OBESITA' E GH

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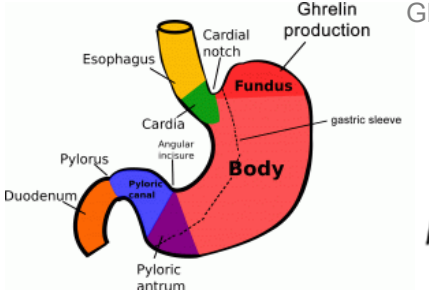
Conflitti di interesse

nessun conflitto di interesse

Asse GH/IGF-1 e obesità

- Ruolo fisiologico dell'asse GH/IGF-1
- Asse GH/IGF-1 e perdita di peso
- Evidenze efficacia terapeutica del GH

Effetti Metabolici del GH



Pituitary gland

GH secretagogue receptor type 1a

Growth hormone (GH)

GHRH (GH-releasing hormone) stimulates the release of GH.

GHIN (GH-inhibiting hormone) inhibits the release of GH.

Muscle growth

Adipocytes break down triglycerides.

Bone growth

IGF-1

The liver breaks down glycogen.

Insulin-like growth factors (IGFs) stimulate amino acid uptake by target cells, promoting protein synthesis.

Effetti Metabolici del GH

GH & organi bersaglio

Muscolo

- ↑ Utilizzo degli aminoacidi
- ↑ Sintesi delle proteine
- ↓ Utilizzo dei carboidrati

Fegato

- ↑ Sintesi proteica
- ↑ Sintesi di RNA
- ↑ Produzione di IGF-I e IGF-II (somatomedine)

Grasso

- ↑ Aumento lipolisi
- ↓ Utilizzo dei carboidrati
- ↑ Degradazione dei grassi

AUMENTO MASSA MUSCOLARE

RIDUZIONE GRASSO VISCERALE

GHD dell'Adulto

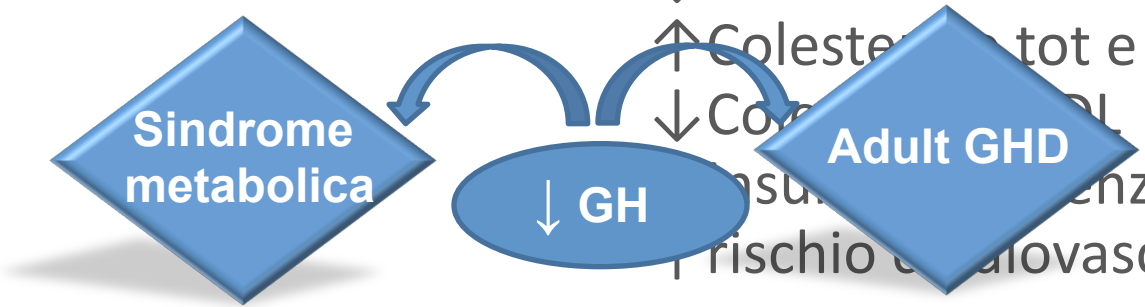
Sintomi

↓benessere psicologico

↓forza muscolare e resistenza fisica

Segni Clinici

↑Obesità addominale
↓Massa muscolare
↓Massa ossea
↓Metabolismo basale
↓GFR
↑Colest tot e trigliceridi
↓Co L
nsu enza
↑rischio ovascolare



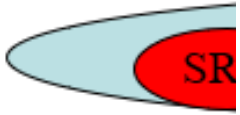
Johannsson G, Bengtsson BA. Growth hormone and the metabolic syndrome. J Endocrinol Invest. 1999;22:41–6.

Cuneo RC et al, Clin Endocrinol, 1992

Sindrome di Prader Willi

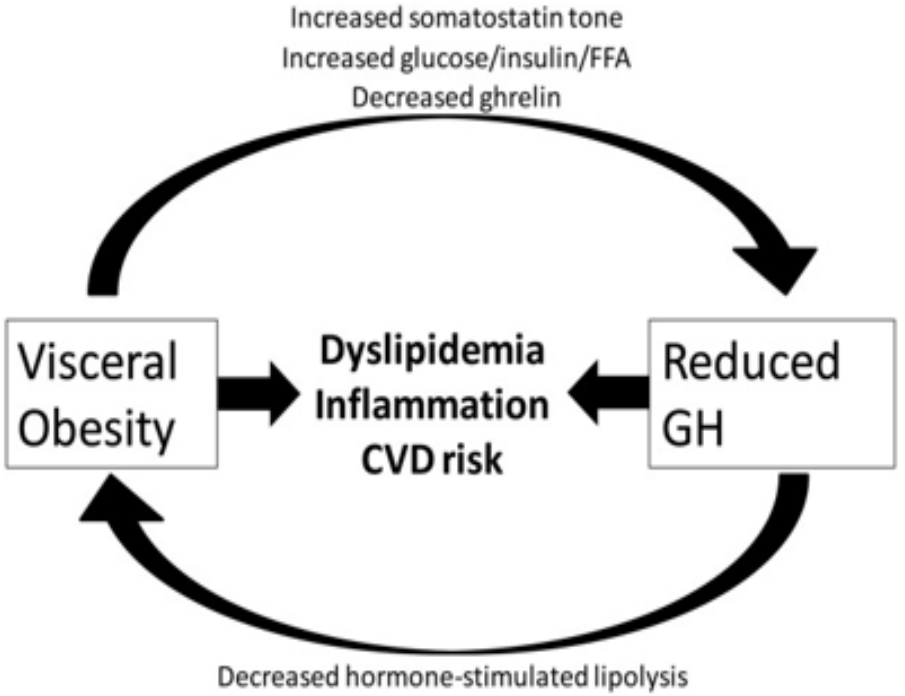
- Malattia genetica rara (1/25.000 nati) con anomalie nella regione critica del cromosoma 15 (15q11-q13)
- Multiple alterazioni ipotalamico-ipofisarie
- Grave ipotonia neonatale
- Precoce insorgenza di iperfagia, che esita in obesità patologica durante l'infanzia e nell'età adulta
- Difficoltà di apprendimento e disturbi comportamentali o problemi psichiatrici gravi
- Alterazioni costitutive dell'asse GH/IGF-1, indipendentemente dall'obesità, nel 40-100% dei pazienti
- Test diagnostici indicativi di deficit di GH
- A parità di BMI, percentuale di tessuto adiposo > rispetto ai pazienti affetti da obesità semplice, mentre il rapporto massa magra/massa grassa è inferiore

Obesità: uno stato di iposecrezione di GH



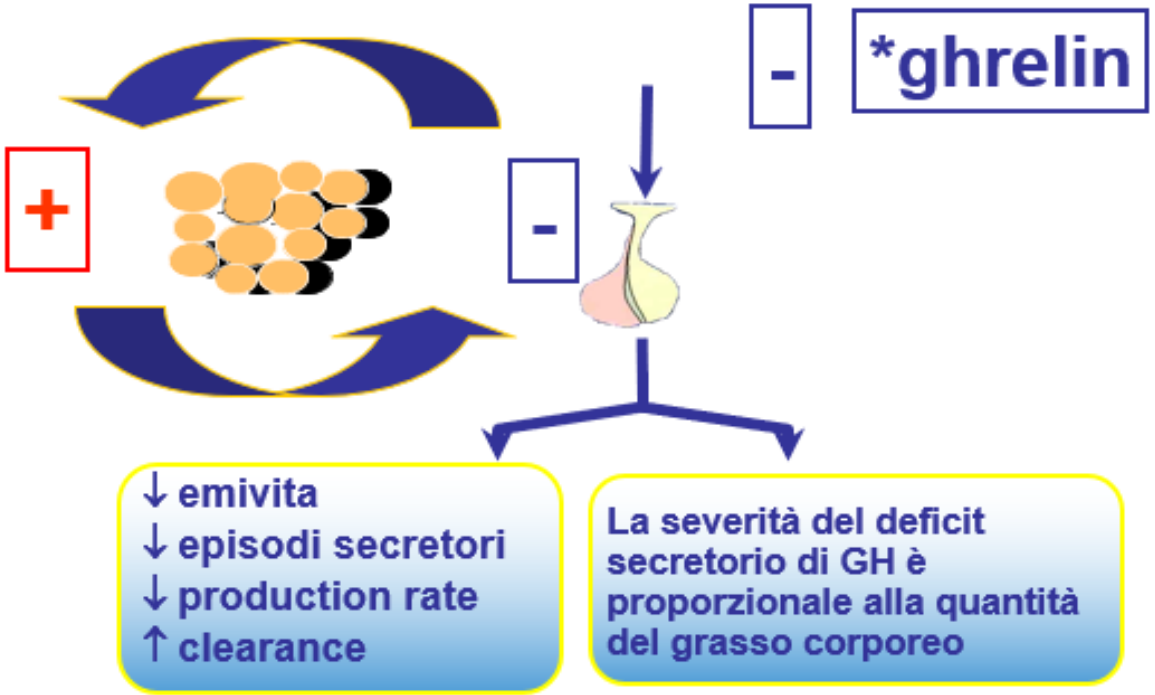
Le alterazioni endocrine sono una conseguenza dell'obesità

Ma le alterazioni endocrine possono anche avere effetti causali nell'obesità



Johannsson G, Bengtsson BA. Growth hormone and the metabolic syndrome. J Endocrinol Invest. 1999;22:41–6.

Obesità: uno stato di iposecrezione di GH



*Casanueva FF et al JCE&M 1987; *Gormsen LC et al Zraika et al EJE 2006*

Associazione asse GH/IGF-1 e grasso viscerale

Table 1. GH/IGF system in conditions associated with visceral adiposity in humans.

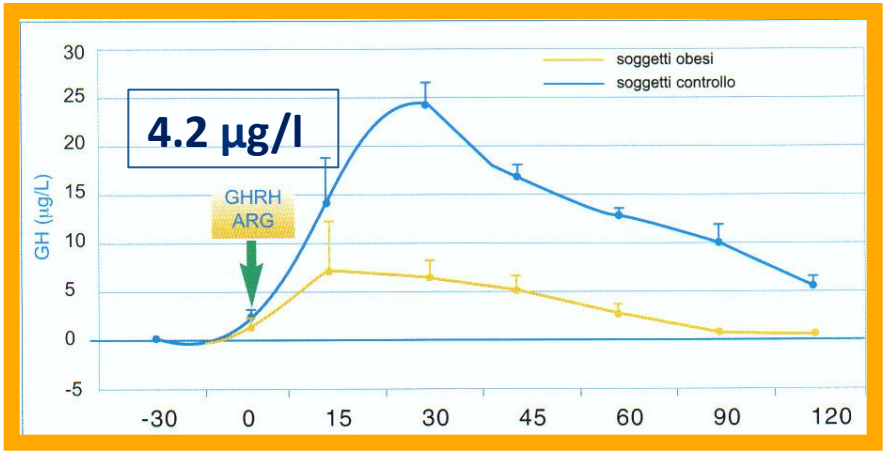
CONDITION	GENERAL ADIPOSITY	VISCERAL ADIPOSITY	GH	IGF-I	IGFBP-1	INSULIN SENSITIVITY
Normal	—	—	N	N	N	N
Ageing	↑	↑	↓	↓	N/↑	↓
Simple obesity	↑	↑	↓	↓	↓	↓/N
Metabolic syndrome	↑/—	↑	↓	↓	↓/↑	↓
GH deficiency	—/↑	↑	↓	↓	↑	↑
GH insensitivity	↑	↑	↑	↓	↑	↑
HIV lipodystrophy	↓/—	↑	↓	↓	↑	↓
Prader-Willi syndrome	↑	↑	↓	↓	N	N

Abbreviations: GH, growth hormone; HIV, human immunodeficiency virus; IGF-1, insulin-like growth factor 1; IGFBP-1, IGF-binding protein 1.

Lewitt MS. Biochem Insights. 2017 Apr 20;10:1178626417703995

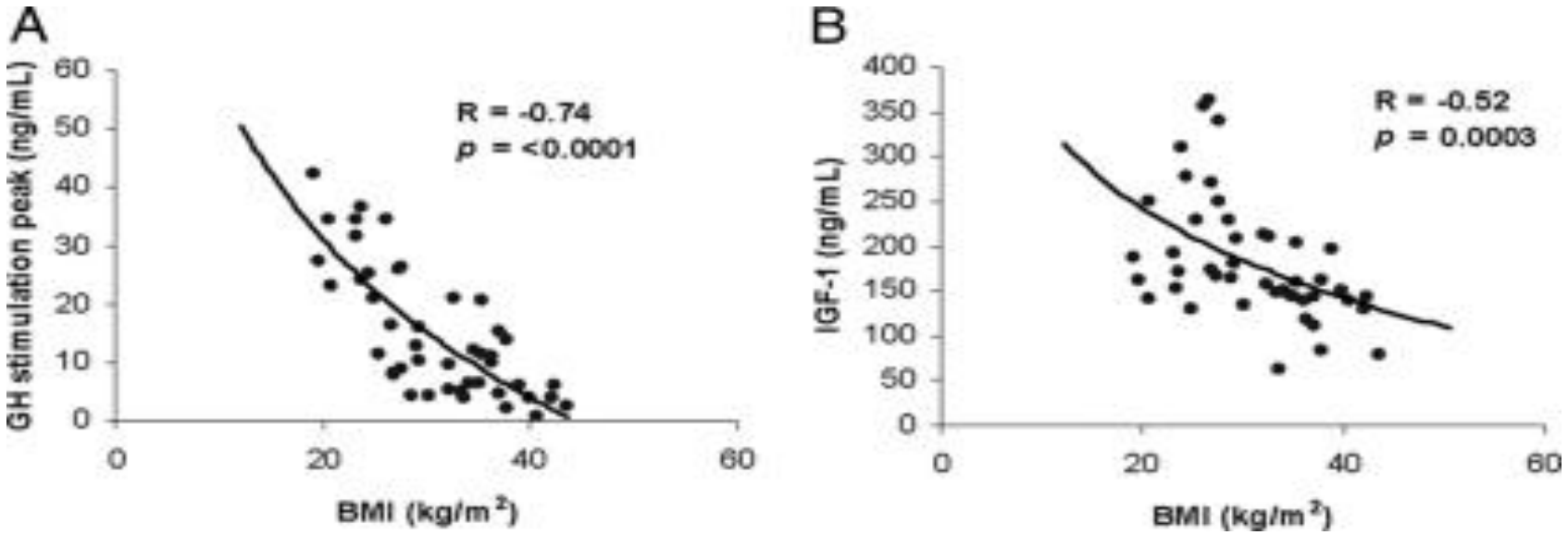
Diagnosing functional somatopenia

- The GHRH + arginine test is likely to be the overall test of choice in clinical practice
- Similarly to other provocative tests, GHRH + ARG is independent of age and gender, but influenced by obesity *per se*



Ghigo E et al, Endocrine 2001
Biller BM et al, JCE&M 2002
Corneli, G, Di Somma C et al, EJE 2005

GHD, obesità e rischio CVD



↑ Rischio CVD in donne obese GHD

UTZ AL et al 2008 JCE&M;93:2507

Obesità ed asse somatotropo

Growth Hormone & IGF Research 24 (2014) 221–226

Contents lists available at ScienceDirect

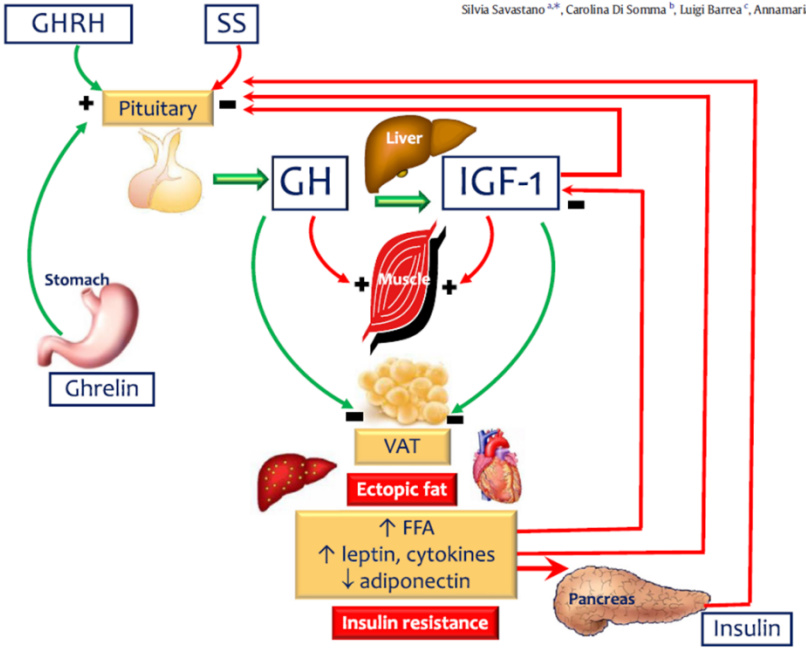
Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Review

The complex relationship between obesity and the somatropic axis: The long and winding road

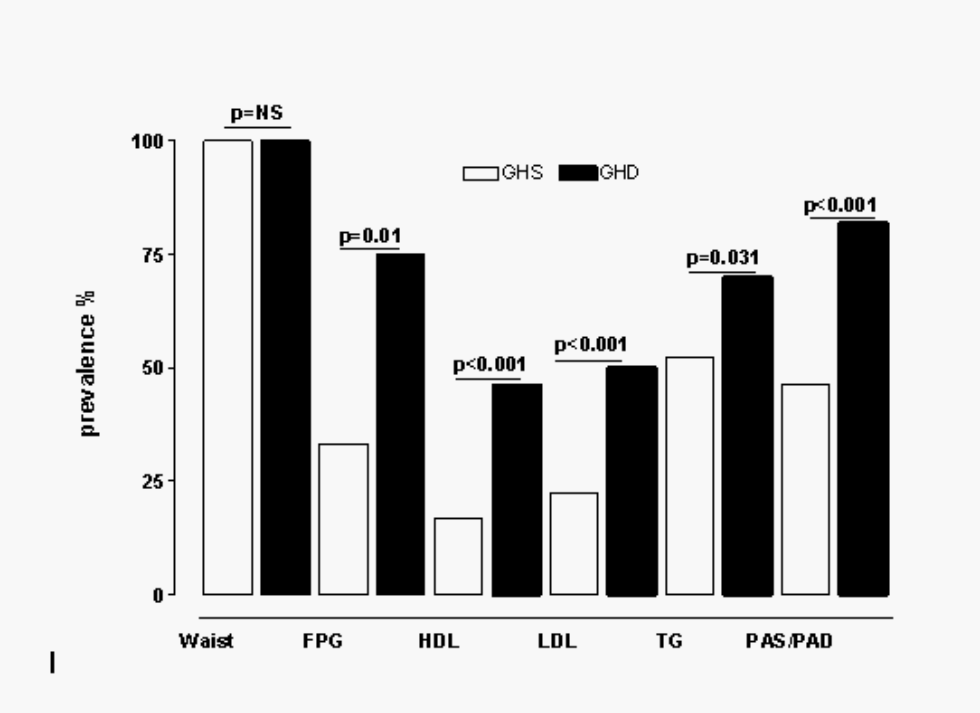
Silvia Savastano [a,*], Carolina Di Somma [b], Luigi Barrea [c], Annamaria Colao [a]



GHD, obesità e SM

GHD Obese Subjects 55 patients → **70.9%**

GHS Obese Subjects 140 patients → **50.2%**



Di Somma C, et al. J Endocrinol Invest. 2010 Mar;33(3):171-7.

Asse GH/IGF-1 e obesità

- Ruolo fisiologico dell'asse GH/IGF-1
- Asse GH/IGF-1 e perdita di peso
- Evidenze efficacia terapeutica del GH

Asse GH/IGF-1 e perdita di peso

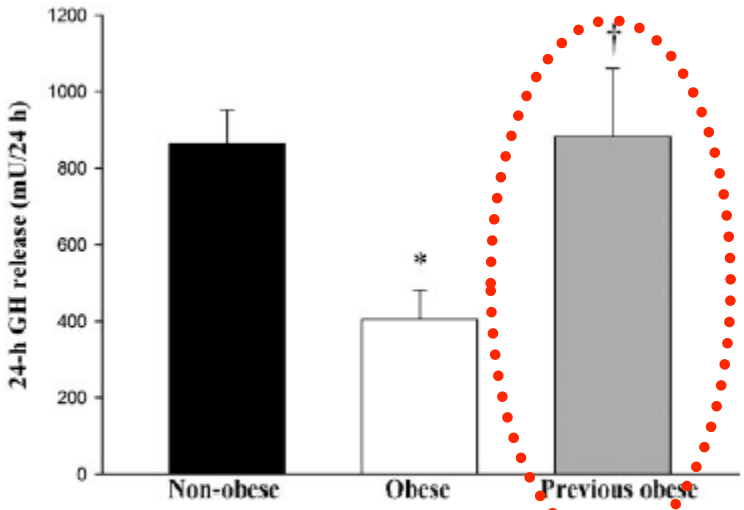


Figure 1: Twenty-four-hour GH release. Columns represent (left to right) levels in non-obese ($n = 16$), obese ($n = 16$), and previously obese women ($n = 8$). * $p < 0.001$ compared with non-obese. † $p < 0.05$ difference before and after weight loss.

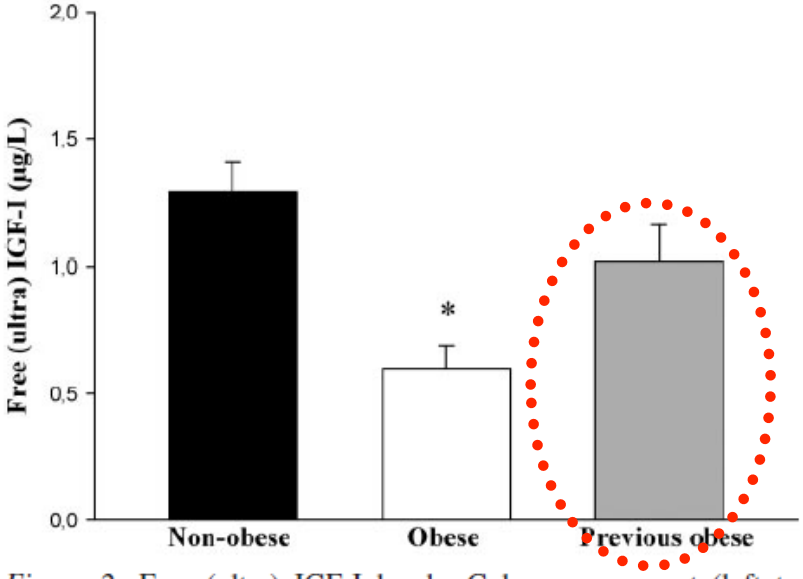


Figure 2: Free (ultra) IGF-I levels. Columns represent (left to right) levels in non-obese ($n = 16$), obese ($n = 16$), and previously obese women ($n = 8$). * $p < 0.001$ compared with non-obese. The difference when comparing previously obese women to the same eight obese women in the pre-diet state did not reach statistical significance.

Rasmussen MH, Juul A, Hilsted J.Obesity (Silver Spring). 2007 Apr;15(4):879-86.

Asse GH/IGF-1 e perdita di peso

J Clin Endocrinol Metab. 2004 Jan;89(1):174-80.

Growth hormone secretion and leptin in morbid obesity before and after biliopancreatic diversion: relationships with insulin and body composition.

De Marinis L, Bianchi A, Mancini A, Gentilella R, Perrelli M, Giampietro A, Porcelli T, Tilaro L, Fusco A, Valle D, Tacchino RM.

Institute of Endocrinology, Catholic University School of Medicine, 00168 Rome, Italy. laurademarinis@yahoo.it

Obes Surg. 2005 Sep;15(8):1118-23.

Impact of gastric banding on plasma ghrelin, growth hormone, cortisol, DHEA and DHEA-S levels.

Ram E, Vishne T, Diker D, Gal-Ad I, Maayan R, Lerner I, Dreznik Z, Seror D, Vardi P, Weizman A.

Division of General Surgery, Rabin Medical Center, Campus Golda, Petach Tikva Sackler Faculty of Medicine, Tel-Aviv University, Israel.

Eur J Endocrinol. 2006 Jan;154(1):53-9.

Effects of gastric bypass on the GH/IGF-I axis in severe obesity--and a comparison with GH deficiency.

Edén Engström B, Burman P, Holdstock C, Ohrvall M, Sundbom M, Karlsson FA.

Department of Medical Sciences, Internal Medicine, Uppsala University Hospital, Sweden. britt.eden_engstrom@medsci.uu.se

Asse GH/IGF-1 e perdita di peso

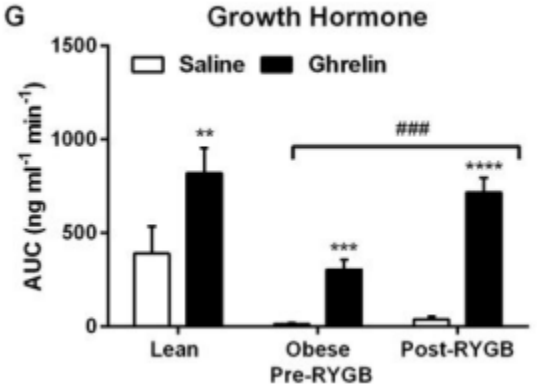
Published in final edited form as:
Diabetes Obes Metab. 2017 September ; 19(9): 1267–1275. doi:10.1111/dom.12952.

Metabolic responses to exogenous ghrelin in obesity and early after Roux-en-Y gastric bypass in humans

Robyn A. Tamboli[1], **Joseph Antoun**[1], **Reem M. Sidani**[1], **B. Austin Clements**[1], **Emily A. Eckert**[1], **Pam Marks-Shulman**[1], **Bruce D. Gaylinn**[2], **D. Brandon Williams**[1], **Ronald H. Clements**[1], **Vance L. Albaugh**[1], and **Naji N. Abumrad**[1]

[1]Department of Surgery, Vanderbilt University Medical Center, Nashville, TN

[2]Division of Endocrinology and Metabolism, Department of Medicine, University of Virginia, Charlottesville. VA



Asse GH/IGF-1 e perdita di peso

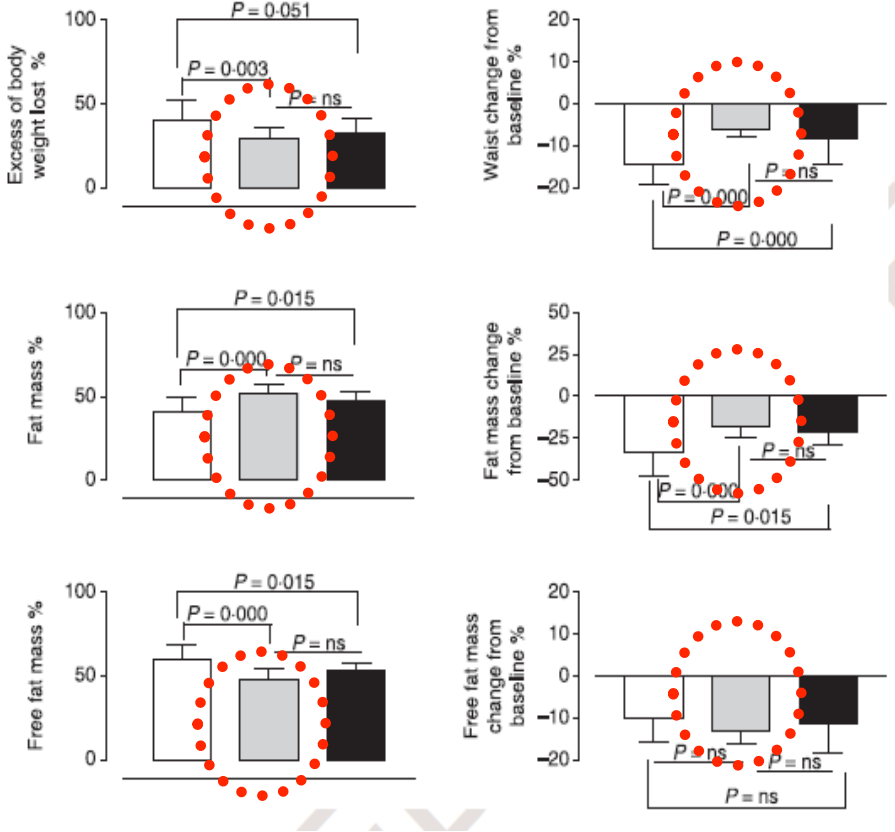
Clinical Endocrinology (2008) doi: 10.1111/j.1365-2265.2008.03183.x

ORIGINAL ARTICLE

GH and IGF-I deficiency are associated with reduced loss of fat mass after laparoscopic-adjustable silicone gastric banding

Carolina Di Somma*, Luigi Angrisani†, Francesca Rota*, Maria Cristina Savanelli*, Teresa Cascella*, Annamaria Belfiore‡, Francesco Orio*, Gaetano Lombardi*, Annamaria Colao* and Silvia Savastano*

*Department of Molecular and Clinical Endocrinology and Oncology, Division of Endocrinology, University Federico II of Naples, via S. Pansini 5, 80131 Naples, Italy, †Department of Surgery, S. Giovanni Bosco Hospital of Naples, via FM Briganti 255, 80144 Naples, Italy and ‡Department of Neuroscience, Unit of Physiology, University Federico II of Naples, via S. Pansini 5, 80131 Naples, Italy



GHS/IGFS (44 pz)

GHD/IGFD (14 pz)

GHS/IGFD (14 pz)

Asse GH/IGF-1 e obesità

- Ruolo fisiologico dell'asse GH/IGF-1
- Asse GH/IGF-1 e perdita di peso
- Evidenze efficacia terapeutica del GH

Obesità e terapia con GH

- Razionale è il ruolo non solo lipolitico ma anche protido-anabolico del GH nella preservazione della massa muscolare in corso di perdita di peso

Eur J Endocrinol. 2012 Apr;166(4):601-11. doi: 10.1530/EJE-11-1068. Epub 2012 Jan 24.

Effects of GH in women with abdominal adiposity: a 6-month randomized, double-blind, placebo-controlled trial.

Bredella MA[1], Lin E, Brick DJ, Gerweck AV, Harrington LM, Torriani M, Thomas BJ, Schoenfeld DA, Breggia A, Rosen CJ, Hemphill LC, Wu Z, Rifai N, Utz AL, Miller KK.

J Clin Endocrinol Metab. 2013 Sep;98(9):3864-72. doi: 10.1210/jc.2013-2063. Epub 2013 Jul 3.

Effects of GH on body composition and cardiovascular risk markers in young men with abdominal obesity.

Bredella MA[1], Gerweck AV, Lin E, Landa MG, Torriani M, Schoenfeld DA, Hemphill LC, Miller KK.

- Il trattamento con GH in assenza di documentata deficienza della secrezione di GH è controverso

Lewitt MS. Biochem Insights. 2017 Apr 20;10:1178626417703995

Massachusetts General Hospital and Harvard Medical School, Boston,

Dosaggio della terapia con GH

24 studies; 18 randomized parallel placebo-controlled

rhGH dose: 3.1 U/week – 10.4 mg/week

TABLE 2. Results of metaanalysis of rhGH therapy in obese adults, including clinical endpoints (body weight, BMI, body composition, fat distribution, calorimetry, and blood pressure)

Endpoint	Weighted mean difference	95% CI	*P* value	No. of studies	No. of subjects (GH)	No. of subjects (placebo)	Total no. of subjects	Q test *P* value	I^2 index (%)	Global effect size
BW (kg)	0.33	−0.44–1.09	0.403	20	207	213	420	0.021	43	
BMI (kg/m^2)	−0.3	−1.0–0.4	0.432	12	151	134	285	0.004	59	
WHR	−0.01	−0.02 to −0.001	0.027	5	65	72	137	0.838	0	
FM (kg)	−0.9	−1.3 to −0.4	<0.001	15	160	165	325	0.632	0	
% FM	−1	−1.3 to −0.7	<0.001	13	127	118	245	0.886	0	
% WLF	0.15	0.10–0.19	<0.001	6	36	36	72	0.129	41	
LBM (kg)	1.8	0.6–2.9	0.003	16	167	165	332	0.417	3	
VAT (cm^2)	−22.8	−39.8 to −5.7	0.009	8	97	93	190	0.984	6	
ST (cm^2)	2.2	−2.6–7	0.363	7	97	93	190	0.947	0	
TM (cm^2)	8.8	−1.4–19.1	0.092	5	55	51	106	0.998	0	
REE (kcal/24 h)	115	−33–262	0.127	7	94	87	181	<0.001	93	
RQ	−0.02	−0.05–0.004	0.102	3	25	27	52	0.049	67	
SBP (mm Hg)	4.6	−7.0–16.2	0.437	4	55	53	108	<0.001	88	
DBP (mm Hg)	1.4	−3.7–6.4	0.591	5	71	67	138	0.006	72	

BW, Body weight; FM, fat mass; ST, sc adipose tissue area; TM, thigh muscle area; VAT, visceral adipose tissue area; WLF, weight lost as fat.

Mekala KC, Tritos NA J Clin Endocrinol Metab. 2009 Jan;94(1):130-7

Obesità e terapia con GH

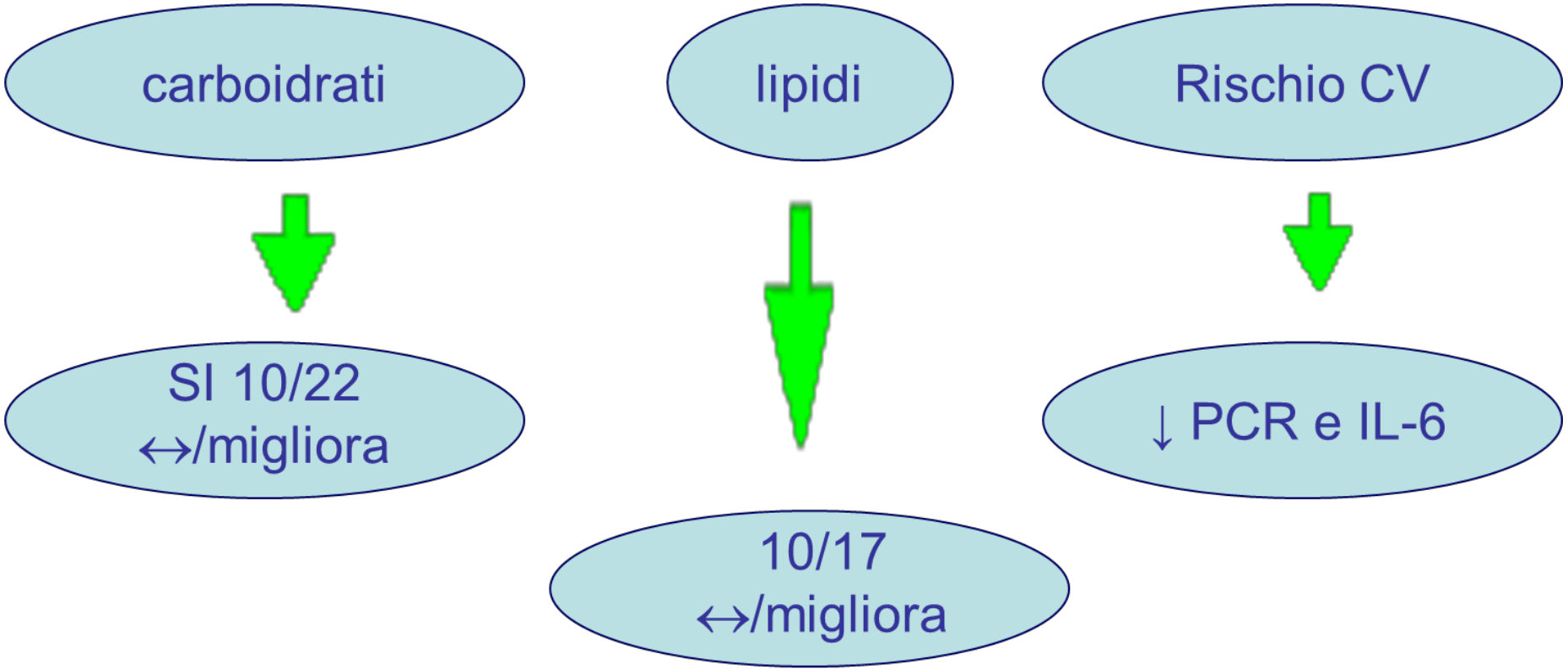
The clinical studies with a duration of treatment of at least 12 weeks. Effects of GH on weight and body composition.

Reference	Subjects		Body composition	Total FM	Abdominal FM	LBM	Body weight	Duration (dose)
	M	F	Method	Mean ± SD	Mean ± SD			
Albert and Mooradian (2004)	12	27	DEXA	↓* 2.89 kg ± 3.76	↓* 1.5 kg** ≈8%	→	↓* 2.4 kg** ≈2.4%	6 Months (3.8/6.0 μg/kg/d)
Ahn et al. (2006)	12	12	CT	↓* 4.0% ± 3.2	↓* 16.4 cm^2 ± 19.2 ≈10%	↑	→	12 Weeks (~500 μg/d)
Attallah et al. (2007), Attallah et al. (2007)	51	30	CT		↓* 23.9 cm^2 ± 7.4 ≈13%		→	40 Weeks (8.0 μg/kg/d)
Franco et al. (2005)		40	CT	→	↓* 6.6 cm^{2**} ≈6%	→	→	12 Months (670 μg/d)
Halpern et al. (2006)	40		DEXA	↓ 9.5% ± 7.9		→	↓* 3.5 kg** ≈2.9%	13 Weeks (50.0 μ/kg/d)
Johannsson et al. (1997)	30		CT	↓ 9.2% ± 2.4***	↓ 14.5% ± 3.8***	→	→	39 Weeks (9.5 μ/kg/d)
Kim et al. (1999)	2	22	BIA, CT	↓ 1.0 kg ± 0.5	↓ 31.5 cm^2 ± 2.3 ≈34%	→	→	12 Weeks (10.0 μg/kg/d)
Nam et al. (2001)	10	8	BIA, CT	↓* 1.0 kg ± 0.4	↓* 39.5 cm^2 ± 3.3 ≈28%	↑	→	12 Weeks (9.0 μg/kg/d)
Pasarica et al. (2007)	30		CT, DEXA	↓* 1.8% ± 0.3	↓* 0.6 kg ± 0.13 ≈5%	↑	↑ 2 kg** ≈1.9%	26 Weeks 10 mg/kg/d
Thompson et al. (1998)		16	DEXA	→		↑	→	12 Weeks (50 μg/kg/d)
Taaffe et al. (2001)		14	DEXA		→			12 Weeks (50 μg/kg/d)

* Significant change compared to placebo.
** No range provided.
*** Mean ± SEM.

Rasmussen MH. Mol Cell Endocrinol. 2010 Mar 25;316(2):147-53

Obesità e terapia con GH



Obesità e terapia con GH

Tempi di somministrazione (almeno 12 settimane)

Prima ↑ insulino resistenza

Dopo ↓ grasso viscerale ↑ massa magra e quindi ↓ insulino-resistenza

Rasmussen MH. Mol Cell Endocrinol. 2010 Mar 25;316(2):147-53

Dosi: 0.2-0.3 mg/die

per ridurre effetti collaterali ed iperinsulinemia che si oppone all'effetto lipolitico

Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II
Ken K Ho et al. 2007 EJE;157: 695

GH therapy dose in adults

Table 5. GH Replacement Therapy for AGHD

Starting dose	
Age <60 y	0.2–0.4 mg/d
Age >60 y	0.1–0.2 mg/d
Dose titration	
Increase by 0.1–0.2 mg/d	6-wk intervals
Dose determinants	
Mid-normal age-adjusted IGF-1 level	

Molitch ME, et al J Clin Endocrinol Metab 2011
Melmed S, et al J Clin Endocrinol Metab 2013
Fleseriu M, et al J Clin Endocrinol Metab 2016

Obesità e terapia con GH

- Se non somministrato in maniera pulsatile, l'incremento dei livelli di IGF-1 potrebbe ulteriormente sopprimere la secrezione endogena del GH

- L'uso degli analoghi del GHRH preserva la capacità secretoria del GH, mantenendo gli effetti positivi sul grasso viscerale, la dislipidemia ed il rischio CV, senza alterazioni della sensibilità insulinica

Stanley TL, Grinspoon SK. Growth Horm IGF Res. 2015 Apr;25(2):59-65

Trattamento con GH

Growth Horm IGF Res. 2018 Jun;40:20-27. doi: 10.1016/j.ghir.2018.03.003. Epub 2018 Mar 10.

The effect of growth hormone on bioactive IGF in overweight/obese women.

Dichtel LE[1], Bjerre M[2], Schorr M[3], Bredella MA[4], Gerweck AV[5], Russell BM[5], Frystyk J[2], Miller KK[3].

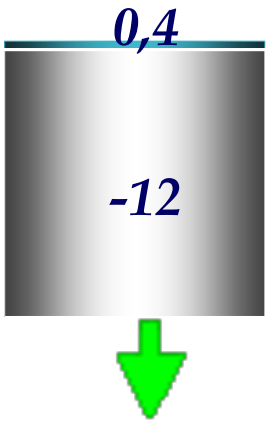
DESIGN: Cross-sectional analysis and 3-month interim analysis of a 6-month randomized, placebo-controlled study of GH administration in 50 overweight/obese women without diabetes mellitus

METHODS: Bioactive IGF (kinase receptor activation assay; KIRA) based on cells transfected with the human IGF-IR gene
Body composition (DXA)

RESULTS: GH administration resulted in an increase in mean serum IGF-I concentrations (144±56 to 269±66μg/L, $p<0.0001$) and bioactive IGF (1.29±0.39 to 2.60±1.12μg/L, $p<0.0001$). The treatment-related increase in bioactive IGF, predicted an increase in lean mass ($r=0.31$, $p=0.03$) and decrease in total adipose tissue/BMI ($r=-0.43$, $p=0.003$).

Obesità e terapia con GH

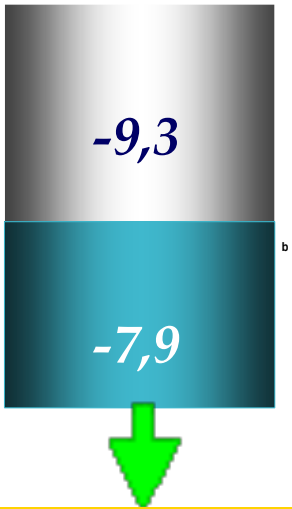
20 pazienti con obesità ed iposecrezione di GH

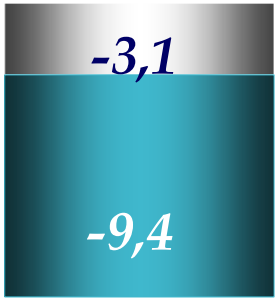


GH treated | **controls**

Massa magra (kg)

- initial dose: 0.15-0.30 mg/day (20-30 μg/kg/day)
- dose adjustment: according to IGF-1 (50-75%) levels up to 0.5±0.13 mg/day



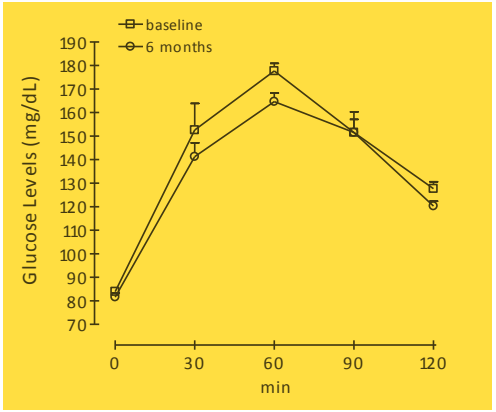


GH treated | **controls**

Massa grassa (kg)

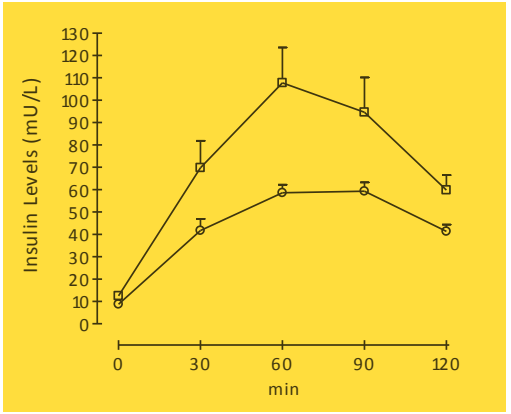
Savastano S, et al. J Clin Endocrinol Metab. 2009 Mar;94(3):817-26.

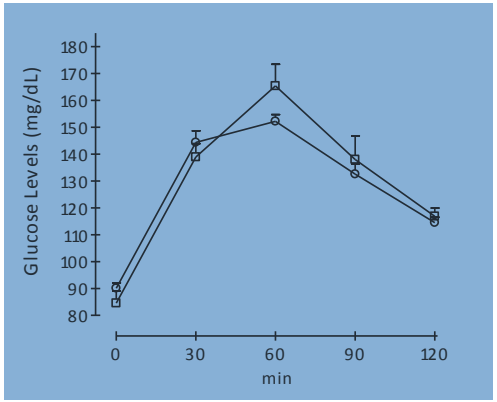
Trattamento con GH



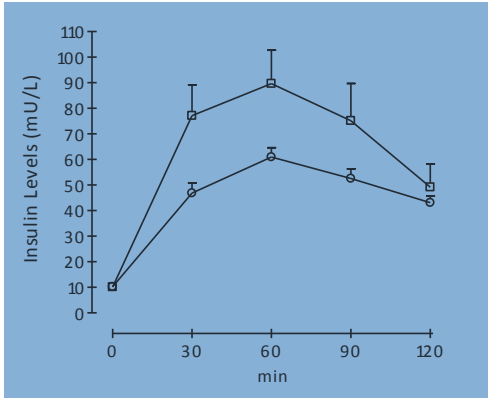
Group A

- In both groups, fasting and post-glucose AUC levels of insulin reduced significantly
- The HOMA and the ISI indices, however, improved only in group A patients

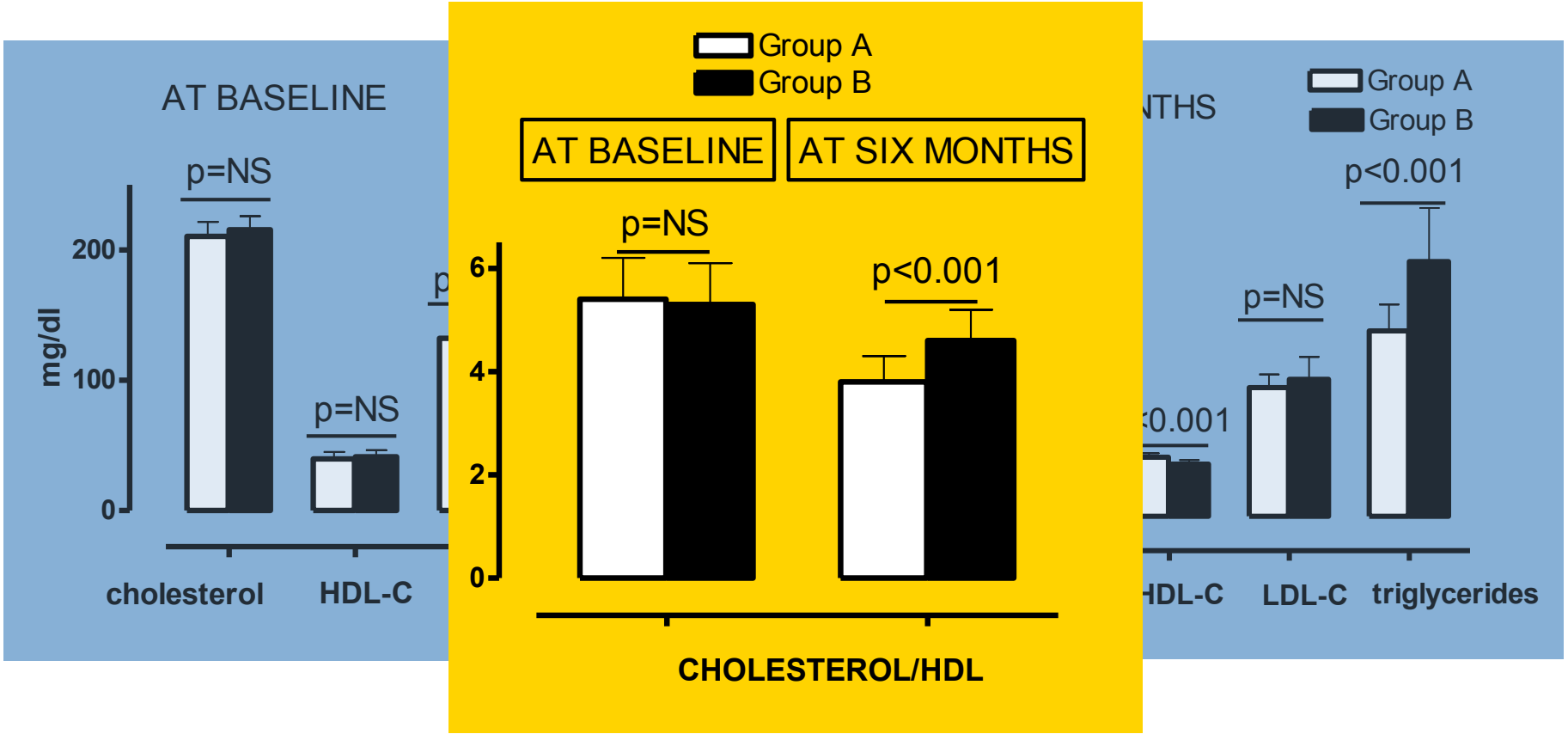




Group B



Trattamento con GH



Take Home Message

- GH esercita un fisiologico controllo sul metabolismo e sulla composizione corporea
- L'obesità è una condizione reversibile di ridotta secrezione del GH
- La ridotta secrezione di GH condiziona il fenotipo clinico
- Il trattamento senza documentata riduzione della secrezione di GH è controverso
- Gli effetti positivi richiedono un trattamento sufficientemente lungo
- Le dosi devono normalizzare i livelli di IGF-1 per evitare per l' effetto anti-lipolitico dell'iperinsulinemia