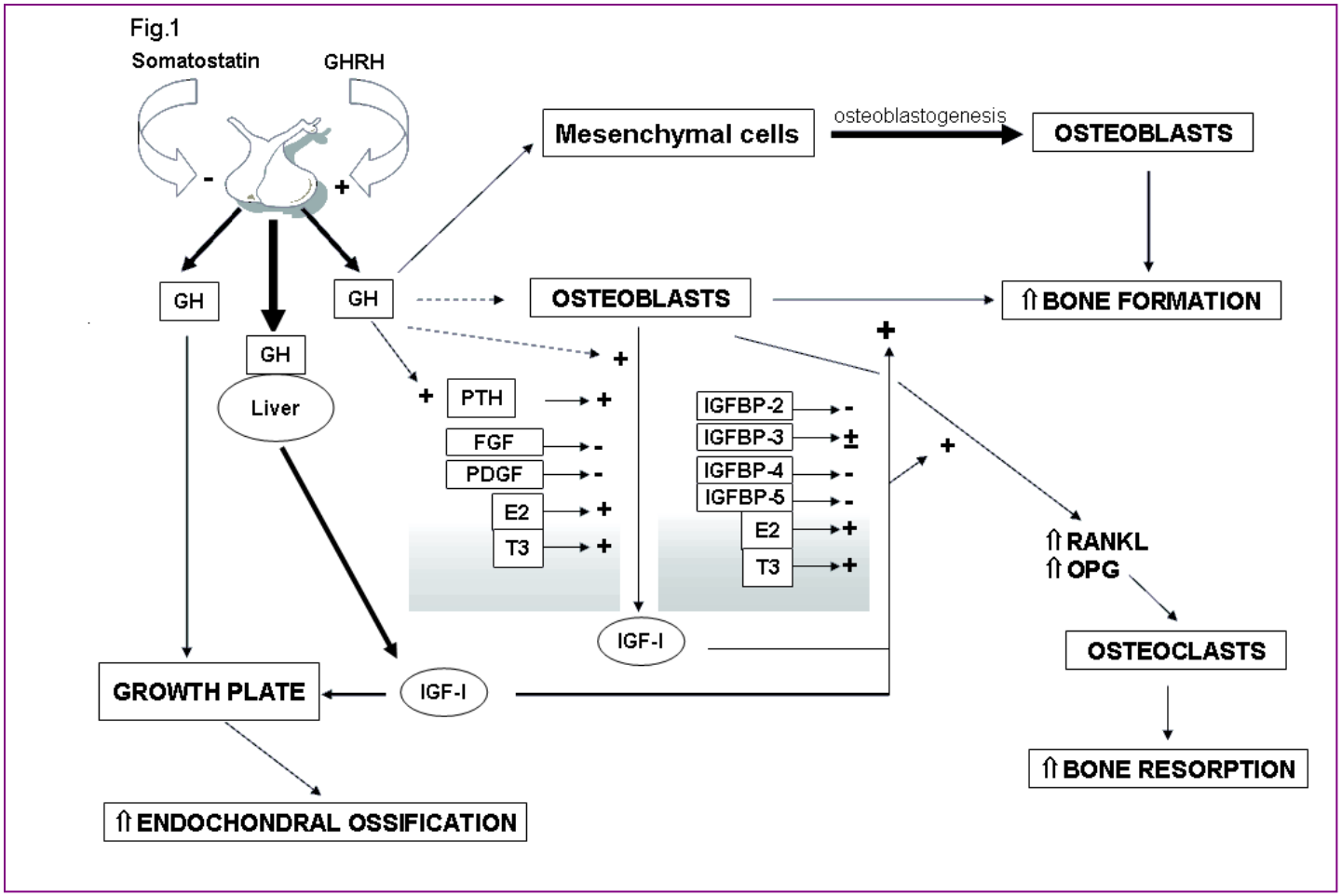
GH-IGF-I ed osteoporosi/sarcopenia dell'anziano

Agenda

1. Effetti fisiologici del GH-IGF-I sul tessuto scheletrico e muscolare.
2. Presentazione clinica del deficit di GH in eta' adulta ed effetti muscolo-scheletrici del trattamento sostitutivo con rhGH.
3. Asse GH-IGF-I in eta' geriatrica: aspetti fisiologici, fisiopatologici e clinici.
4. Effetti della terapia con rhGH sulla salute scheletrica e performance muscolare in eta' geriatrica.
5. Modelli clinici di GHD in età geriatrica.

Aspetti Fisiologici/1

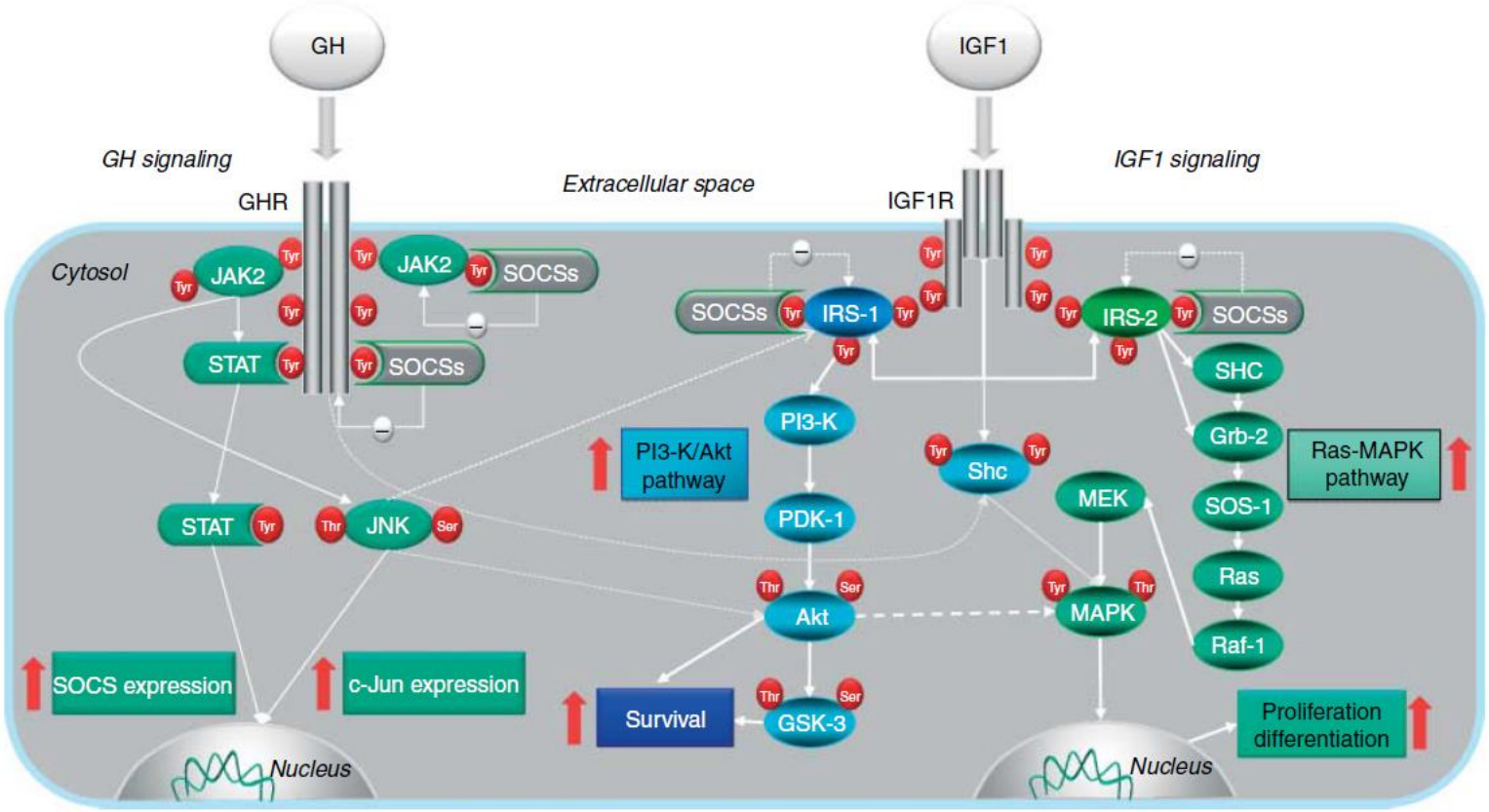
Effetti del GH e dell'IGF-I sul rimodellamento osseo



Giustina et al., Endocr Rev 2008

Aspetti Fisiologici/2

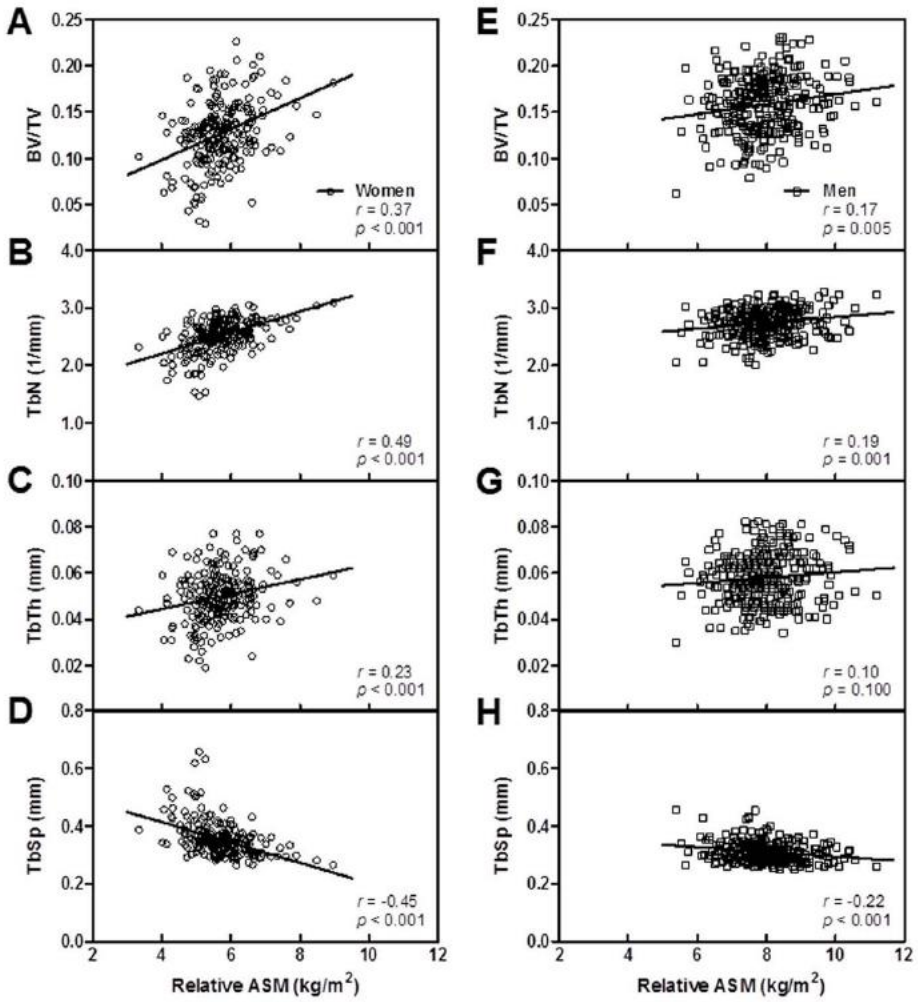
Effetti dell'IGF-I sulla cellula muscolare/1



Perrini et al., J Endocrinol 2010

Aspetti Fisiologici/3

Correlazione tra massa muscolare e struttura scheletrica



LeBrasseur et al., J Bone Miner Res 2012

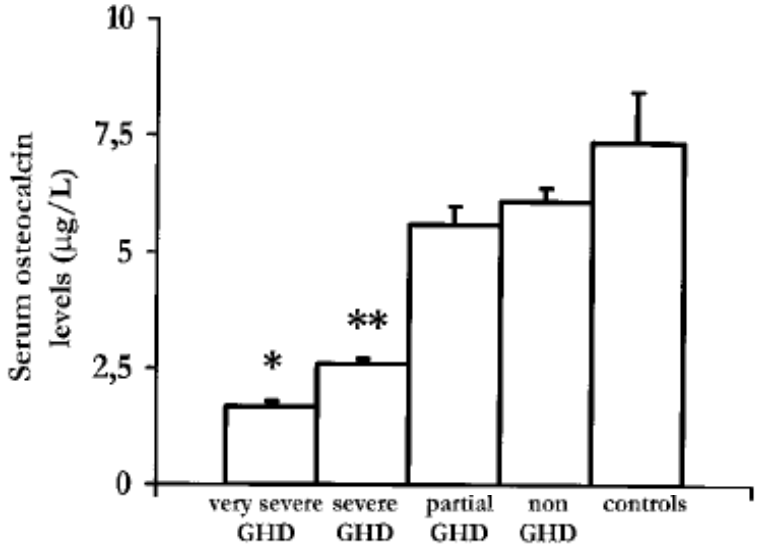
GHD dell'adulto/1

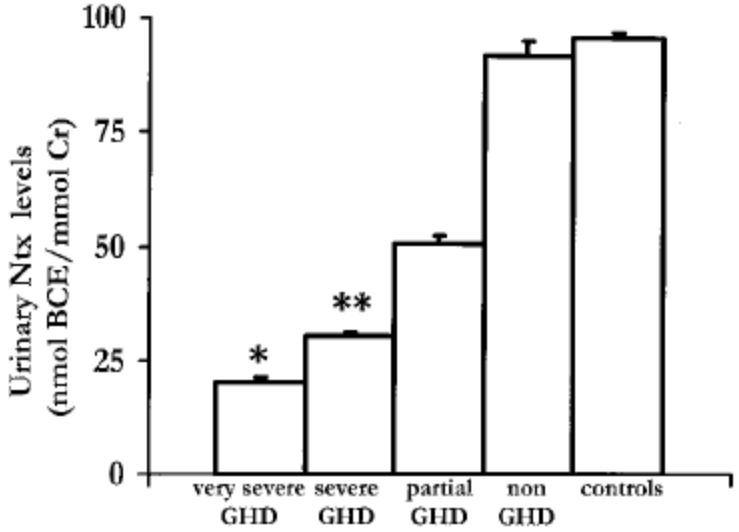
Quadro clinico

- **Obesità viscerale**
- **Insulino-resistenza**
- **Dislipidemia mista**
- **Ridotta performance muscolare**
- **Ridotta qualità di vita**
- **Fragilità scheletrica**

GHD dell'adulto/2

Turnover osseo





Colao et al., J Clin Endocrinol Metab 1999

GHD dell'adulto/3

BMD

	Patients	Total BMD	L1-L4	Forearm
Kaufman	30 (CO)	⇓	⇓	
Johansson	29 (AO)	⇓		
Hyer	60 (CO)	⇓	⇓	
Amato	7 (CO)			⇓
O'Halloran	12 (CO)	⇓	⇓	⇓
Thoren	33 (CO-AO)		⇓	
De Boer	70 (AO)		⇓	⇓
Holmes	26 (AO)	⇓	⇓	
Behyah	64 (CO-AO)	⇓	⇓	
Rosen	95 (CO-AO)		⇓	⇓
Degerblad	88 (CO-AO)	⇓	⇓	
Colao	101 (AO)		⇓	
Murray	125 (CO-AO)	⇔ ⇓	⇓	⇓

GHD dell'adulto/4

Fratture da fragilita'/1

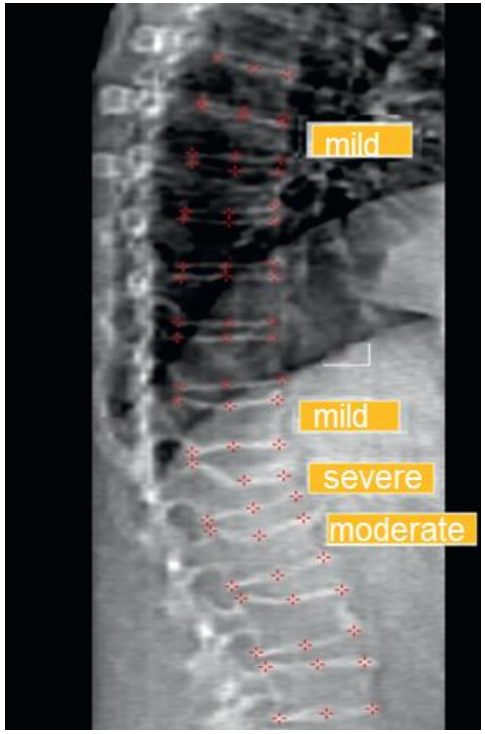
TABLE 2. Risk of fractures in adult-onset GHD patients untreated and treated with rhGH

Study (Ref.)	No. of patients	Type of fractures	Fracture Risk
			Untreated
Rosen *et al.* (273)	107	Clinical nonvertebral	Increased
Wuster *et al.* (227)	2084	Clinical nonvertebral	Increased
Vestergaard *et al.* (275)	199	Clinical nonvertebral	Increased
Bouillon *et al.* (274)	66	Clinical nonvertebral	Increased
Mazziotti *et al.* (234)	107	Morphometric vertebral	Increased

Giustina et al., Endocr Rev 2008

GHD dell'adulto/5

Fratture da fragilita'/2



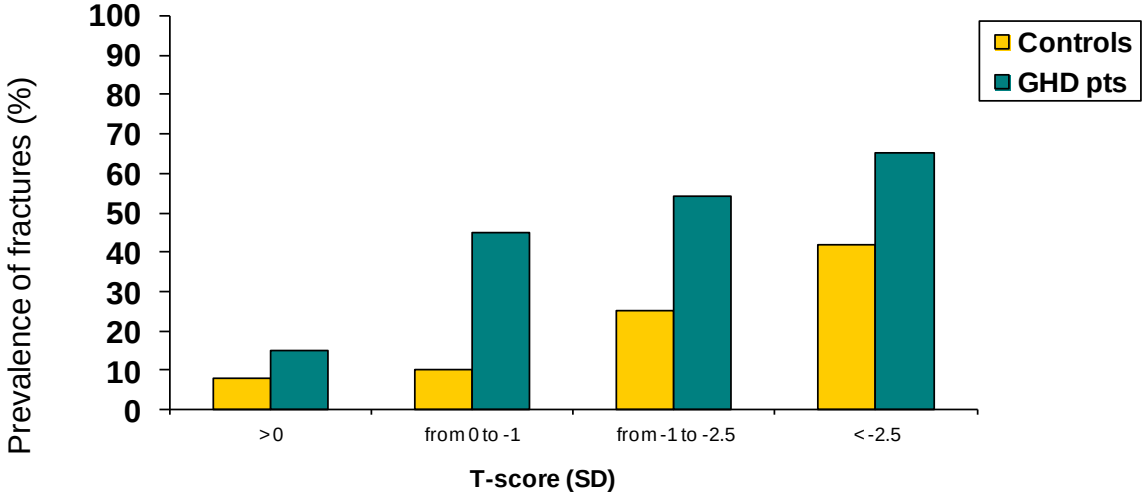


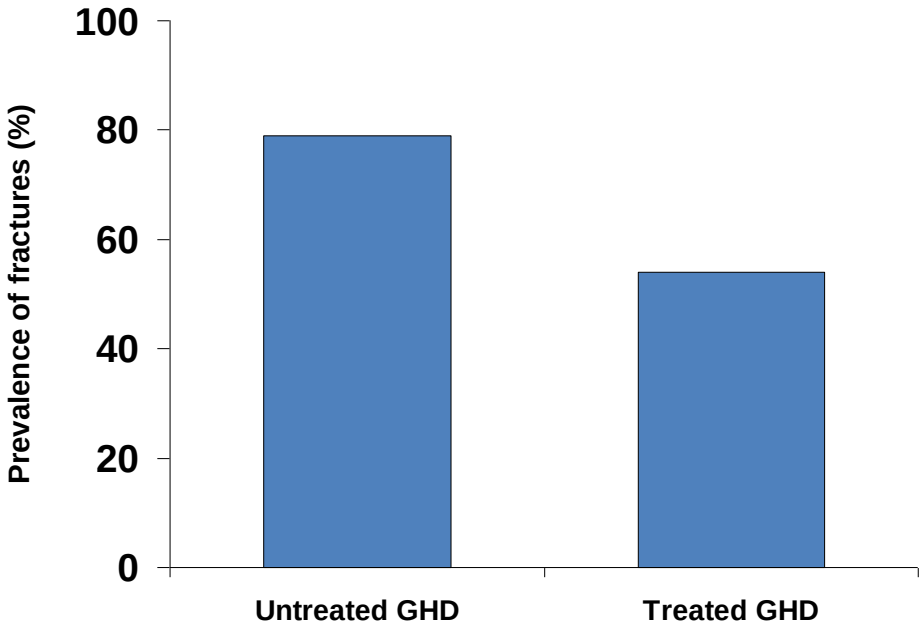
TABLE 3. CLINICAL PRESENTATION OF RADIOLOGICAL SPINAL DEFORMITIES IN 68 GHD PATIENTS STRATIFIED FOR NUMBER AND SEVERITY OF THE FRACTURES

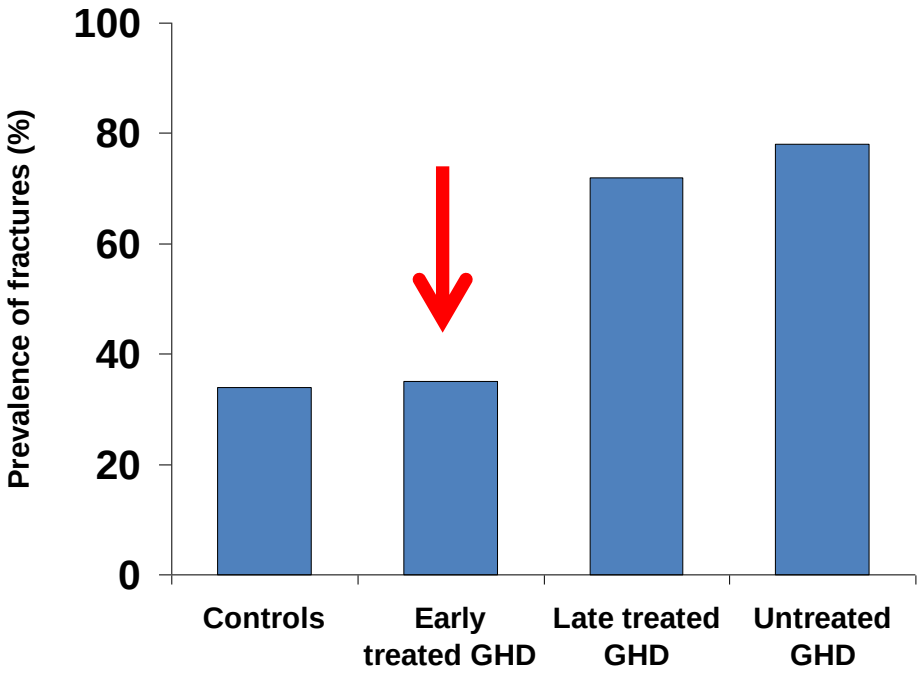
		Clinical presentation of vertebral deformities in 68 GHD patients		
Spinal deformities	*Cases*	*Back pain*	*Kyphosis/scoliosis*	*Functional impairment*
Number				
One spinal deformity	30	43.3%	0	13.3%
Two or more spinal deformities	38	68.4%	7.9%	28.9%
p		0.03	0.15	0.02
Severity				
Mild	47	48.9%	0	12.8%
Moderate	16	68.8%	12.5%	43.8%
Severe	5	100%	20.0%	40.0%
p		0.05	0.02	0.02

Mazziotti et al., J Bone Min Res 2006

GHD dell'adulto/6

Effetti della terapia con rhGH sul rischio di fratture/1





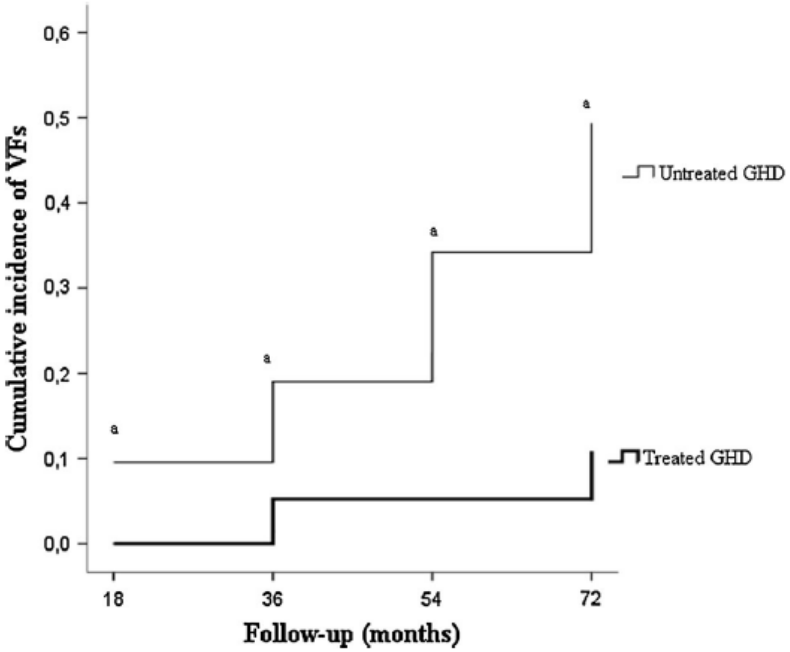
Mazziotti et al., J Bone Min Res 2006

GHD dell'adulto/7

Effetti della terapia con rhGH sul rischio di fratture/2

	Adjusted HR (95% CIs)	
Predictive Variable	**Patients with and without PO**	**Patients without PO**
GH therapy	0·69 (0·54-0·88) *	0·66 (0·51-0·85) *
Age older than 60 years	1·90 (1·57-2·30)	1·90 (1·54-2·33)
Female sex	1·35 (1·10–1·65)	NA
Corticosteroid use	1·24 (1·02-1·50)	NA
Fracture history	1·80 (1·27-2·55)	1·82 (1·14-2·88)
Body weight#	1·01 (1·00-1·01)	1·01 (1·00-1·01)
Depression	1·78 (1·45-2·17)	1·84 (1·48-2·27)
PO	1·72 (1·33-2·23)	NA

Mo et al., Lancet Diabetes Endocrinol 2015



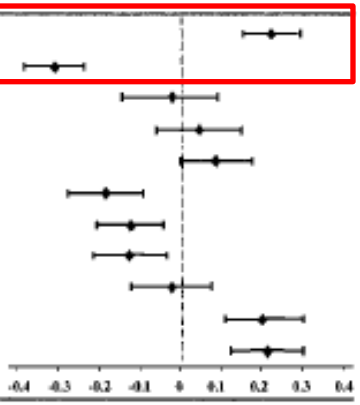
Mazziotti et al., Endocrine 2016

GHD dell'adulto/8

Effetti della terapia con rhGH sulla composizione corporea/1

Factors	No. of trials	Treatment		Q test	Weighted mean (SD) change (GH-placebo)
		GH	Placebo		
Lean B mass	19	473	474	ns	2.82 kg (2.68)
Fat mass	13	352	345	ns	−3.05 kg (3.29)
BMI	8	134	134	ns	−0.12 kg/m^2 (1.40)
TG	11	202	203	ns	0.07 mmol/liter (0.36)
HDL Chol.	13	267	261	ns	0.06 mmol/liter (0.09)
LDL Chol.	13	255	248	ns	−0.53 mmol/liter (0.29)
Total Chol.	15	310	306	ns	−0.34 mmol/liter (0.31)
D.B.P.	10	200	201	ns	−1.80 mm Hg (3.77)
S.B.P.	9	190	191	ns	2.06 mm Hg (5.34)
Insulin	11	192	194	ns	8.66 pmol/liter (6.98)
Glucose	13	254	257	ns	0.22 mmol/liter (0.14)

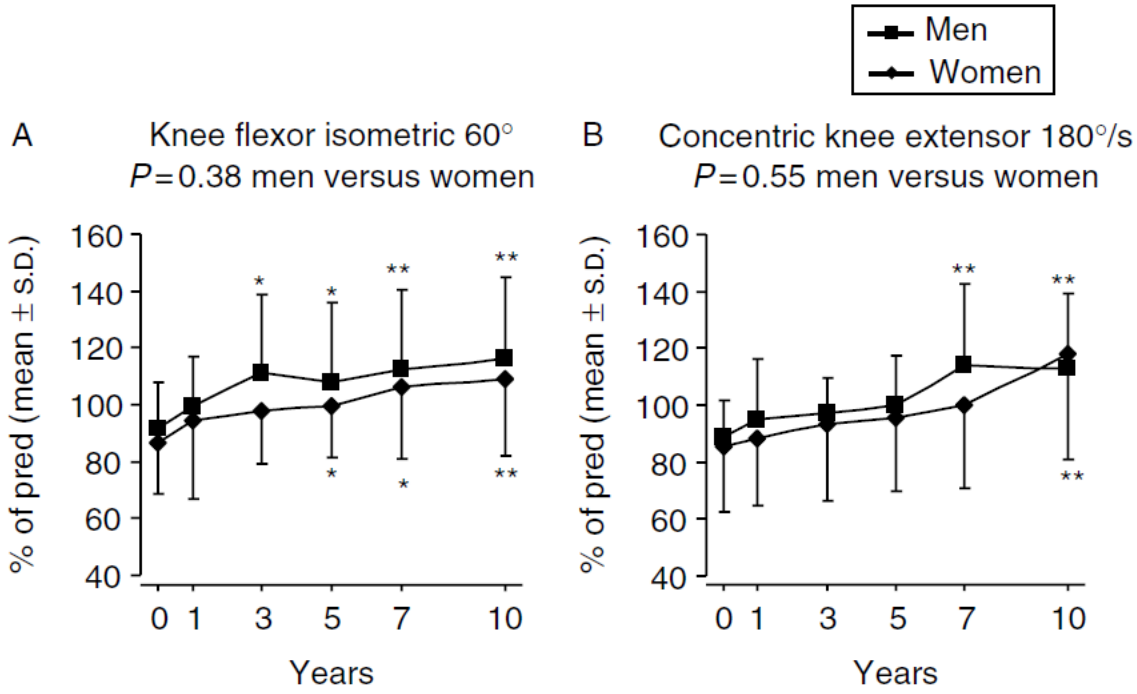
Global effect size (95% CI)



Maison et al., J Clin Endocrinol Metab 2004

GHD dell'adulto/9

Effetti della terapia con rhGH sulla performance muscolare



Gotherstrom et al., Eur J Endocrinol 2010

GHD dell'adulto/12

Linee guida terapeutiche

Evaluation and Treatment of Adult Growth Hormone Deficiency: An Endocrine Society Clinical Practice Guideline

Mark E. Molitch, David R. Clemmons, Saul Malozowski, George R. Merriam, and Mary Lee Vance

3.1 Recommendation

We recommend that GH therapy of GH-deficient adults offers significant clinical benefits in body composition and exercise capacity (1/⊕⊕⊕○).

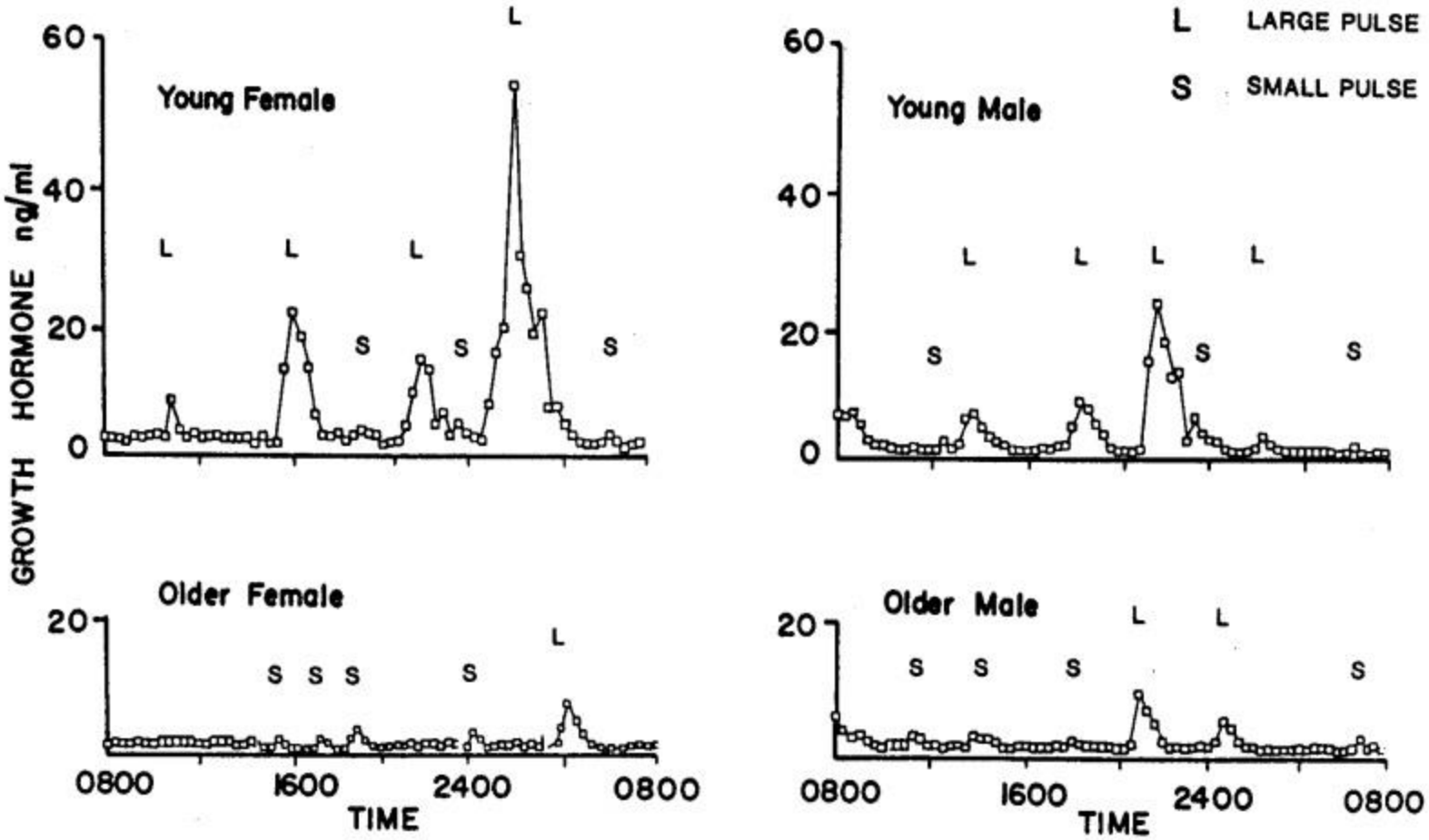
3.2 Recommendation

We suggest that GH therapy of GH-deficient adults offers significant clinical benefits in skeletal integrity (2/⊕⊕○○).

J Clin Endocrinol Metab 2011

Somatopausa/1

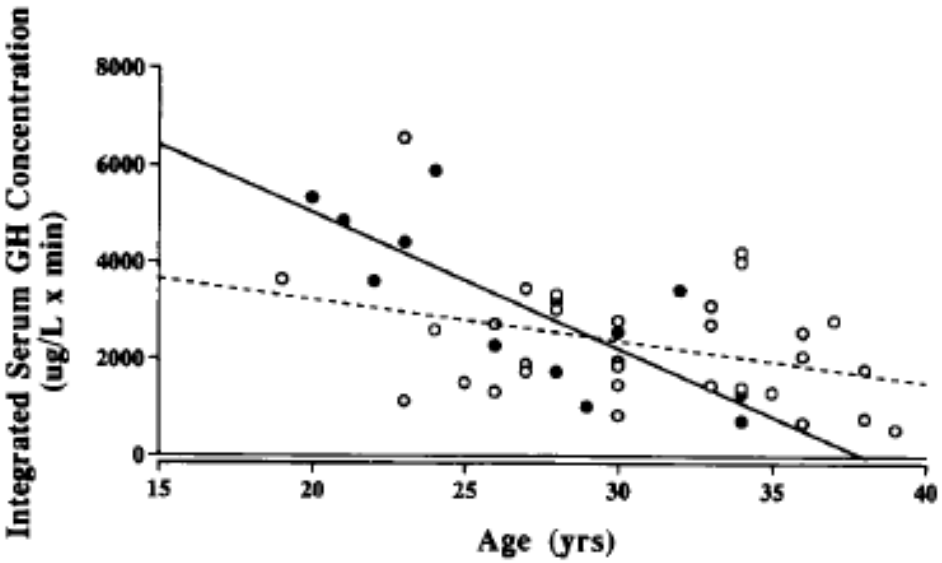
Aspetti fisiologici/1

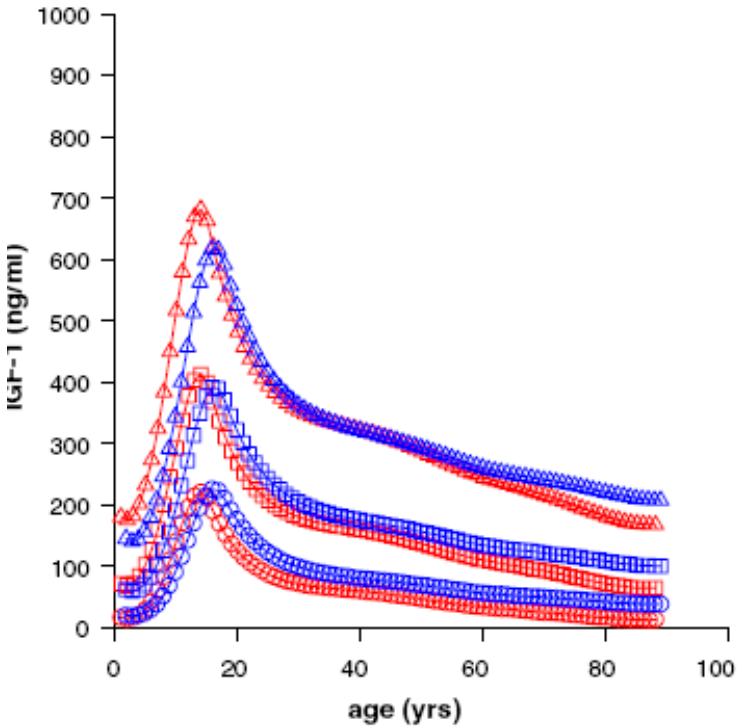


Chertman et al., 2015

Somatopausa/2

Aspetti fisiologici/2

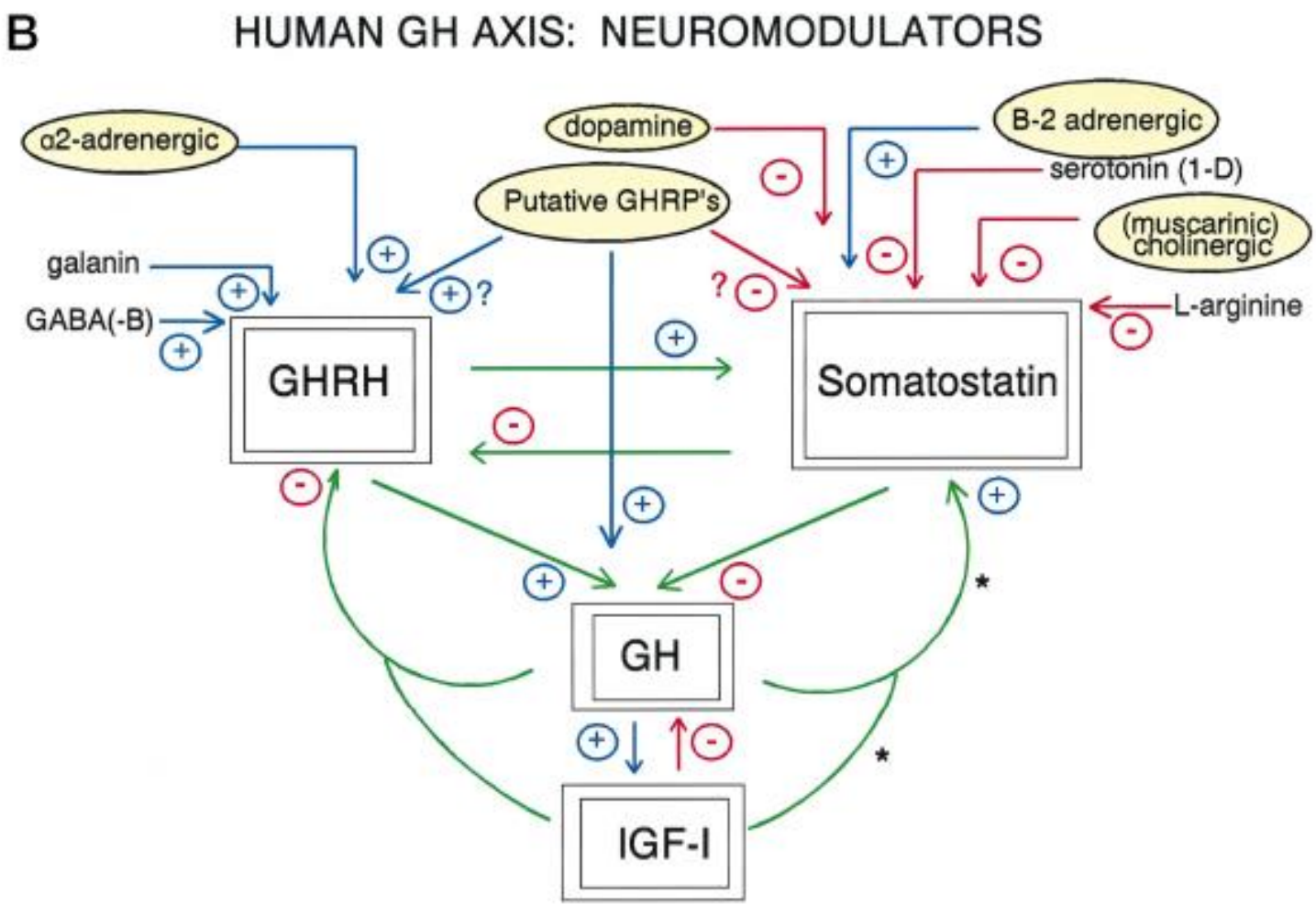




Giustina & Veldhuis, Endocr Rev 1998
Brabant & Wallaschofski, Pituitary 2007

Somatopausa/3

Aspetti fisiologici/3



Giustina & Veldhuis, Endocr Rev 1998

Somatopausa/4

Aspetti fisiopatologici/1

Oxidative stress and the ageing endocrine system

Nat. Rev. Endocrinol. **9**, 228–240 (2013);

Giovanni Vitale, Stefano Salvioli and Claudio Franceschi

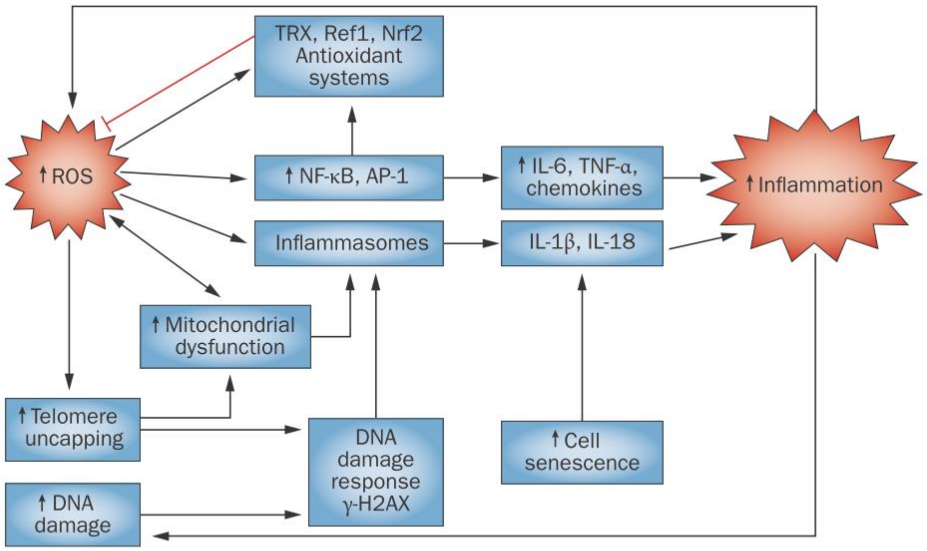
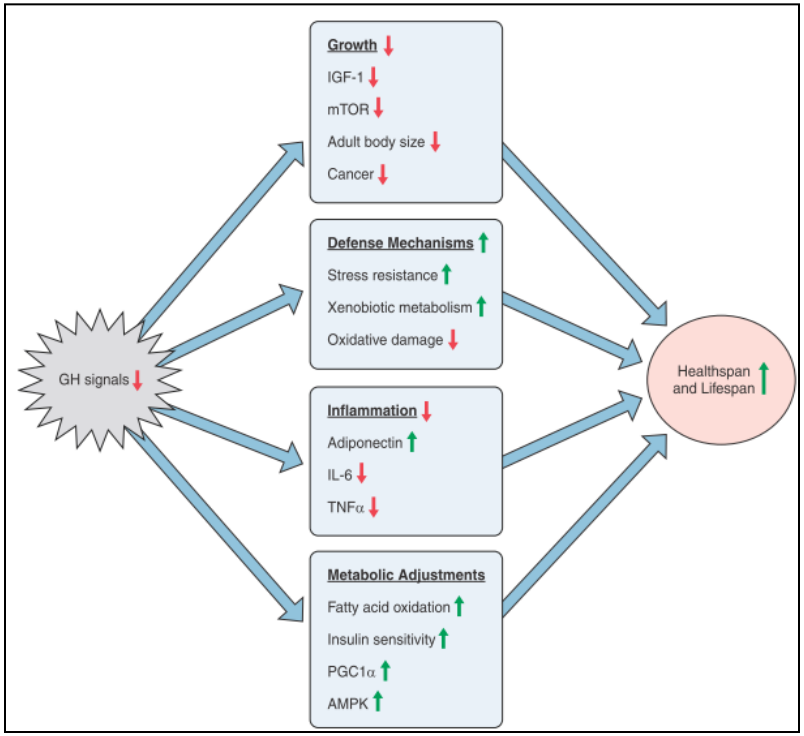


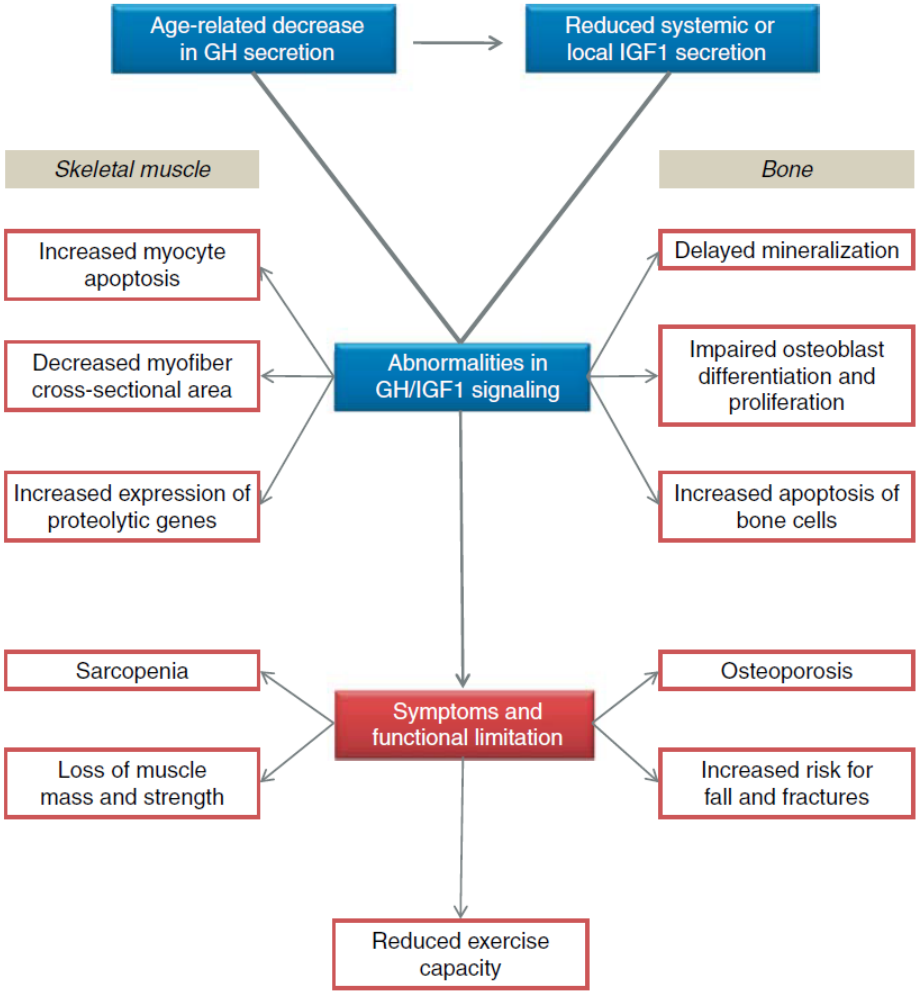
Figure 4 | Schematic representation of the connections between oxidative stress and inflammation and their modification during ageing. Small upright arrow: increase with age.[164,167,171,201–205] Abbreviation: ROS, reactive oxygen species.



Somatopausa/5

Aspetti fisiopatologici/2

SARCOPENIA

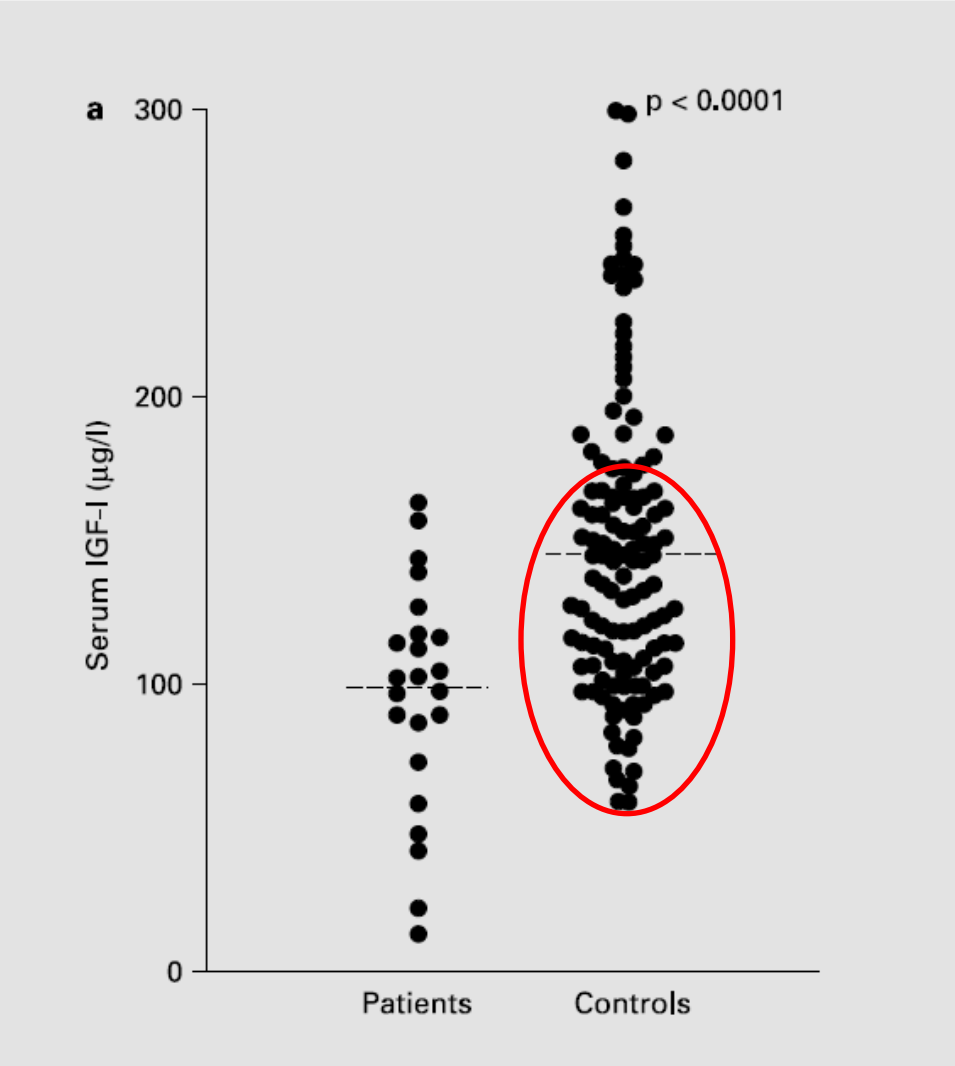


OSTEOPOROSI

Perrini et al., J Endocrinol 2010

Somatopausa/6

Aspetti clinici



Anziani con livelli di IGF-I comparabili a quelli di pazienti con GHD

Toogood, Horm Res 2003

Somatopausa/7

Livelli di IGF-I e rischio di fratture da fragilita'/1

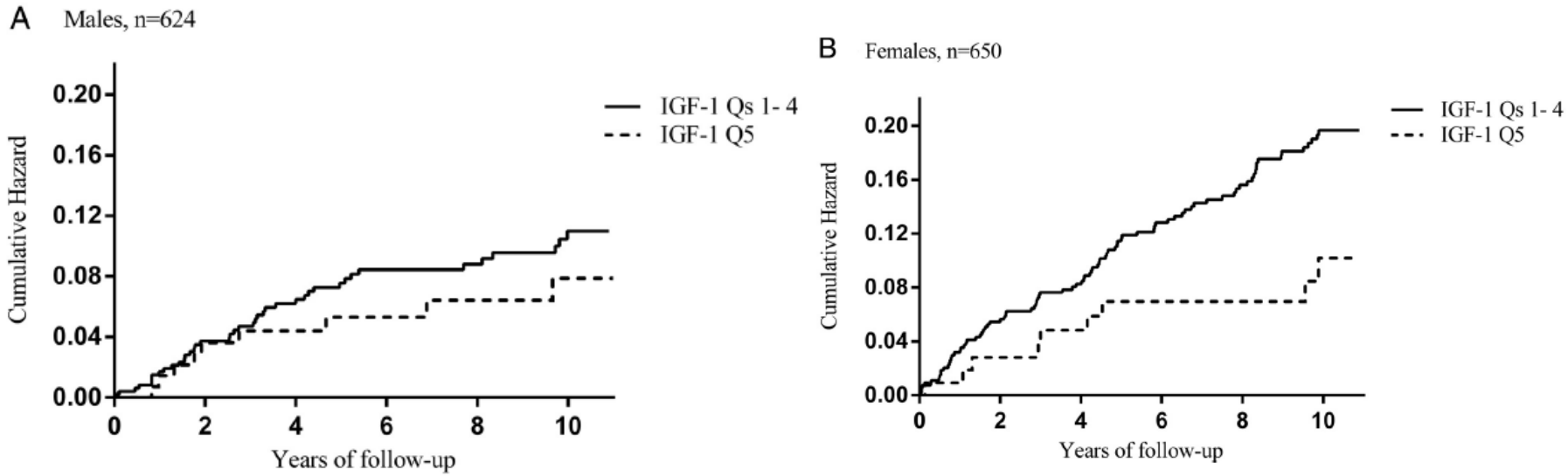


Table 5. Associations Between Baseline IGF-1 Concentration in Quintiles and Risk of Fracture During Follow-up in Males and Females

Fracture Risk (n = 1274)	Unadjusted Model		Fully Adjusted Model	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Males				
IGF-1 Q1Q4	1.42 (0.69–2.92)	.34	1.09 (0.52–2.28)	.83
IGF-1 Q5	Reference		Reference	
Females				
IGF-1 Q1-Q4	2.05 (1.03–4.07)	.04	1.98 (1.00–3.96)	.05
IGF-1 Q5	Reference		Reference	

Van Vasserveld et al., J Clin Endocrinol Metab 2015

Somatopausa/8

Livelli di IGF-I e rischio di fratture da fragilita'/2

Table 2. Associations between the Incidence of Osteoporotic Fractures Versus Serum IGF-I, BMD, and HbA1c.

	Men		Postmenopausal women	
	OR (95% CI)	p	OR (95% CI)	p
Serum IGF-I	0.52 (0.19-1.40)	0.193	0.48 (0.23-0.99)	0.047
L-BMD	1.38 (0.60-3.18)	0.448	0.87 (0.45-1.66)	0.670
HbA1c	0.41 (0.12-1.40)	0.157	0.89 (0.50-1.59)	0.691

Miyake et al., Int Med 2017

Somatopausa/9

Livelli di IGF-I e deficit muscolare

TABLE 5. Odds ratios of self-reported difficulty in physical function associated with a 50 μg/liter decline in IGF-I level from the mean

Task	Age-adjusted [OR (95% CI)]	Multivariate-adjusted [OR (95% CI)]
Getting in/out of a chair	1.59 (1.26–2.02)[a]	1.42 (1.10–1.83)[a]
Walking up 10 steps	1.41 (1.12–1.77)[a]	1.31 (1.00–1.70)[a]
Lifting/carrying 10 lb	1.21 (0.98–1.49)	0.99 (0.78–1.20)
Walking 2–3 blocks	1.12 (0.92–1.38)	0.92 (0.73–1.17)
Performing heavy housework	1.23 (1.01–1.50)[a]	1.09 (0.86–1.39)

[a] $P < 0.05$.

Cappola et al., J Clin Endocrinol Metab 2001

Somatopausa/10

Effetti del rhGH sulla composizione corporea: studi clinici/1

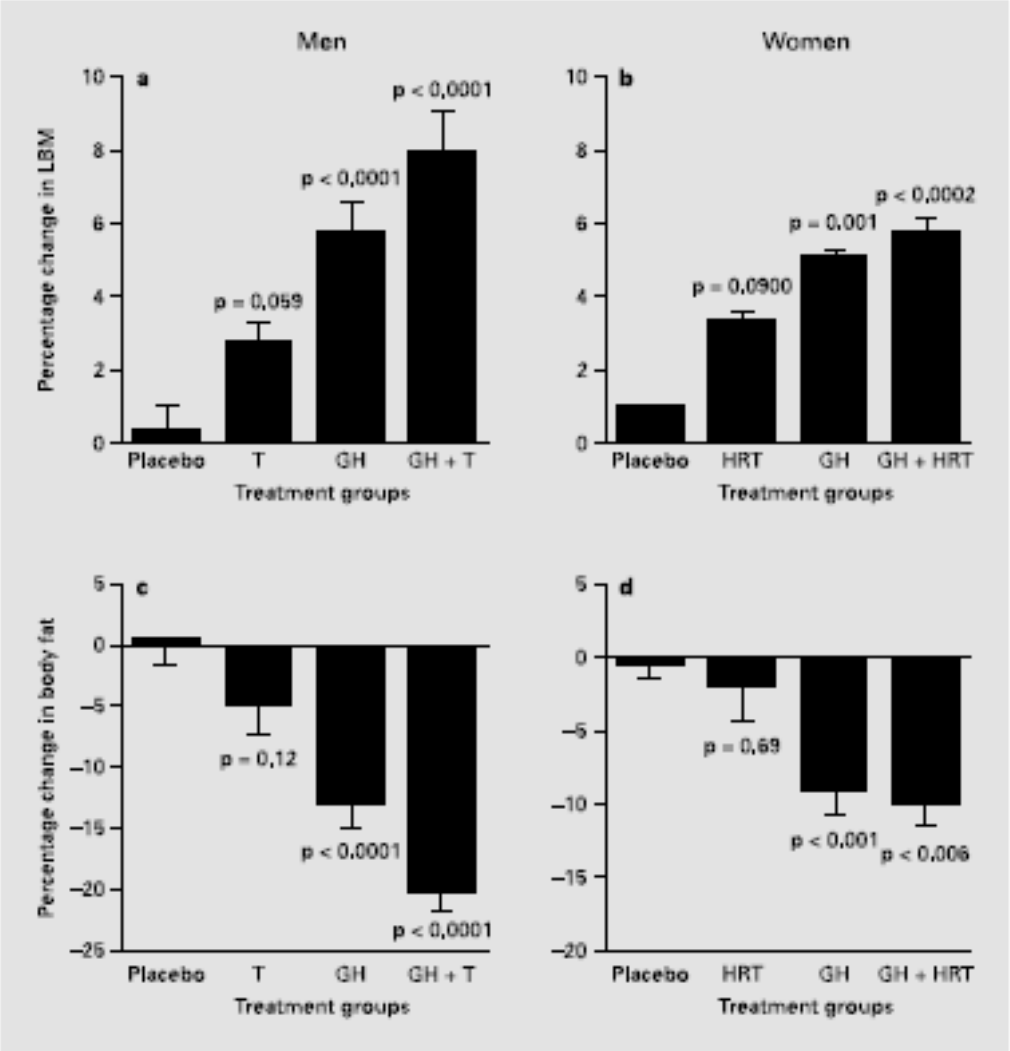
Table 4. Effect of the Administration of Human Growth Hormone on Weight, Lean Body Mass, Adipose-Tissue Mass, Skin Thickness, and Bone Density in Healthy Older Men.*

Variable	Group	End of Base-Line Period	End of Treatment Period	P Value†	Difference in Changes‡
Weight (kg)	1	77.2±11.4	78.2±12.1	0.26	+1.0 (−1.4 to +3.4)
	2	83.3±11.1	83.3±9.7	0.97	
Lean body mass (kg)	1	53.0±7.4	57.7±9.1	0.0005	+3.7 (+0.7 to +6.6)
	2	54.2±7.1	55.2±7.3	0.17	
Adipose-tissue mass (kg)	1	24.1±5.0	20.6±5.6	0.05	−2.4 (−5.7 to +0.8)
	2	29.0±6.4	28.0±4.0	0.43	
Sum of skin thickness at four sites (mm)	1	9.9±1.2	10.6±1.5	0.07	+0.8 (−0.1 to +1.7)
	2	9.3±0.9	9.23±0.80	0.69	
Bone density (g/cm^2)					
Mid-shaft radius	1	0.74±0.10	0.74±0.12	0.85	+0.04 (−0.02 to +0.10)
	2	0.76±0.10	0.71±0.07	0.09	
Distal radius	1	0.37±0.07	0.36±0.08	0.12	−0.004 (−0.03 to +0.02)
	2	0.34±0.04	0.33±0.05	0.26	
Average, lumbar vertebrae 1–4	1	1.23±0.12	1.25±0.13	0.04	+0.006 (−0.04 to +0.05)
	2	1.29±0.25	1.29±0.26	0.64	
Ward's triangle	1	0.70±0.14	0.69±0.13	0.15	−0.018 (−0.08 to +0.05)
	2	0.70±0.17	0.70±0.17	0.69	
Greater trochanter	1	0.85±0.13	0.85±0.13	0.72	+0.007 (−0.05 to +0.03)
	2	0.81±0.15	0.81±0.13	0.55	
Femoral neck	1	0.92±0.15	0.91±0.14	0.53	−0.029 (−0.08 to +0.03)
	2	0.89±0.14	0.85±0.14	0.14	
Mandibular-height ratio	1	0.45±0.15	0.46±0.11	0.87	−0.003 (−0.07 to +0.06)
	2	0.47±0.12	0.47±0.12	0.98	

Rudman et al., NEJM 1990

Somatopausa/11

Effetti del rhGH sulla composizione corporea: studi clinici/2



Harman & Blackman, Horm Res 2003

Somatopausa/12

Effetti del rhGH sulla composizione corporea: studi clinici/3

Fat mass		
All study populations	14	−2.08 kg (−2.80 to −1.35)
Intervention evaluated		
GH only‖	9	−2.34 kg (−3.22 to −1.45)
GH and lifestyle intervention¶	5	−1.55 kg (−2.82 to −0.27)
Length of GH administration		
<26 weeks	7	−1.86 kg (−2.86 to −0.85)
≥26 weeks	7	−2.32 kg (−3.37 to −1.27)
Sex**		
Male	8	−2.27 kg (−3.11 to −1.43)
Female	5	−1.55 kg (−3.03 to −0.07)
Lean body mass		
All study populations	14	2.13 kg (1.32 to 2.94)
Intervention evaluated		
GH only‖††	9	1.66 kg (0.44 to 2.88)
GH and lifestyle intervention¶	5	2.78 kg (1.85 to 3.70)
Length of GH administration		
<26 weeks	7	2.62 kg (1.90 to 3.35)
≥26 weeks††	7	1.64 kg (0.17 to 3.10)
Sex**		
Male	8	2.62 kg (1.92 to 3.32)
Female††	5	1.39 kg (−0.39 to 3.17)
$Vmax_{o2}$	4	0.32 mL/min per kg (−1.19 to 1.84)
Femoral neck BMD††	4	0.03 g/m^2 (−0.07 to 0.13)
Lumbar spine BMD	5	0.00 g/m^2 (−0.04 to 0.03)
Total cholesterol level	5	−0.29 mmol/L (−0.49 to −0.08)‡‡
LDL cholesterol level	5	−0.12 mmol/L (−0.29 to 0.05)
HDL cholesterol level	5	−0.01 mmol/L (−0.08 to 0.06)
Triglycerides level††	5	−0.27 mmol/L (−0.59 to 0.04)
Fasting glucose level††	6	−0.03 mmol/L (−0.28 to 0.21)
Fasting insulin level††	5	3.27 pmol/L (−9.55 to 16.09)

Lee et al., Ann Int Med 2007

Somatopausa/13

Sicurezza del trattamento con rhGH

Adverse Event	Studies, *n*	GH-Treated Participants		Non–GH-Treated Participants	
		Mean Proportion (Range), %†	Participants, *n*	Mean Proportion (Range), %†	Participants, *n*
Soft tissue edema‡	15	50 (23–89)	194	8 (0–25)	194
Carpal tunnel syndrome‡	16	19 (0–50)	244	1 (0–7)	212
Arthralgias‡	14	21 (0–50)	181	5 (0–25)	186
Gynecomastia§	3	6 (0–12)	95	0 (0–0)	63
New IFG, IGT, or DM	4	22 (6–53)	100	14 (0–25)	69
New DM	4	5 (0–12)	100	1 (0–5)	69

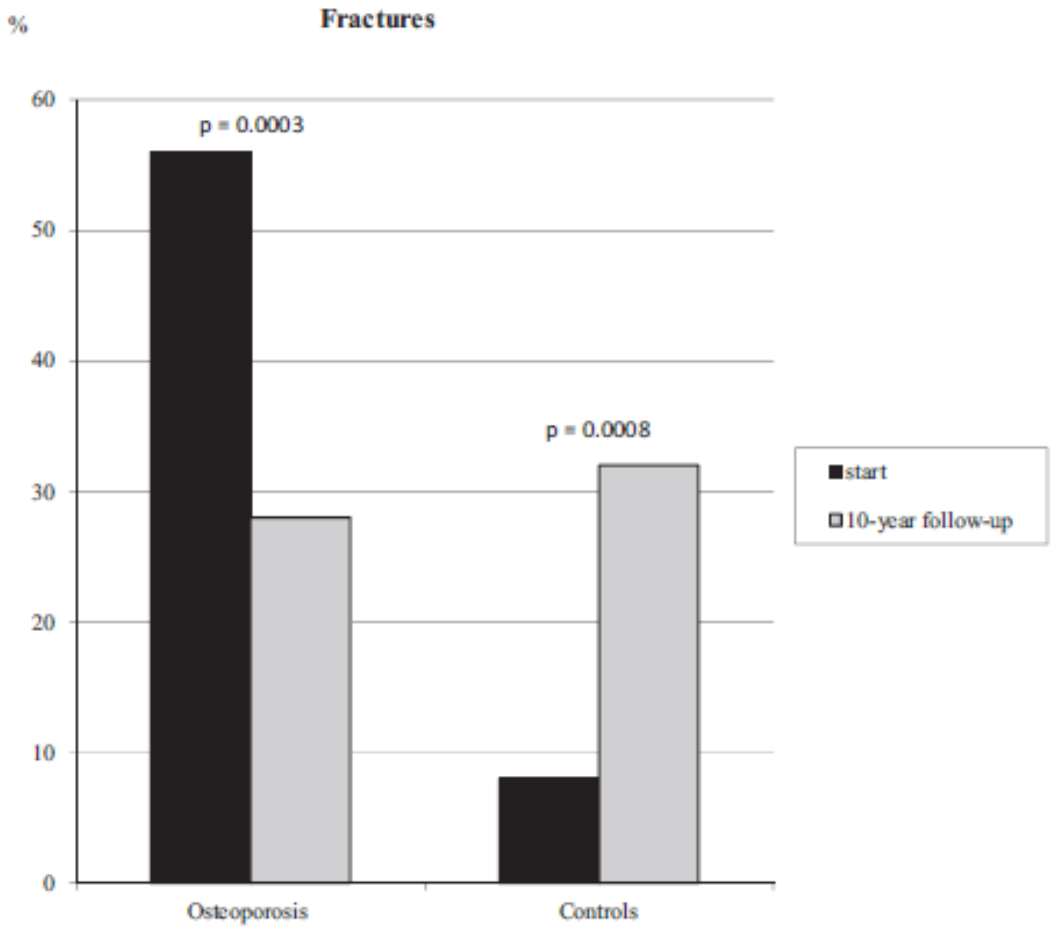
Table 5. **Proportion of Patients Experiencing Soft Tissue Edema***

Subgroup	Studies, *n*	GH-Treated Participants		Non–GH-Treated Participants	
		Mean Proportion (Range), %†	Participants, *n*	Mean Proportion (Range), %†	Participants, *n*
Sex‡					
Male	8	47 (23–75)	119	13 (0–25)	113
Female	5	61 (38–89)	60	2 (0–14)	65
Initial daily GH dosage					
> 0.02 mg	3	52 (23–89)	32	3 (0–14)	38
≤ 0.02 mg	12	49 (25–75)	162	10 (0–25)	156
Age					
>70 y	7	56 (25–75)	89	11 (0–25)	89
≤70 y	8	45 (23–89)	105	6 (0–21)	105

Lee et al., Ann Int Med 2007

Somatopausa/13

Effetti del rhGH sul rischio di fratture



Krantz et al., J Clin Endocrinol Metab 2015

Somatopausa/14

Trattamento con rhGH

Growth Hormone Should Be Used Only for Approved Indications

David R. Clemmons, Mark Molitch, Andrew R. Hoffman, Anne Klibanski, Christian J. Strasburger, David L. Kleinberg, Ken Ho, Susan M. Webb, Marcello D. Bronstein, Roger Bouillon, Anat Ben-Shlomo, Amir H. Hamrahian, Philippe Chanson, Ariel L. Barkan, George R. Merriam, Marc R. Blackman, and Roberto Salvatori

J Clin Endocrinol Metab 2014

Terapia con rhGH in Italia

Nota AIFA 39

Età adulta

E' indicata la terapia con rGH in pazienti adulti (con BMI <29.9 kg/m2), con età maggiore di 25 anni, se presentano un picco di GH dopo test dell'ipoglicemia insulinica (ITT) < 3 µg/L oppure dopo test GHRH + arginina < 9 µg/L; per pazienti obesi (BMI > 30 kg/m2) il picco di GH dopo GHRH + arginina dovrà essere < 4 µg/L.

GHD nell'ambulatorio di Geriatria/1

Patologie ipofisarie

- **Neurochirurgia o RT ipofisaria**
- **Macroadenomi**
- **Tumori parasellari**
- **Sella vuota**
- **Pregresso trauma cranico**
- **Ipofisite**
- **Altro**

GHD nell'ambulatorio di Geriatria/1

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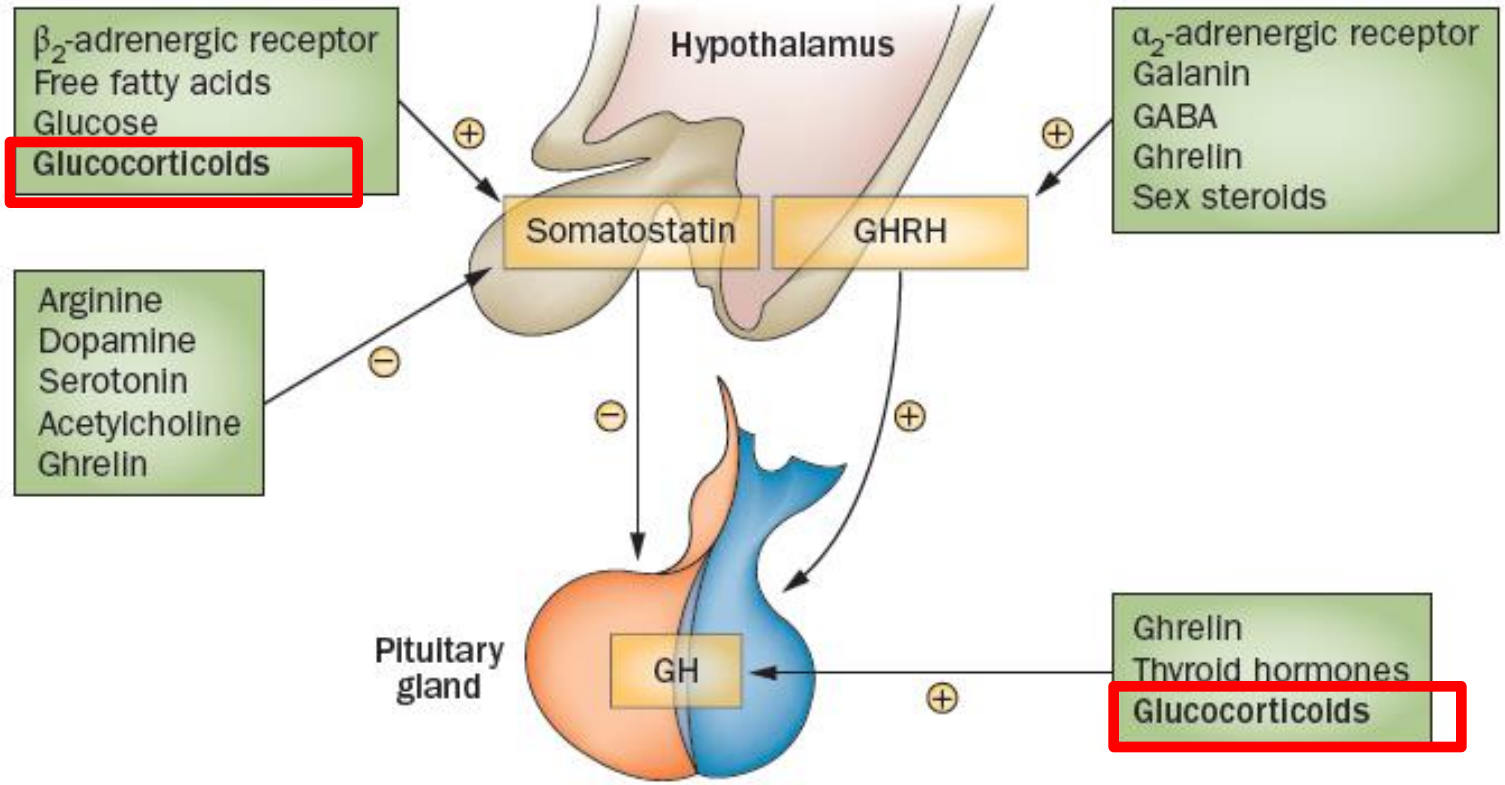
Il GHD è sempre causato da malattie organiche dell'ipofisi?

GHD nell'ambulatorio di Geriatria/2

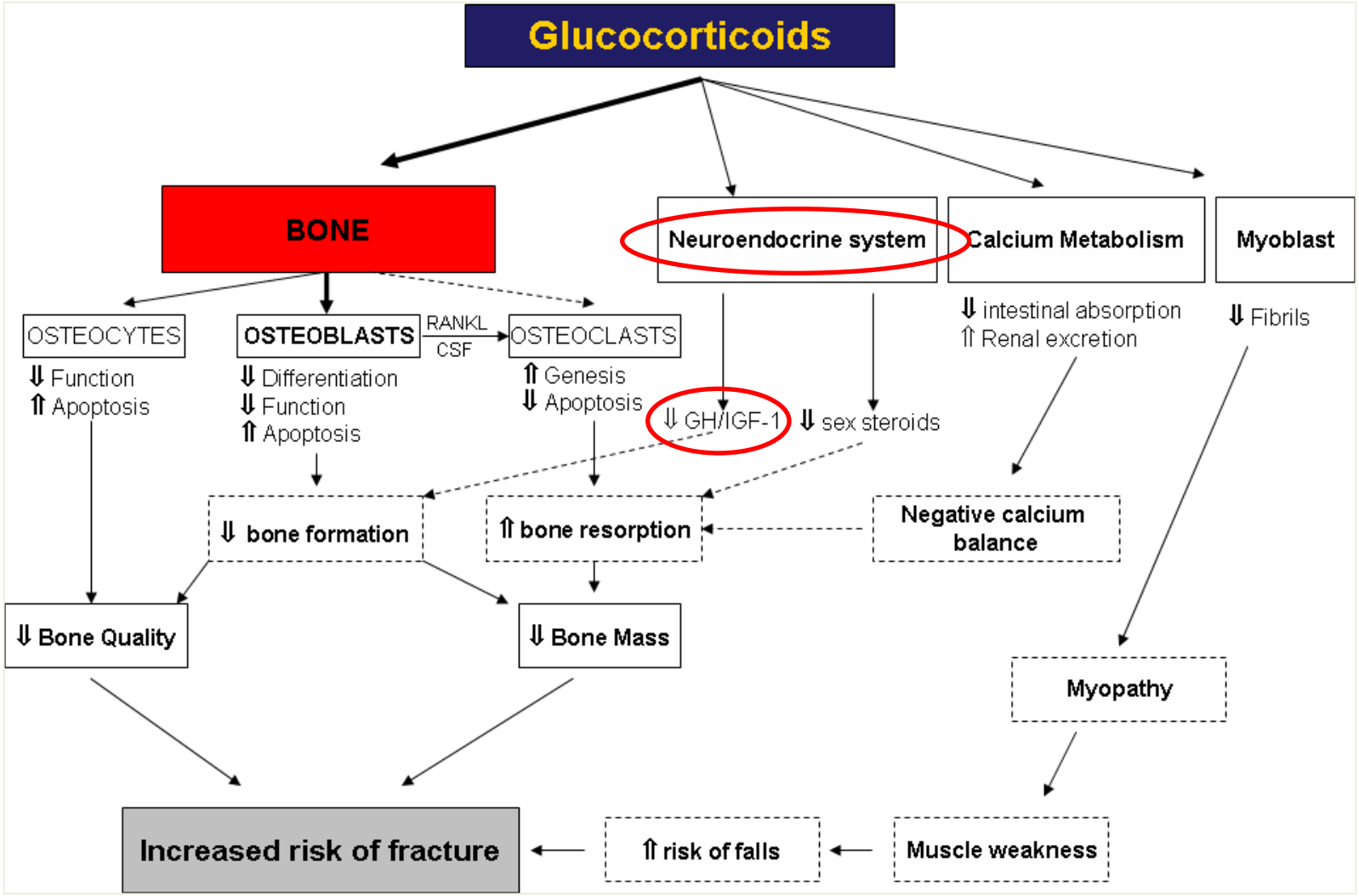
GHD funzionale indotto da glucocorticoidi



Mazziotti & Giustina, Nature Rev Endocrinol 2013

GHD nell'ambulatorio di Geriatria/3

GHD funzionale nella GIO/1

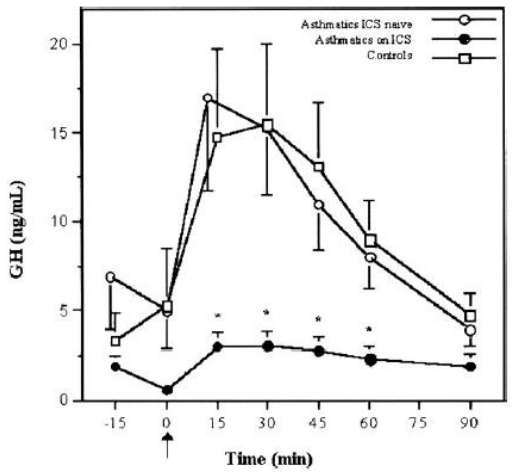


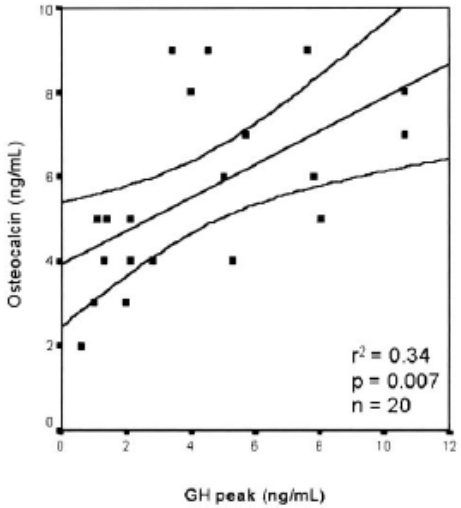
Canalis et al., Osteoporos Int 2007

GHD nell'ambulatorio di Geriatria/4

GHD funzionale nella GIO/2

Cortisonici inalatori





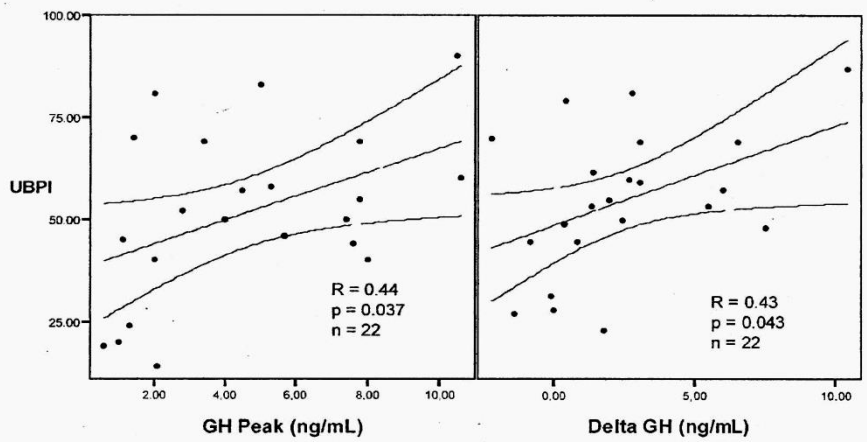


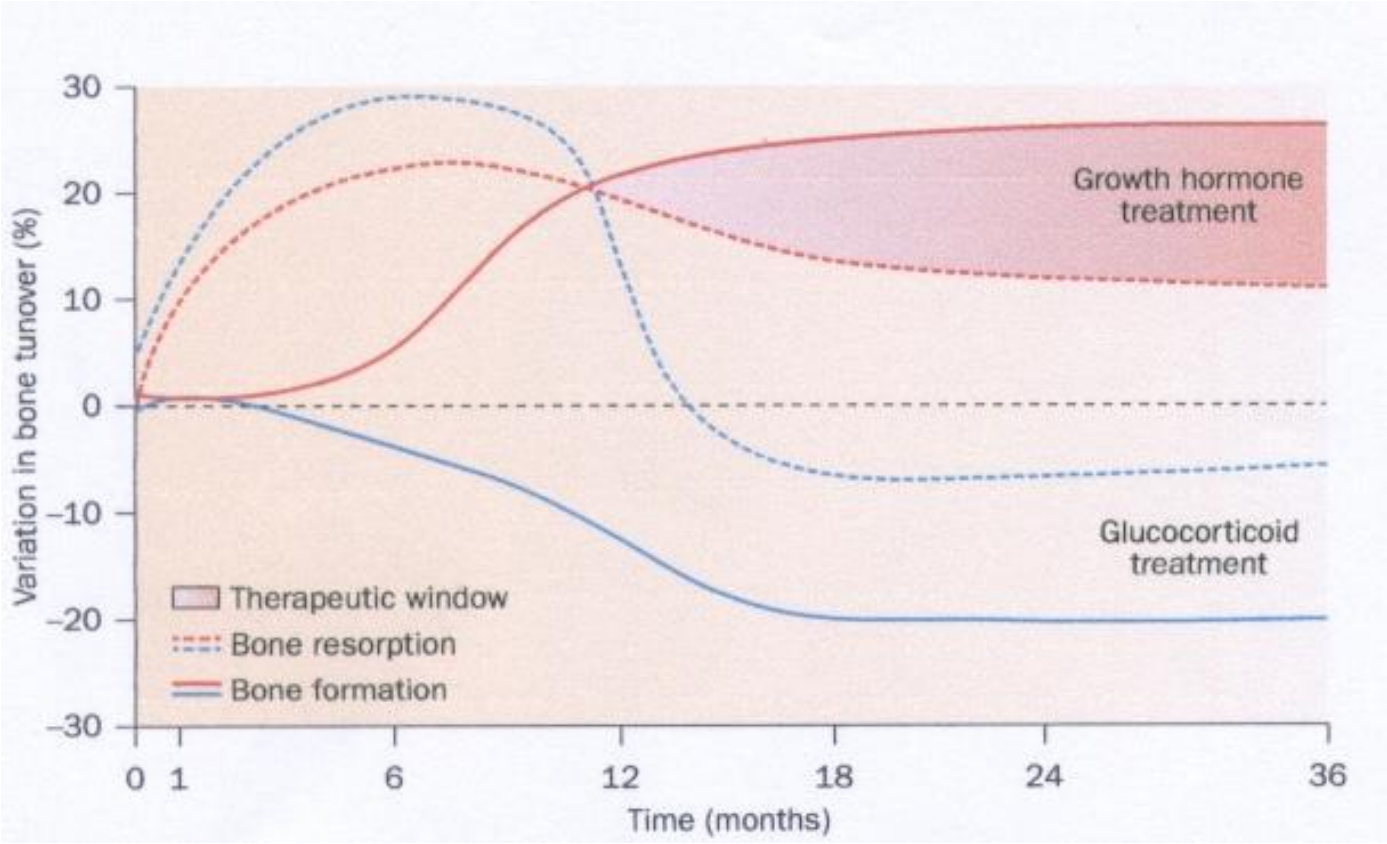
Fig. 2. Correlation between ultrasound bone profile index (UBPI) values, growth hormone (GH) peak and ΔGH in asthmatic patients treated with long-term inhaled corticosteroid therapy.

Malerba et al., Chest 2005
Malerba et al., Bone 2006

GHD nell'ambulatorio di Geriatria/5

Terapia della GIO con rhGH

"Finestra anabolica" del GH nell'osteoporosi da glucocorticoidi



Mazziotti & Giustina, Nature Rev Endocrinol 2013

Conclusioni

1. L'invecchiamento si accompagna ad una riduzione della secrezione di GH ("somatopausa") che può favorire la comparsa di un quadro clinico-sindromico simile al GHD dell'eta' adulta.
2. In alcuni soggetti in eta' geriatrica senza evidenza di patologia ipofisaria si puo' sviluppare un GHD funzionale potenziale fattore di rischio per fragilita' scheletrica e sarcopenia.
3. L'efficacia del trattamento sostitutivo con rhGH è ben documentata nel GHD, mentre i dati di efficacia e sicurezza nel trattamento della "somatopausa" sono ancora pochi e contrastanti .
4. Futuri studi consentiranno di definire le caratteristiche clinico-fenotipiche dei pazienti con GHD funzionale o con "somatopausa" che possono beneficiare del trattamento con rhGH.