Milano 23 Novembre 2012
SIMPOSIO SIGG-ISSAM

Il ruolo della disregolazione ormonale multipla nel soggetto anziano

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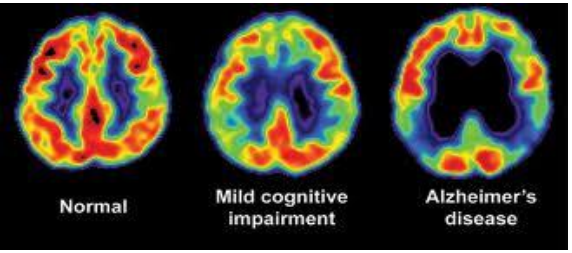
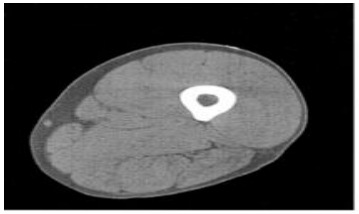
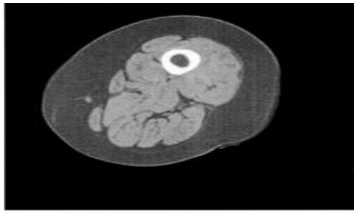
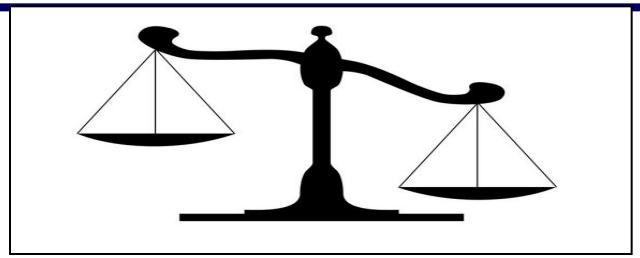
University of Parma, Italy



Outline







- Il concetto di disregolazione ormonale multipla
- Relazione tra singola modificazione anabolica e outcome clinico-funzionale: recenti studi d'intervento
- Implicazioni del concetto di disregolazione anabolica multipla: vecchie e nuove strategie di modulazione

Hormonal changes with age in older men

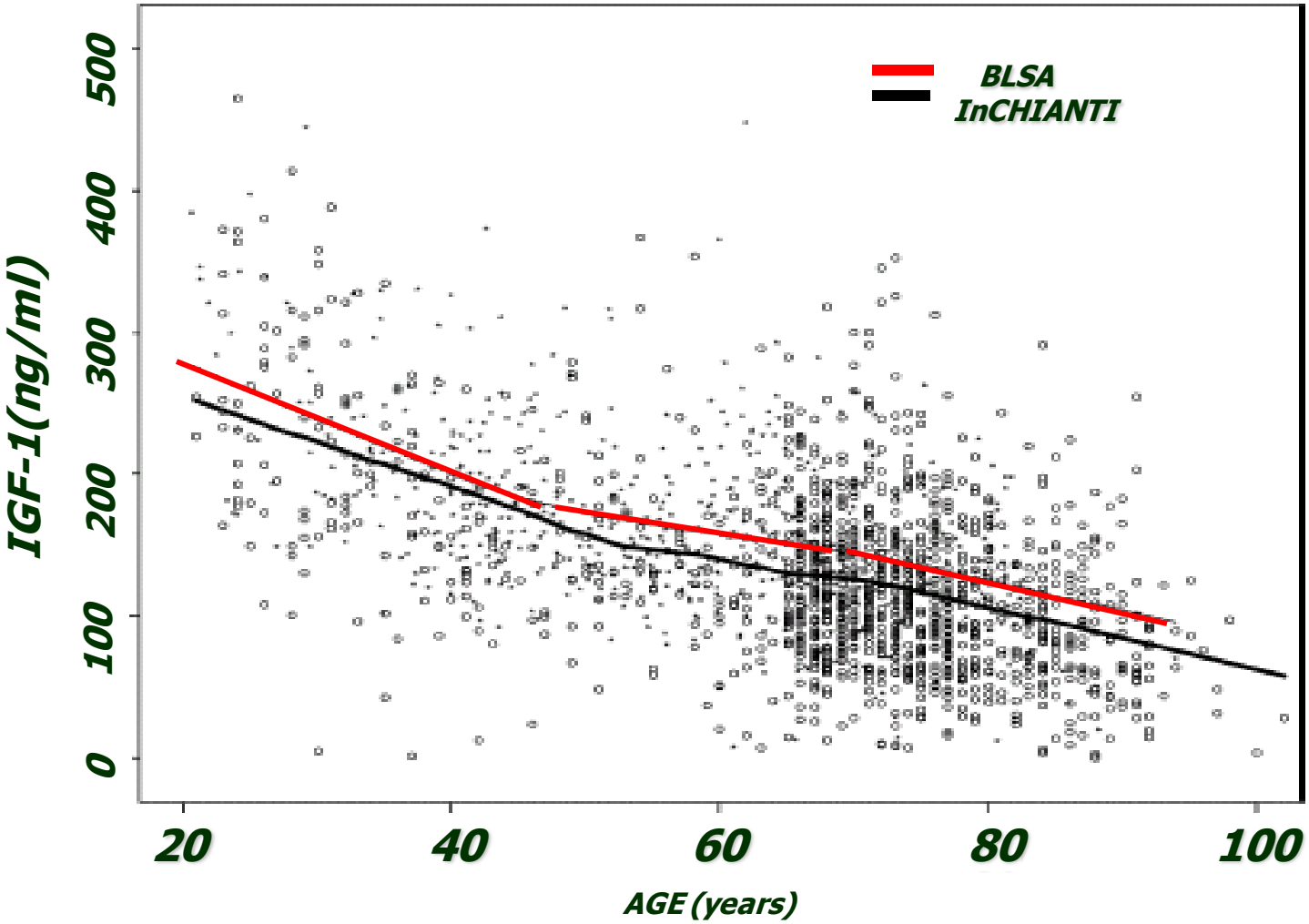
In older men <u>multiple hormonal dysregulation</u>:

<u>relative prevalence of catabolic hormones:</u> thyroid hormones and cortisol

<u>decline in anabolic hormones:</u> dehydroepiandrosterone sulphate (DHEAS),testosterone (T) and insulin like growth factor 1 (IGF-1).

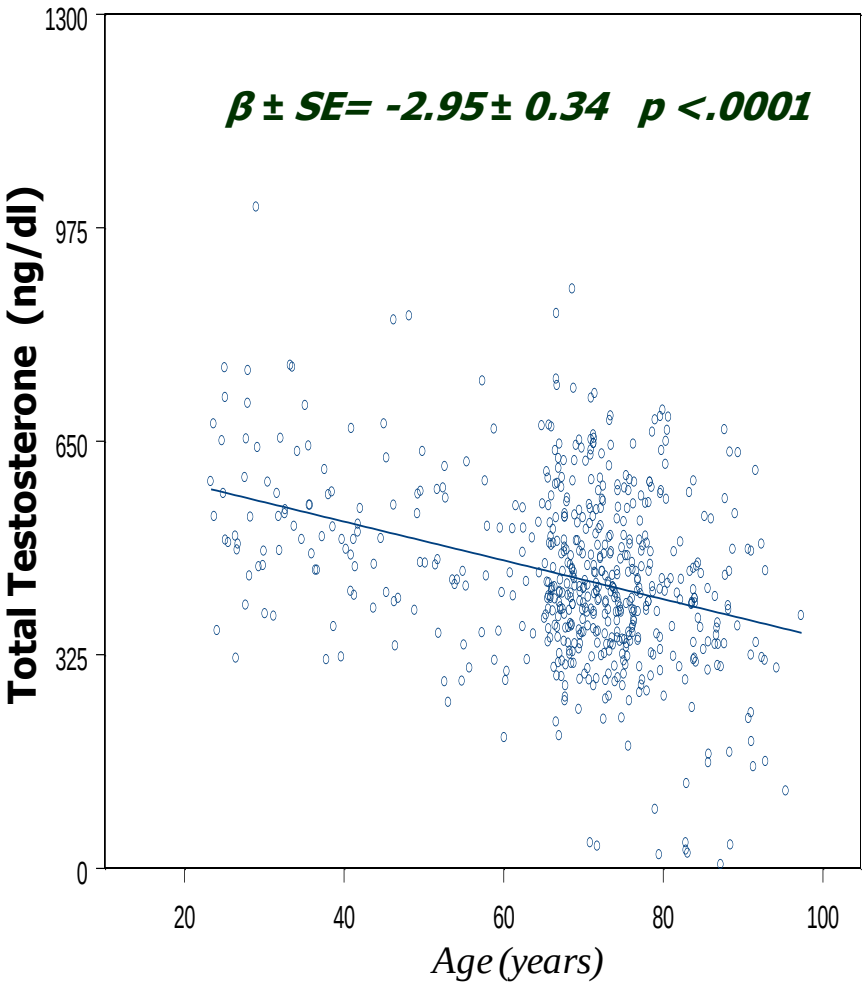
Maggio M et al. J Nutr Health Aging. 2012 Jan;16(1):40-54. Review

Relationship between IGF-1 and age in men and women



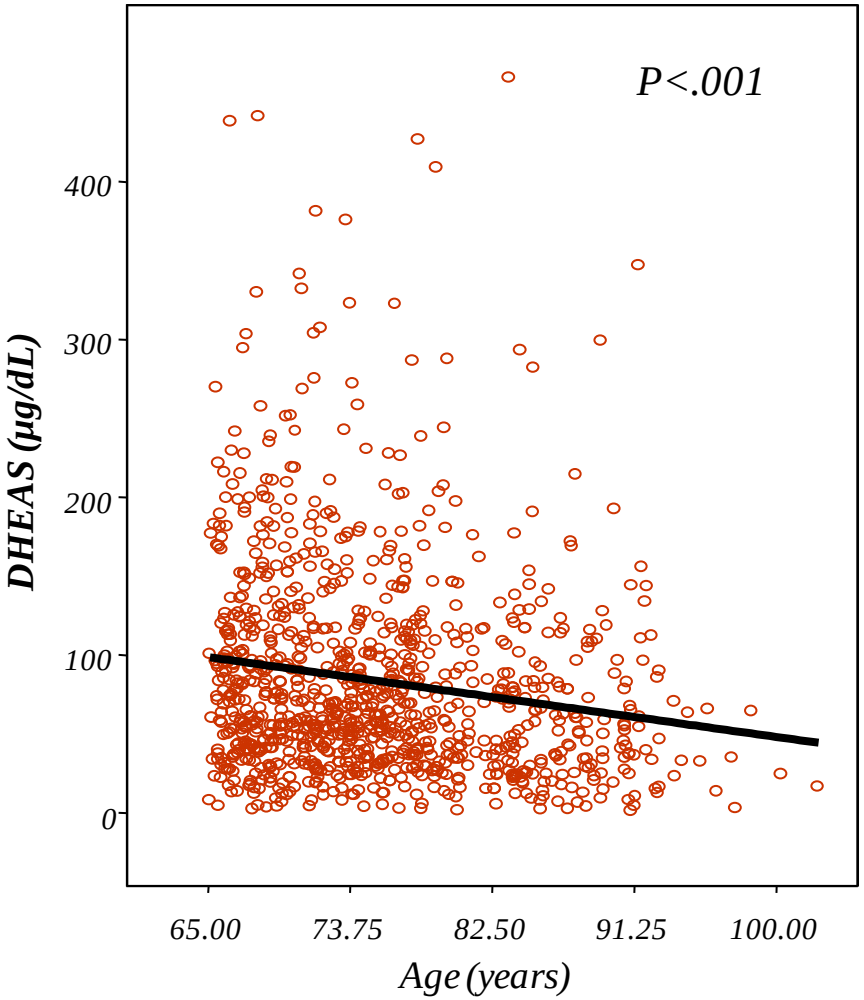
Maggio M et al. J Gerontol A Biol Med Sci 2006;61:182-3

Relationship between testosterone and age in men



Maggio M et al. 2012 in press

Relationship between DHEAS and age in 755 (410 men and 345 women)



Valenti G. et al J Endocrinol Invest 2009, 32, 766-72

Reduction of Anabolic Hormones:

-testosterone

-DHEAS

-IGF-1

-Vit. D

increase of Catabolic Hormones:

-Cortisol

-Thyroid

Cognitive function

Motor Neurons

Muscle function

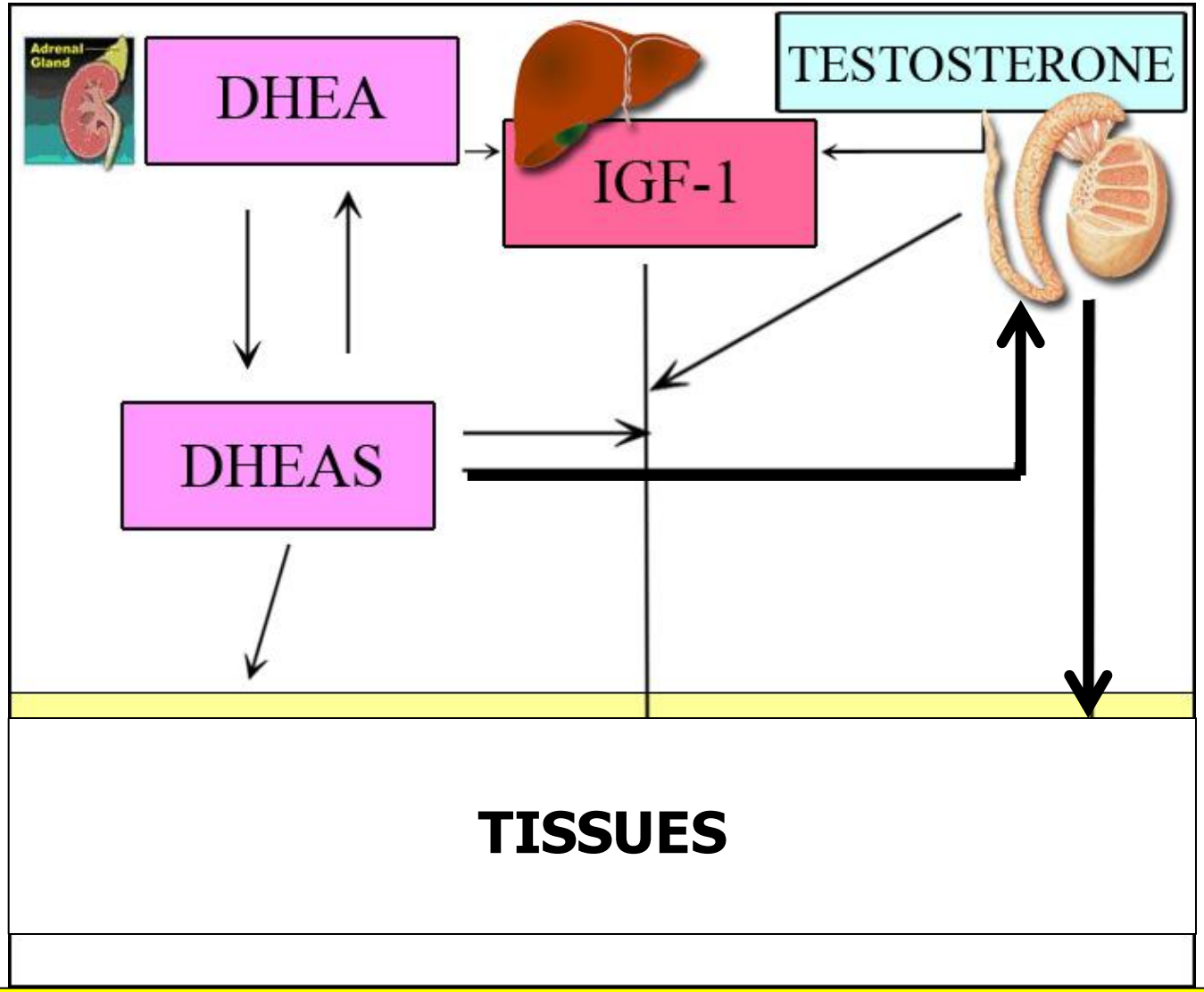
Energy expenditure

Physical performance

Mobility

Maggio M et al. Current Pharm Design 2013 in press

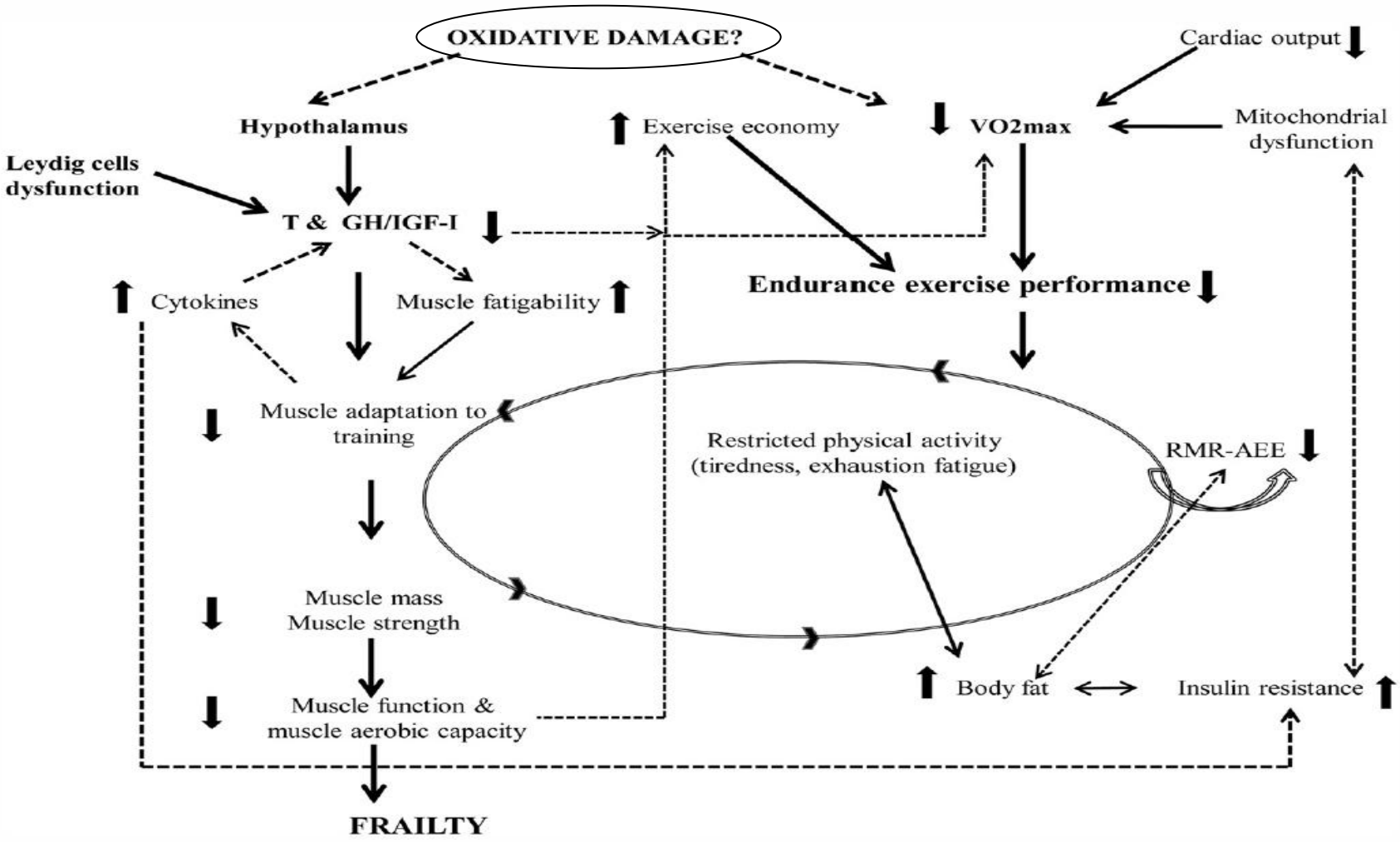
Interaction between anabolic hormones



From Maggio M, Cattabiani C, Ceda GP. Italian textbook of geriatric endocrinology:
Chapter 3 'La disregolazione ormonale multipla nel soggetto anziano'
Editor Maurizio Gasperi, Nicola Ferrara, 2010

Causes and Consequences of anabolic hormonal deficiency

Focus on testosterone and GH-IGF-1

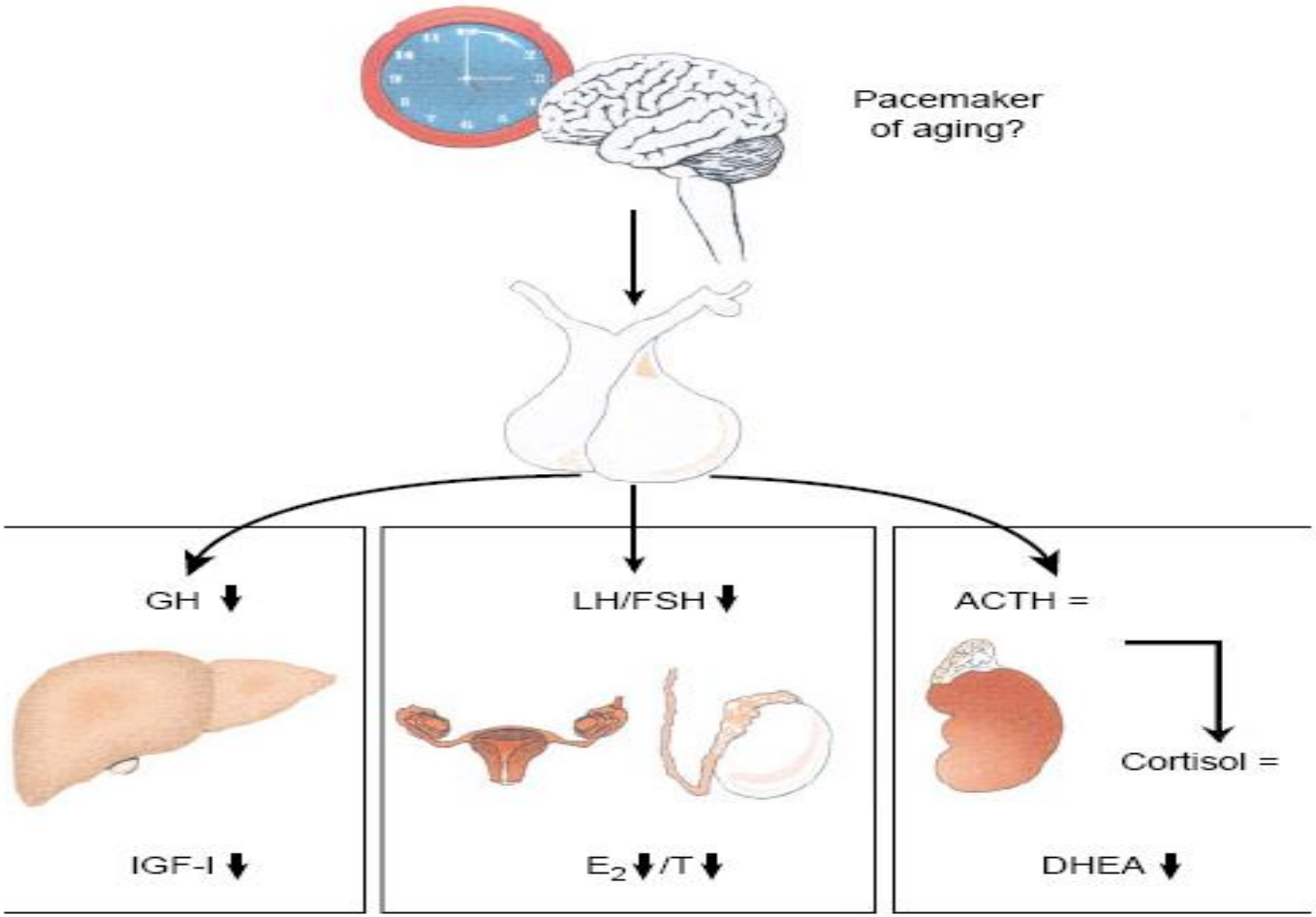


Giannaoulis et al. Endocrine reviews 2012;33:314-377

The Endocrinology of Aging

Steven W. J. Lamberts,* Annewieke W. van den Beld,
Aart-Jan van der Lely

SCIENCE • VOL. 278 • 17 OCTOBER 1997



Somatopause | *Andropause* / *Menopause* | *Adrenopause*

Overlapping of syndromes

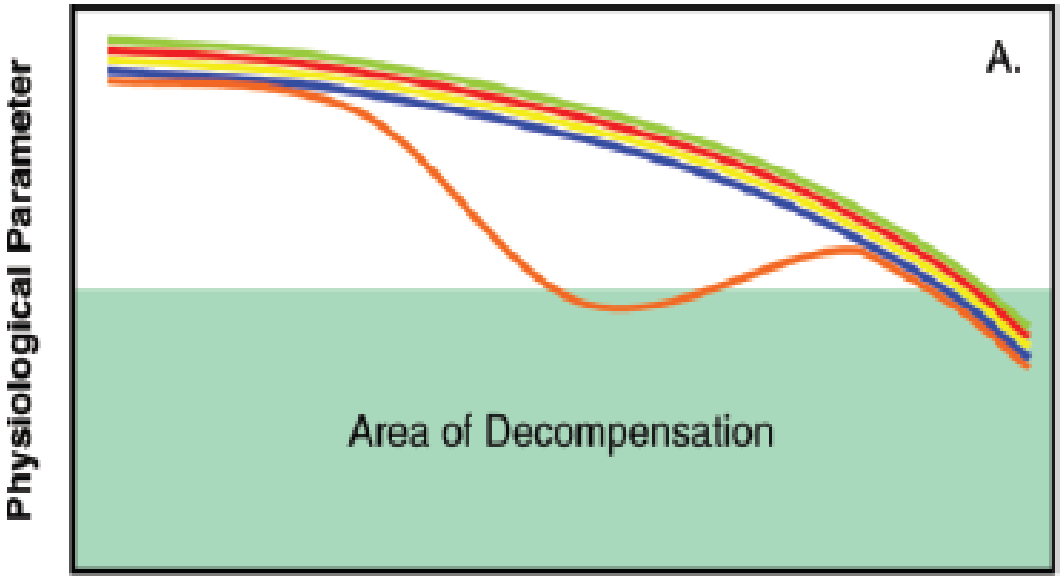
Overlapping of syndromes related to single anabolic hormone deficiency (adrenopause, andropause, somatopause)

Despite the profound interaction between anabolic hormones……..

Maggio M et al Acta Biomed. 2010;81 Suppl 1:19-29

Approach in the past

One Deficiency one therapy model



Cappola AR, Maggio M, Ferrucci L. J Gerontol A Biol Sci Med Sci. 2008;63(7):696-7

Illusions of Octavio Ocampo
Celaya-Mexico 1943

Cochrane Database Syst Rev 2007;(2):CD000304.WITHDRAWN:

Dehydroepiandrosterone (DHEA) supplementation for cognitive function

The data offer no support at present for an improvement in memory or other aspects of cognitive function following DHEA treatment in normal older people.

In view of the growing public enthusiasm for DHEA supplementation, particularly in the USA, and the possibility that any neuroprotective effect of DHEA/S may only be evident in the long term, there is a need to undertake high quality trials in which the duration of DHEA treatment is longer than one year, and the number of participants is large enough to detect effects if they exist.

Huppert FA,Van Niekerk JK
Cochrane Database Syst Rev 2007;(2):CD000304.

RCT addressing the effects of DHEA on muscle strength and physical function in older men (2005-2012)

between 2005 and 2012.

Author	Populations	Baseline DHEA	Oral DHEA Dose	Duration of Treatment	Effects of DHEA supplementation	Notes
Kenny AM et al. 2010	87 women, aged ≥ 65	0.30-0.32 µg/mL	DHEA 50 mg/d (N =43) vs Placebo (N = 44)	6 months	**Markers of muscle strength:** - *Handgrip (Jamar dynamometer)*: no difference from baseline with DHEA vs placebo - *Leg press*: significantly greater improvement in DHEA group vs placebo group, when combined with gentle exercise **Physical Function and Performance:** - *composite scores:* significant improvement in favour of DHEA supplementation	Gentle exercise: chair aerobics or yoga held during two 90-minute session per week
Igwebuike A et al. 2008	31 sedentary women, aged 54-72	0.39-0.43 µg/mL	DHEA 50 mg/d (N=17) vs Placebo (N=14)	3 months	**Markers of muscle strength:** - *Chest press*: no significant effect - *Leg press:* no significant changes **Physical Function and Performance:** - *peak of oxygen uptake (marker of peak aerobic activity)*: no significant improvement in VO_{2peak}	Exercise training: endurance training (cycle ergometry) 4 days per week and resistance training 3 days per week
Muller M et al. 2006	49 men, aged ≥ 70 With low strength scores	0.66 µg/mL	DHEA 50 mg/d (N=25) vs Placebo (N=24)	9 months	**Markers of muscle strength:** - *Handgrip (Jamar dynamometer)*: no difference from baseline with vs placebo - *knee extensor and flexor*: no significant effect of DHEA on isometric knee extension or flexion when compared with placebo **Physical Function and Performance:** - *composite scores* no significant improvement between DHEA and placebo groups	

Maggio M et al. Curr Opin Med Car and Nutr. 2012 in press

RCT on DHEA and physical function in older men (2005-2012)

Nair KS et al. 2007 (18)	30 men and 87 women, aged ≥ 60	Men with DHEA-S < 1.57 µg/mL and Women with DHEA-S < 0.95 µg/mL	DHEA 75mg/d (N=56; men 24.7%) vs Placebo (N=61; men26.5%)	24 months	**Markers of muscle strength:** - *Chest press*: no significant effect - *Leg press:* no significant effect - *knee extensor and flexor*: no significant effect of DHEA on isometric knee extension or flexion when compared with placebo **Physical Function and Performance:** - *peak of oxygen uptake (marker of peak aerobic activity)*: no significant differences in improvement in VO_{2peak} between DHEA and placebo groups	
Villareal DT et al. 2006 (19)	28 men and 28 women, aged 65-78	< 0.33 µg/mL	DHEA 50 mg/d (N=29; men 51.7%) vs Placebo (N=27; men 48.1%)	10 months	**Markers of muscle strength:** - *chest press:* significant increasing from baseline when combined with resistance training at 10 months, both in men and women - *leg press:* significantly greater improvement with DHEA, when combined with resistance training than with training alone - *knee extensor and flexor*: greater improvement only in knee extension with DHEA plus resistance training than with training alone	All patients participated in a supervised weight-training program 3 day per week

Maggio M et al. Curr Opin Med Car and Nutr. 2012 in press

Relationship between testosterone and cognitive function in elderly

Author/Reference	Type of survey	Population	Follow up	Results
Yonkers J.E. et al. 88	Cross-sectional	450 healthy men aged 35-80 years, stratified to testosterone levels	--	Participants with low free T performed at a superior level on both the block design task and draw-a-figure task as compared to participants with high free T.
Martin DM, et al . 78	Cross-sectional	1046 community-dwelling men aged 35–80 years	--	Higher TT and FT levels were associated with better performance on a measure of processing speed and poorer performance on measures of both learning and memory and executive function.
Chu L. et al. 80	Cross-sectional	203 Chinese older men, aged 55-93 yr 48 with mild) cognitive impairment (aMCI 66 with Alzheimer disease (AD) 89 with normal cognition	--	Bioavailable T levels, but not Total T, were significantly lower in the aMCI and AD groups than in the normal controls with no significant difference between the aMCI and AD groups.
Yeap B.B. et al. 81	Cross-sectional	2932 men aged 70-89 yr	--	There is a positive association between serum free testosterone levels and cognitive function assessed by MMSE.
Chu L, et al. 79	Longitudinal	153 ambulatory healthy Chinese men, aged 55 yr or over	1 yr	The baseline serum bioavailable testosterone level predicted a reduced risk of Alzheimer's disease in older men
Maggio M et al. 82	Cross-sectional	455 men aged > 65 1) severely hypogonadal (T<230 ng /dl); 2) moderately hypogonadal (230< T<350 ng/dL), 3) eugonadal (T > 350 ng/dL)	--	In the age and BMI adjusted analysis, a significant difference in MMSE score, was observed among the three groups, with severely hypogonadal men having lower values of MMSE. However, in a fully-adjusted analysis MMSE did not remain significantly associated with testosterone levels.

Maggio M et al. J Nutr Health Aging. 2012 Jan;16(1):40-54. Review

RCT on testosterone on cognitive function in older men

Author/Reference	Type of survey	Population	Follow up	Results
Vaughan C. et al. 97	RCT	69 healthy men aged 65-83 years; 24 testosterone group (T-only), 22 testosterone + finasteride group (T+F), 23 placebo group	36 months 1) T-only group, T enanthate (200 mg im every 2 weeks + orally placebo daily; 2) T+F group, TE 200 mg im every 2 weeks + finasteride (5 mg/d orally) 3) placebo group, sesame oil injections, 1 mL im every 2 weeks + placebo pill daily.	T replacement, whether given alone or in combination with finasteride, in healthy older men without cognitive impairment at baseline has no clinically significant effect on cognitive function.
Maki P.M. et al. 99	RCT	15 cognitively normal men, aged 66-86 yr	9 months testosterone enanthate 200 mg im every other week (for 90 d) or placebo im	T treatment leads to a significant decrease in short-delay verbal memory and a nonsignificant decrease on a composite verbal memory measure.
Emmelot-Vonk M.H. et al. 98	RCT	237 healthy men aged 60- 80 yr with testosterone lower than 13.7 nmol/L	6 months 80 mg of testosterone undecenoate or a matching placebo twice daily	Testosterone supplementation in older men with a low normal testosterone concentration did not affect cognition.
Fukai S et al. 95	No RCT	11 men with cognitive impairment, and 13 controls aged 81±6	6 months oral testosterone undecanoate 40 mg daily	At 3 months subjects on testosterone treatment showed no significant increase in MMSE and HDS-R, whereas at 6 months, cognitive scores were significantly greater than the baseline.

Maggio M et al. J Nutr Health Aging. 2012 Jan;16(1):40-54. Review

RCT testing the effects of T on muscle strength and physical function in older men (2005-2012)

Author	Populations	Baseline Total Testosterone	Form of testosterone	Duration of treatment	Effects	Notes
Kenny AM et al._2010	131 men (mean age 77.1 +/- 7.6)	<350ng/dl	Transdermal	12-24 months	↑lean mass ↓fat mass in testosterone group but no differences in strength or physical performance	Calcium and Vitamin D Treatment was also performed
Srinivas-Shankar U, et al 2010	24 healthy, community-dwelling older men (60–85 yr)	<350ng/dl	transdermal hydro-alcoholic T gel (Testogel 1%;) at a dose of 50 mg/d	6 months	Improved lower limb muscle strength and improve body composition, quality of life, and physical function	Intermediate frail population
Travison TG et al 2011	209 randomized participants, 165 had follow-up efficacy measures. Mean (SD) age was 74 (5.4) years	100-350 ng/dL	10g testosterone gel daily	6 months	↑ muscle strength and stair-climbing power	Participants with mobility limitation: stopped because of higher prevalence of CVD
Bhasin S et al 2012	8 treatment groups received (4 groups) or 2.5 mg/d of dutasteride (4 groups)	300-1200 ng/dl	testosterone enanthate 50, 125, 300, or 600 mg/wk of for plus placebo	20 weeks	Changes in fat-free mass in response to graded testosterone doses did not differ in men in whom DHT was suppressed by dutasteride	with and without a dual 5α-reductase inhibitor

Maggio M et al. Curr Opin Med Car and Nutr. 2012 in press

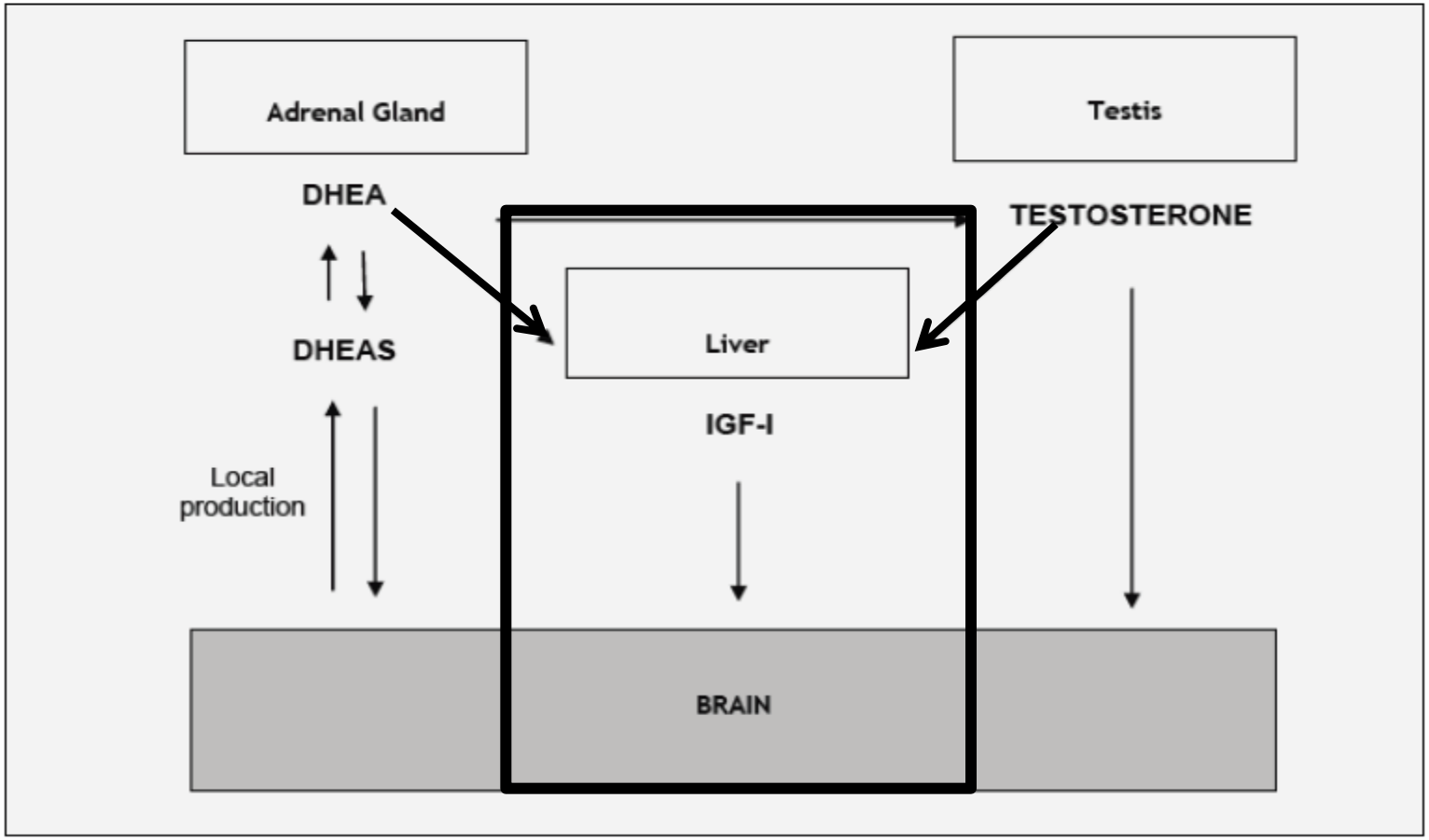
Brief Summary on DHEAS, testosterone and physical and cognitive function in older men

Inconclusive data from RCT including cognitively and physically active adult or young old normal and with normal baseline hormonal levels

Maggio M et al. Curr Opin in Clin Nutr and Med Care 2013 in press

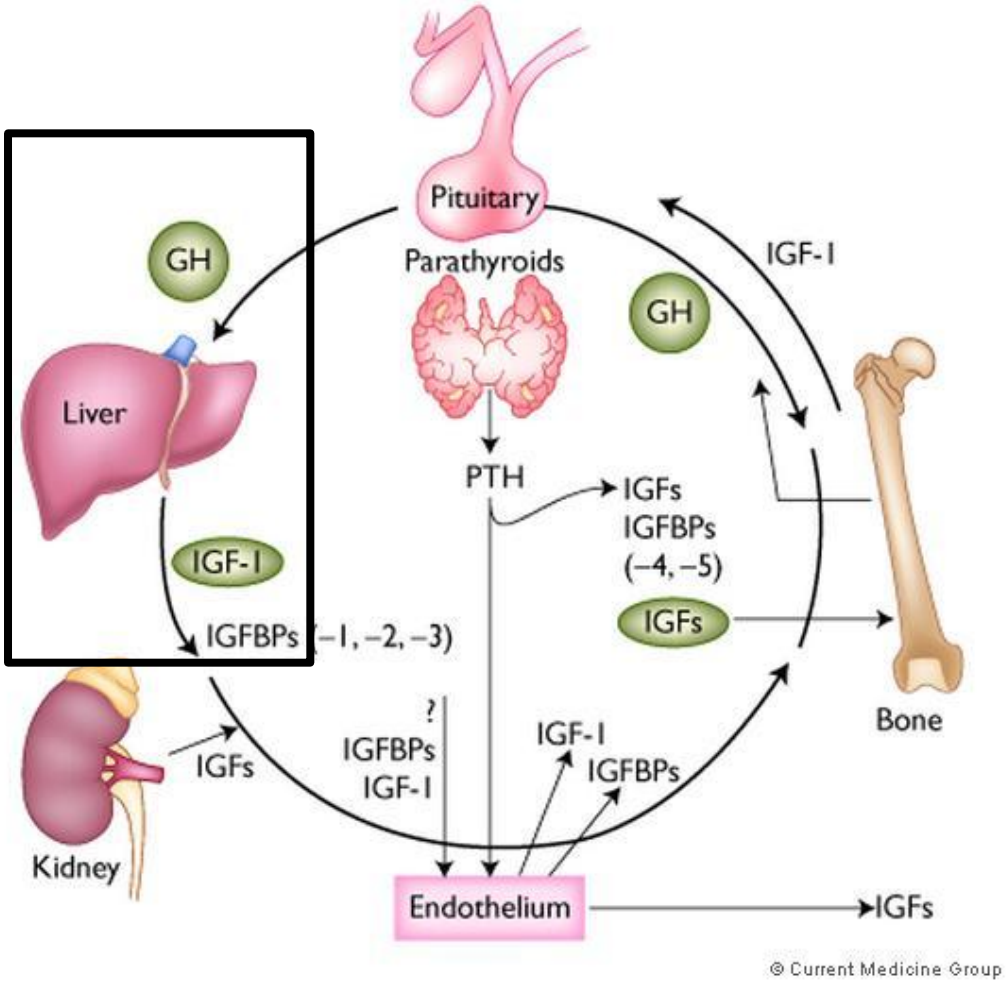
Maggio M et al. J Nutr Health Aging. 2012 Jan;16(1):40-54. Review

Interaction between anabolic hormones in human physiology



Maggio M et al. J Nutr Health Aging. 2012 Jan;16(1):40-54. Review

Physiology of GH IGF-1 system



Effects of 52 week GH treatment on cognition in GHD older men

N= 34 (age range 60-77)

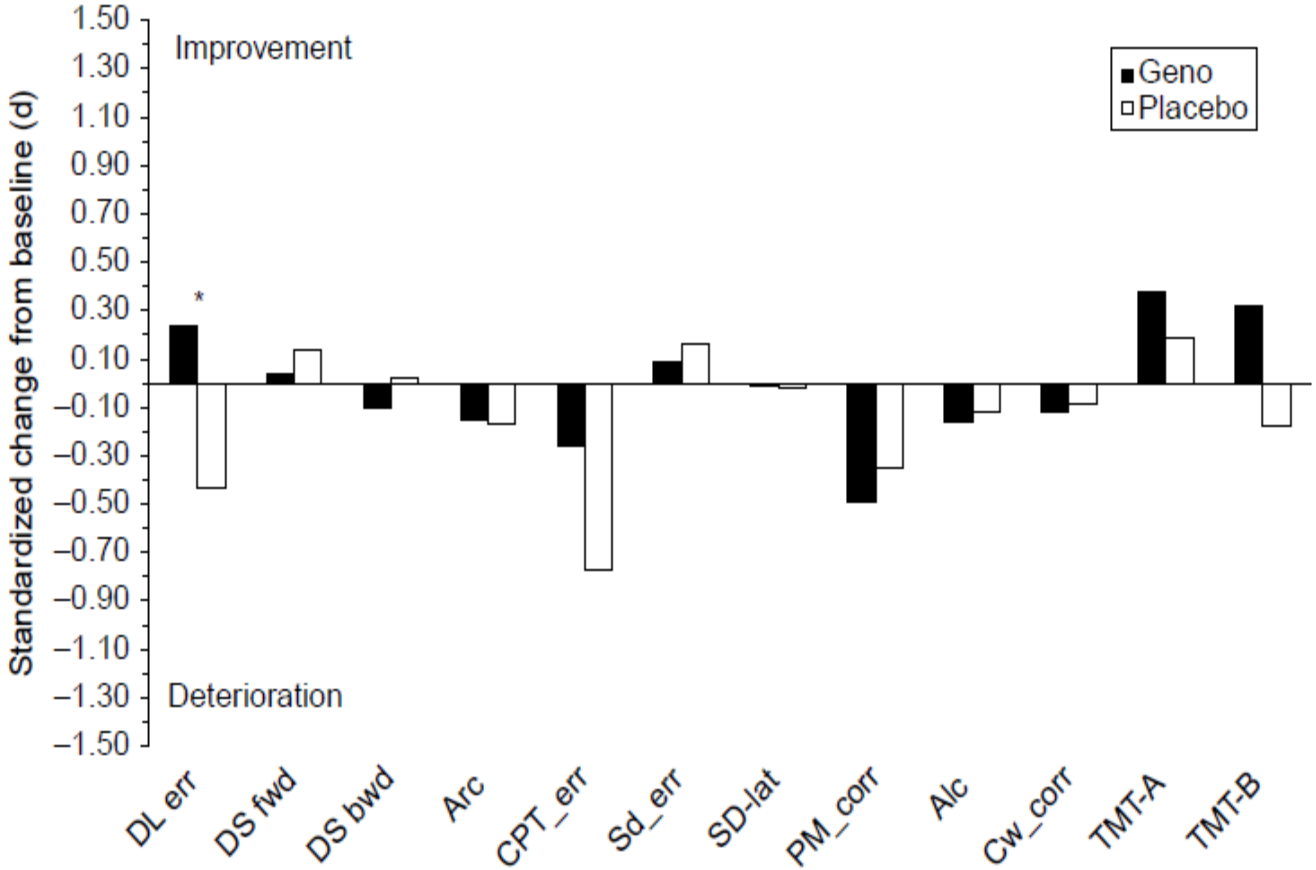


Figure 1 Differences in performance between the GH and the placebo groups for each measure of cognitive function at 24 weeks, *$P<0.05$. DL err, serial digit learning (error); DS fwd, digit span (forward); DS bwd, digit span (backward); Arc, associate learning (recall); CPT_err, continuous performance; Sd_err, symbol digit (errors); Sd-lat, symbol digit (latency); PM_corr, pattern memory; Alc, associate learning; Cw_corr, colour word; TMT-A, trail making test, version A; TMT-B, trail making test, version B.

Sathiavageeswaran M et al. Eur J Endocrinol 2007; 156: 439-447

GH treatment on muscle function in healthy older men: a review

First author, year (Ref.)	Study protocol, active treatment, duration, no. of subjects	Main subject characteristics	Main findings and remarks
Papadakis, 1996 (94)	Parallel groups	Healthy older men	LBM increased and BF decreased; no changes in muscle function, VO_2max
	GH, 30 μg/kg 3 times/wk; doses adjusted according to IGF-I levels	Age, 70–85 yr	
	Duration, 6 months	IGF-I, <161 ng/ml	
	Act, n = 26; PL, n = 29 (dropouts, Act, n = 2; PL, n = 2)	Baseline IGF-I, 75.2 ± 4.5 ng/ml	
Munzer, 2001 (576); Blackman, 2002 (49); Christmas, 2002 (583); Huang, 2005 (598); Münzer, 2009 (645)	Parallel groups	Community-dwelling healthy older men	Increased LBM and decreased total and sc fat; no changes in BMD, VO_2max, protein kinetics, or muscle function
	GH starting dose, 30 reduced to 20 μg/kg, 3 times/wk	Age, 65–88 yr	
	Duration, 6 months	IGF-I, <230 ng/ml	
	Act, n = 17 to 21; PL, n = 17 (dropouts, Act, n = 1)	Baseline IGF-I, 146 ± 10 ng/ml	
Giannoulis, 2006 (48, 646); 2008 (597)	Parallel groups	Community-dwelling healthy older men	LBM and whole body protein turnover increased
	GH starting dose, 0.1 mg/d; increased gradually to a mean of 0.54 mg/d	Age, 65–85 yr	No changes in BF, muscle function, VO_2max, lipid profile, VLDL metabolism
	Target IGF-I, 250 ng/ml	IGF-I, <145 ng/ml	No changes in insulin levels; no glucose intolerance, diabetes, or other adverse events
	Duration, 6 months	Baseline IGF-I, 102 ± 5.3 ng/dl	
	Act, n = 18; PL, n = 20 (dropouts, Act, n = 2; PL, n = 4)		
Lange, 2001 (595)	Parallel groups	Healthy older men	LBM increased, BF decreased
	GH increased gradually over 3 wk to 12 μg/kg · d	Age, 74 ± 1 yr	
	Duration, 12 wk	Baseline IGF-I, 162 ± 22 ng/ml	
	Act, n = 8; PL, n = 8 (dropouts, Act, n = 2)		
Rudman, 1990 (20)	No placebo control study	Healthy older men	Increased LBM, decreased BF, marginal improvement in BMD
	GH, 30 μg/kg 3 times/wk	Age, 61–81 yr	
	Duration, 6 months	IGF-I, <189 ng/ml (350 U/liter)	
	Act, n = 12; controls, n = 9 (no treatment was given)	Baseline IGF-I, 162 ± 11.9 ng/ml	
Cohn, 1993 (593)	No placebo control study	Community-dwelling healthy older men	High incidence of adverse events observed when IGF-I levels were above the 75%ile for the young age-specific normal range
	GH, 30 μg/kg 3 times/wk	Age, >60 yr	
	Duration, 6 months	IGF-I, <189 ng/ml	
	Act, n = 50; controls, n = 18 (no treatment was given) (dropouts, Act, n = 27; PL, n = 2)	Baseline IGF-I, 165 ± 12.6 ng/dl	
Lange, 2002 (594)	Parallel groups	Community-dwelling healthy older men	Changes in body composition, but muscle strength, power, muscle CSA, fiber size did not change
	GH ± Ex	Age, 70–82 yr	No additional improvement in muscle strength was observed when GH was co-prescribed with Ex
	GH increased gradually over 3wk to 12 μg/kg · d	Baseline IGF-I, 145 ± 14 ng/dl	
	Duration, 12 wk		
	Act GH, n = 8; Act GH+Ex, n = 8; Ex, n = 8; PL, n = 7		

Giannoulis et al. Endocrine Reviews 2012; 33: 314–377

GH treatment on muscle function in healthy older men: a review

First author, year (Ref.)	Study protocol, active treatment, duration, no. of subjects	Main subject characteristics	Main findings and remarks
Taaffe, 1996 (461); 1994 (607)	Parallel groups	Healthy older men	GH failed to further improve the muscle function, muscle CSA, and fiber size observed after Ex alone
	14-wk Ex program followed by 10-wk treatment period	Age, 65–82 yr	
	GH, 20 μg/kg · d	Baseline IGF-I, 113 ± 10 ng/ml	
	Duration, 10 wk		
	Act GH+Ex, n = 10; Ex+PL, n = 8 (dropouts, Act, n = 2)		
Yarasheski, 1995 (512); 1997 (589)	GH ± resistance Ex	Healthy older men	High doses of GH were used, hampered by high incidence of adverse events
	GH, 12.5–24 μg/kg · d	Age, 67 ± 1 yr	Short-term GH administration in conjunction with Ex program did not confer any additional benefits on muscle function outcomes
	Duration, 16 wk	Baseline IGF-I, 106 ± 13 ng/ml	
	Act GH+Ex, n = 12–8; PL+Ex, n = 15 to 11 (dropouts, Act GH+Ex, n = 5)		

All studies included are randomized, placebo-controlled and double blind unless otherwise stated. Nine trials were identified where GH was administered in healthy subjects and not in older men (aged >60 yr) who were frail or had other associated comorbidities that were reported on outcome measurements related to physical function. From the 309 subjects included, 169 received GH. Act, Active treatment; PL, placebo; Ex, exercise.

Giannoulis et al. Endocrine Reviews 2012; 33: 314–377

Guest Editorial

Is Research on Hormones and Aging Finished? No! Just Started!

Anne R. Cappola,[1] Marcello Maggio,[2] and Luigi Ferrucci[2]

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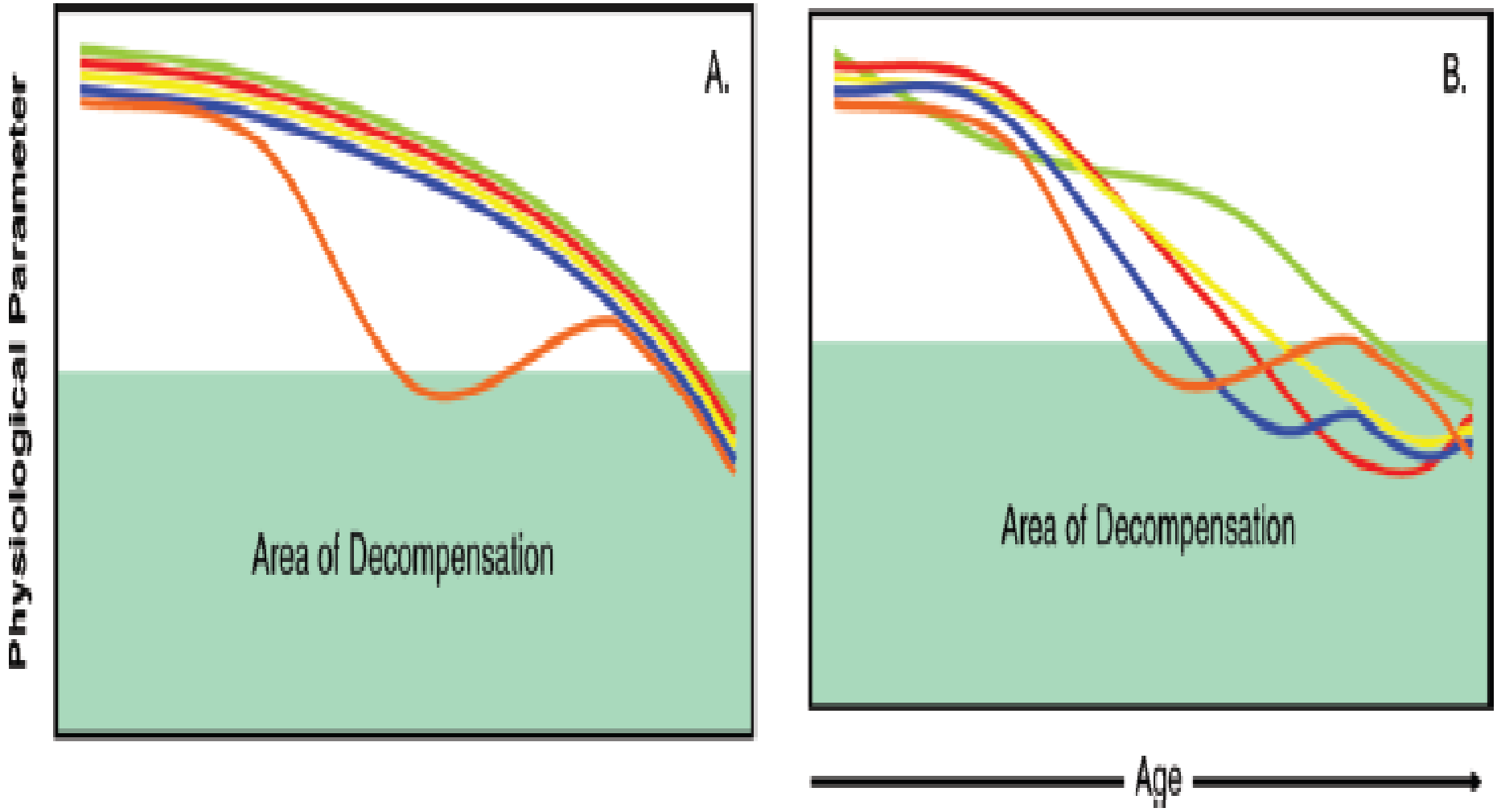
Cappola AR, Maggio M, Ferrucci L. J Gerontol A Biol Sci Med Sci. 2008;63(7):696-7

Individual hormones do not operate independently of each other

Individual hormones do not operate independently of each other. Rather, one hormonal problem may trigger the onset of another. In a younger person, correction of the original hormonal problem may correct both, such as resolution of hypogonadism after cure of Cushing's syndrome. In an older person, this simplistic approach is less likely to be successful for several reasons. First, the abnormalities are subtle, progressive, and not clinically discernable from the effects of nonendocrine comorbidities. Second, in the absence of overt glandular dysfunction, the inciting hormonal problem may not be apparent. Finally, the interdependence of hormones can lead to a synergistic effect, creating a vicious cycle where intervention on a single hormone has a negligible effect.

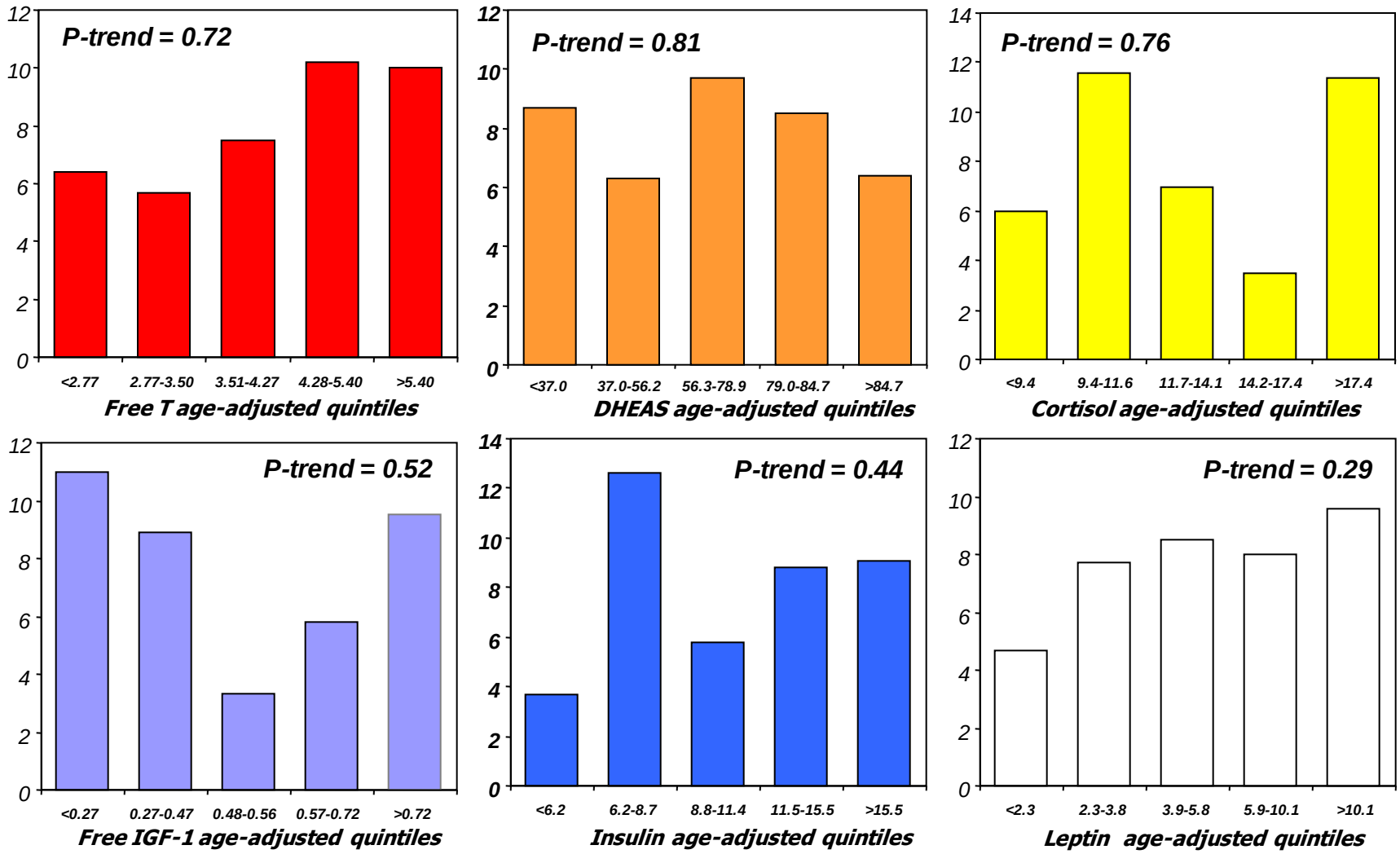
Cappola AR, Maggio M, Ferrucci L. J Gerontol A Biol Sci Med Sci. 2008;63(7):696-7

From 1 Deficiency therapy model to multisystem decline model



Cappola AR, Maggio M, Ferrucci L. J Gerontol A Biol Sci Med Sci. 2008;63(7):696-7

Prevalence of the Frailty Syndrome According to Age-Adjusted Quintiles of Hormonal Levels



Maggio M et al. ***J Endocrinol Invest. 2005;28(11 Suppl Proceedings):15-9. Review.***

Odds-Ratios for Frailty Syndrome associated with hormonal dysregulation in older men

Hormonal pattern	OR*	95% C.I.
Cort DHEAS	2.9	(0.7-12.2)
DHEAS FTe	0.6	(0.1-5.1)
Cort FTe	3.8	(0.9-14.5)
DHEAS IGF-1	4.3	(1.1-16.4)
Cort DHEAS FTe	10.0	(1.6-64.4)

* Adjusted for age

Maggio M et al. *J Endocrinol Invest. 2005;28(11 Suppl Proceedings):15-9. Review.*

Journal of Gerontology: MEDICAL SCIENCES
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2009, Vol. 64A, No. 2, 243–248
doi:10.1093/gerona/gln026

Advance Access publication on January 31, 2009

Multiple Hormonal Deficiencies in Anabolic Hormones Are Found in Frail Older Women: The Women's Health and Aging Studies

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[2]Division of Geriatric Medicine and Gerontology, Department of Medicine, and Center on Aging and Health, Johns Hopkins Medical Institutions, Baltimore, Maryland.
[3]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York.

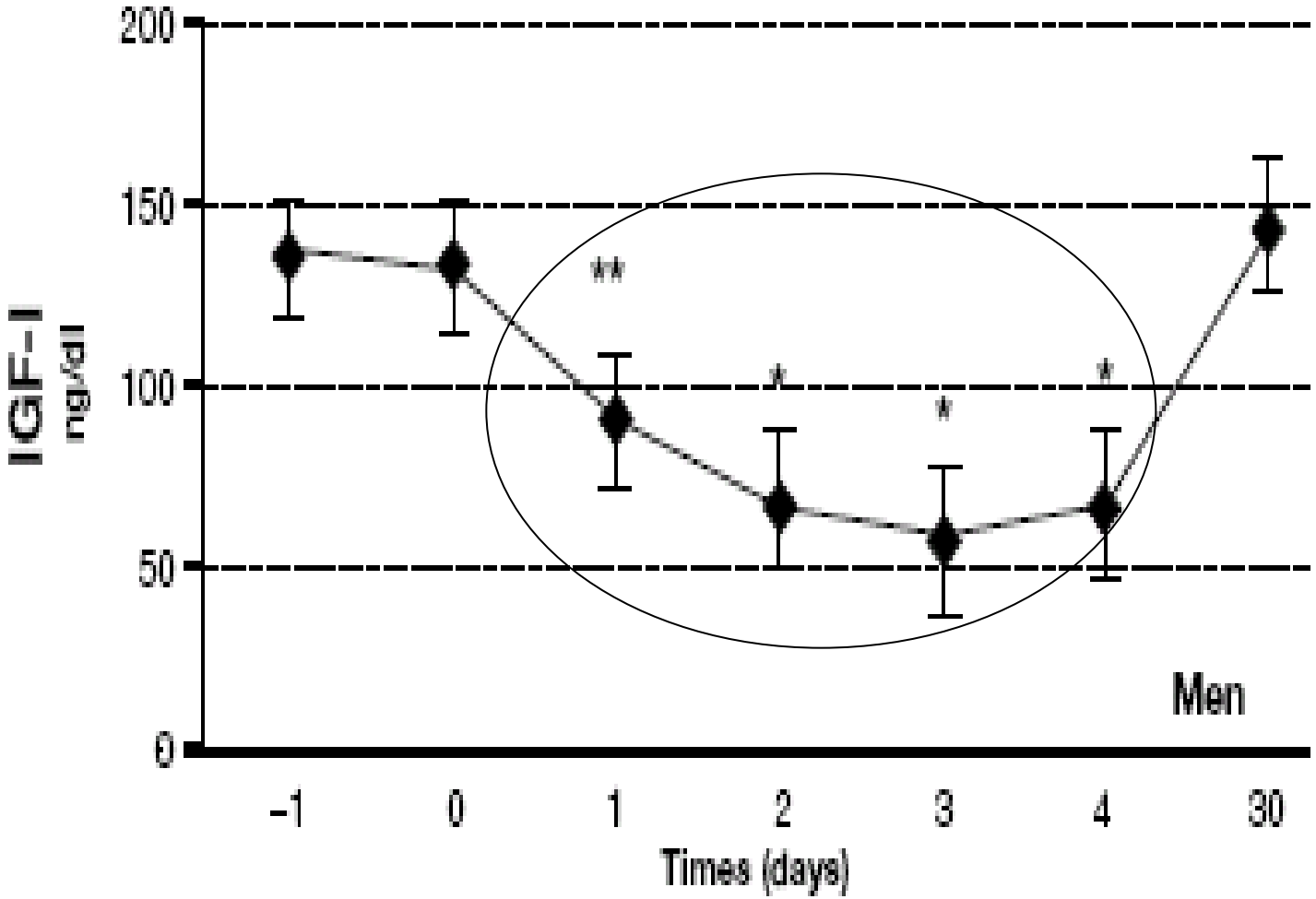
	Age Adjusted Odds Ratio		Multivariate Adjusted Odds Ratio[†]	
Number	Prefrail vs Nonfrail	Frail vs Nonfrail	Prefrail vs Nonfrail	Frail vs Nonfrail
0	1	1	1	1
1	1.55 (0.98–2.45)	1.18 (0.53–2.64)	1.71 (1.03–2.85)	1.15 (0.49–2.68)
2 or 3	1.61 (0.93–2.79)	2.73 (1.28–5.86)	2.25 (1.12–4.53)	2.79 (1.06–7.32)

Notes: *For each hormone, deficiency was defined as the bottom quartile.

[†]Adjusted for age, race, education, smoking status, body mass index, number of diseases, corticosteroid use, and estrogen use (n=485 with complete data on covariates).

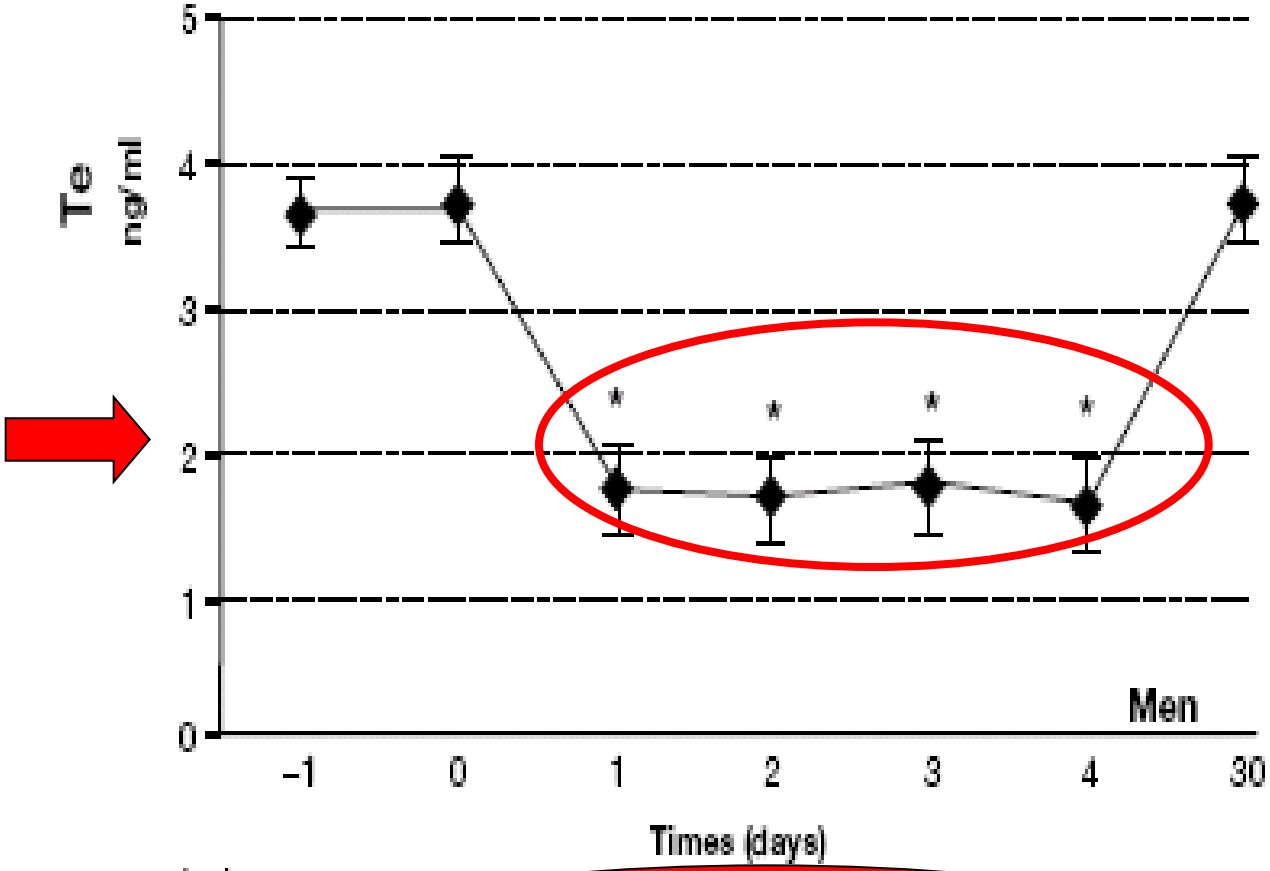
Cappola AR et al. J Gerontol A Biol Sci Med Sci. 2009 Feb;64(2):243-8.

Changes in IGF-1 levels in older men undergoing Cardiac surgery (on pump CABG)

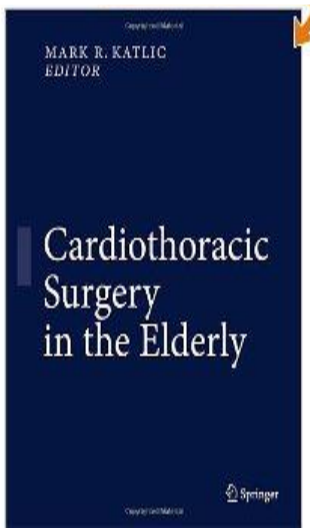


Maggio M et al. J End Invest 2005; 28: 711-719

Testosterone levels in older men undergoing Cardiac surgery (on pump CABG)



FRANK HYPOGONADISM



Chapter 25
Hormonal Changes During and After Cardiac Surgery

Marcello Maggio, Chiara Cattabiani, and Gian Paolo Ceda

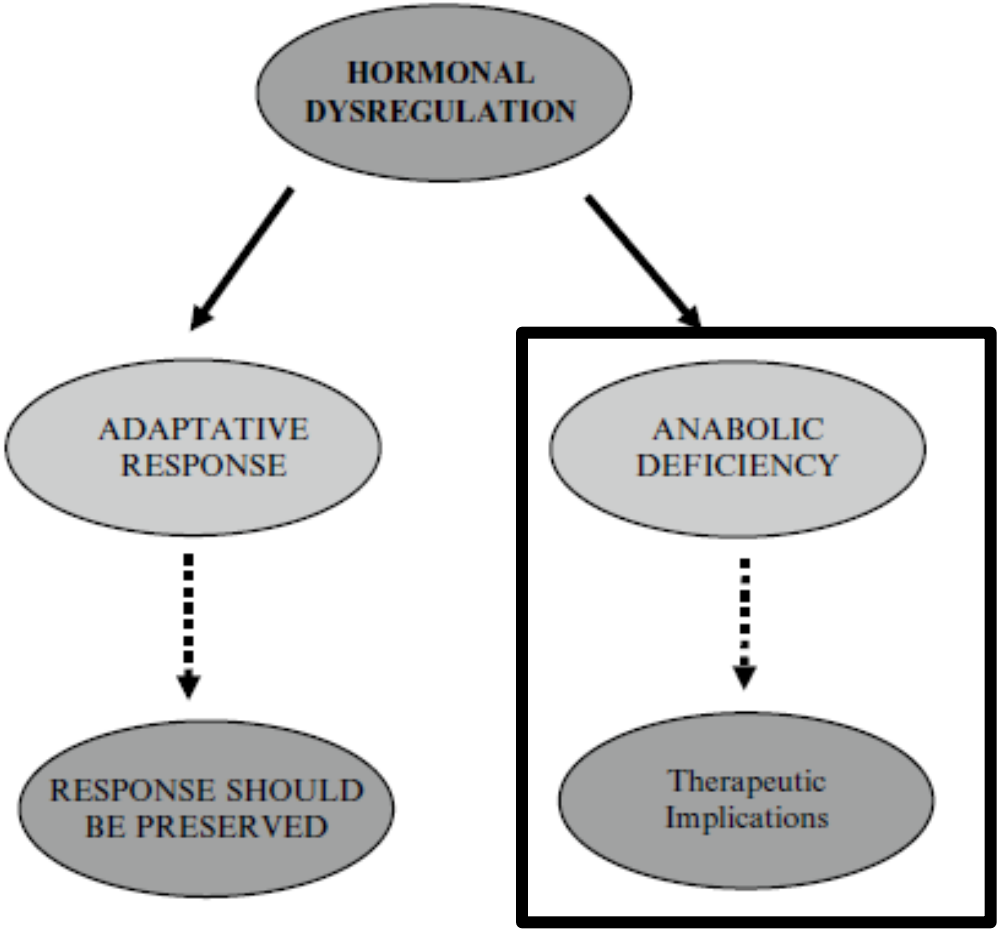
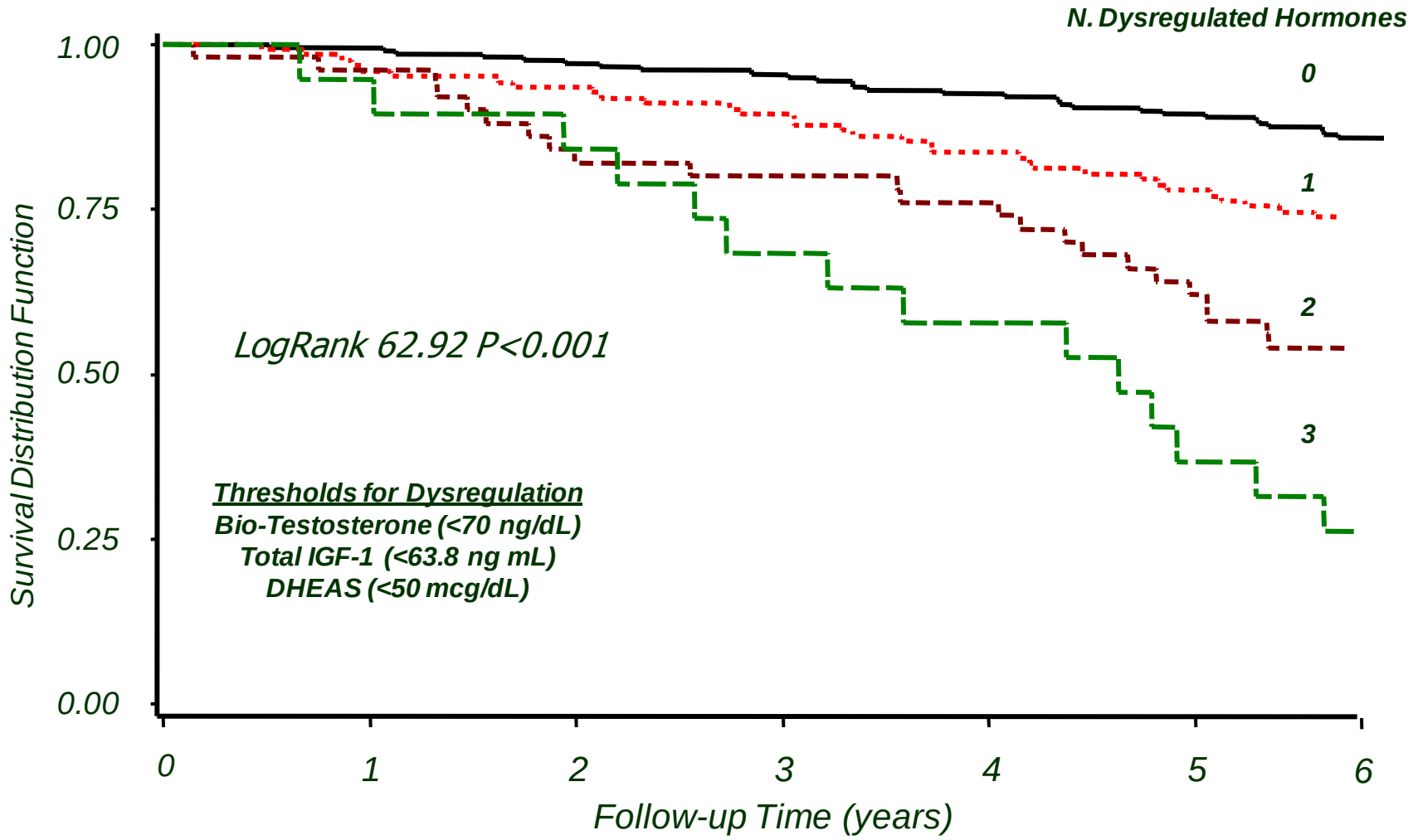


Fig. 25.2 Interpretation and possible therapeutic implications of endocrine changes after cardiac surgery in older patients

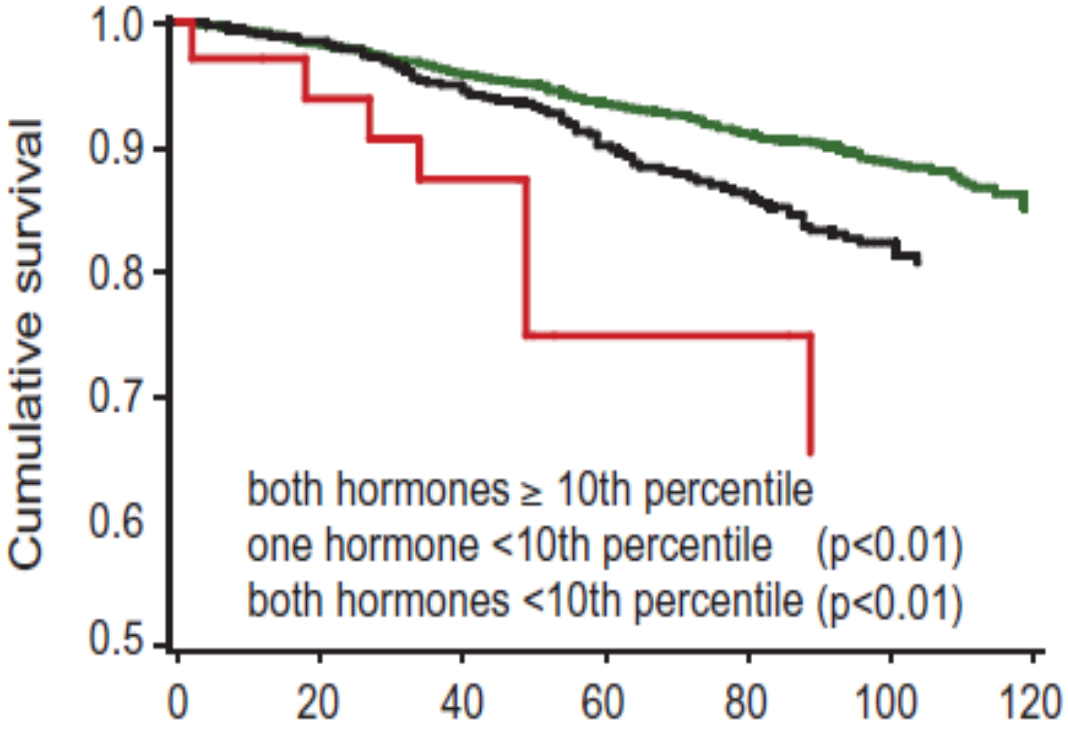
Relationship between the Number of Anabolic Hormones in the Lowest serum Level Quartile and 6-Year Survival in Older Men InCHIANTI

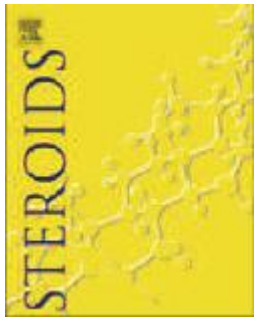


Maggio M et al. Archives of Internal Medicine 2007;167(20):2249-54

2 german prospective cohort studies: DETECT and SHIP with 3492 men

Improved prediction of all-cause mortality by a combination of serum total testosterone and insulin-like growth factor I in adult men





Friedrich N et al. Steroids 2012; 77:52-58

Combined GH and T treatment in healthy older men

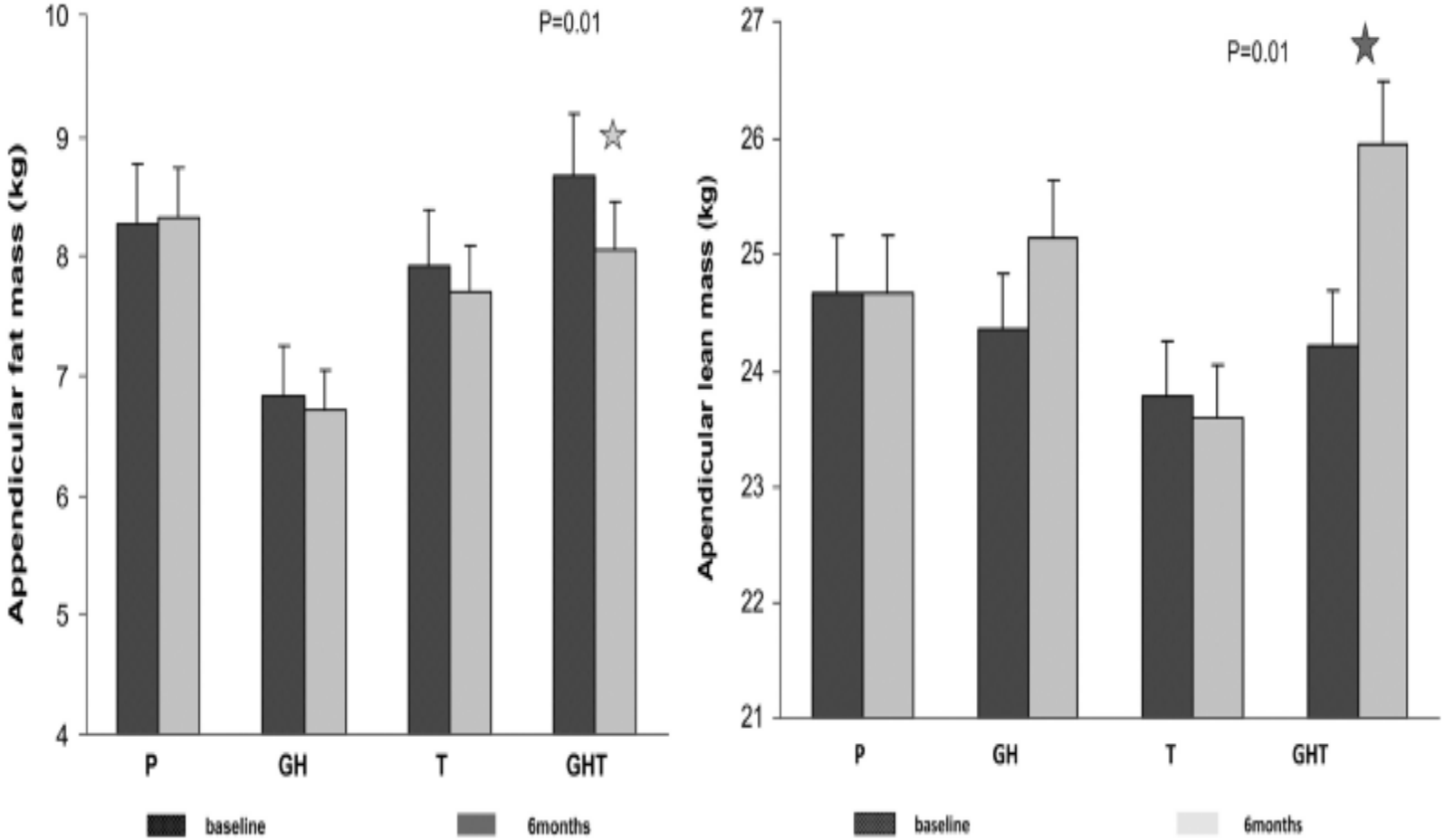


Figure 5. The effects of placebo (P), GH, testosterone (T), and GH plus T (GHT) on appendicular fat mass (*top*) and appendicular lean mass (*bottom*). *Columns* show results at baseline and 6 months. [Reproduced from M. G. Giannoulis *et al.*: The effects of growth hormone and/or testosterone in healthy elderly men: a randomized controlled trial. *J Clin Endocrinol Metab* 91:477–484, 2006 (48), with permission. © The Endocrine Society; and http://encore.ulrls.lon.ac.uk/iii/encore/record/C_Rb3127431~S1?lang=eng.

Giannoulis et al. Endocrine Reviews 2012; 33: 314–377

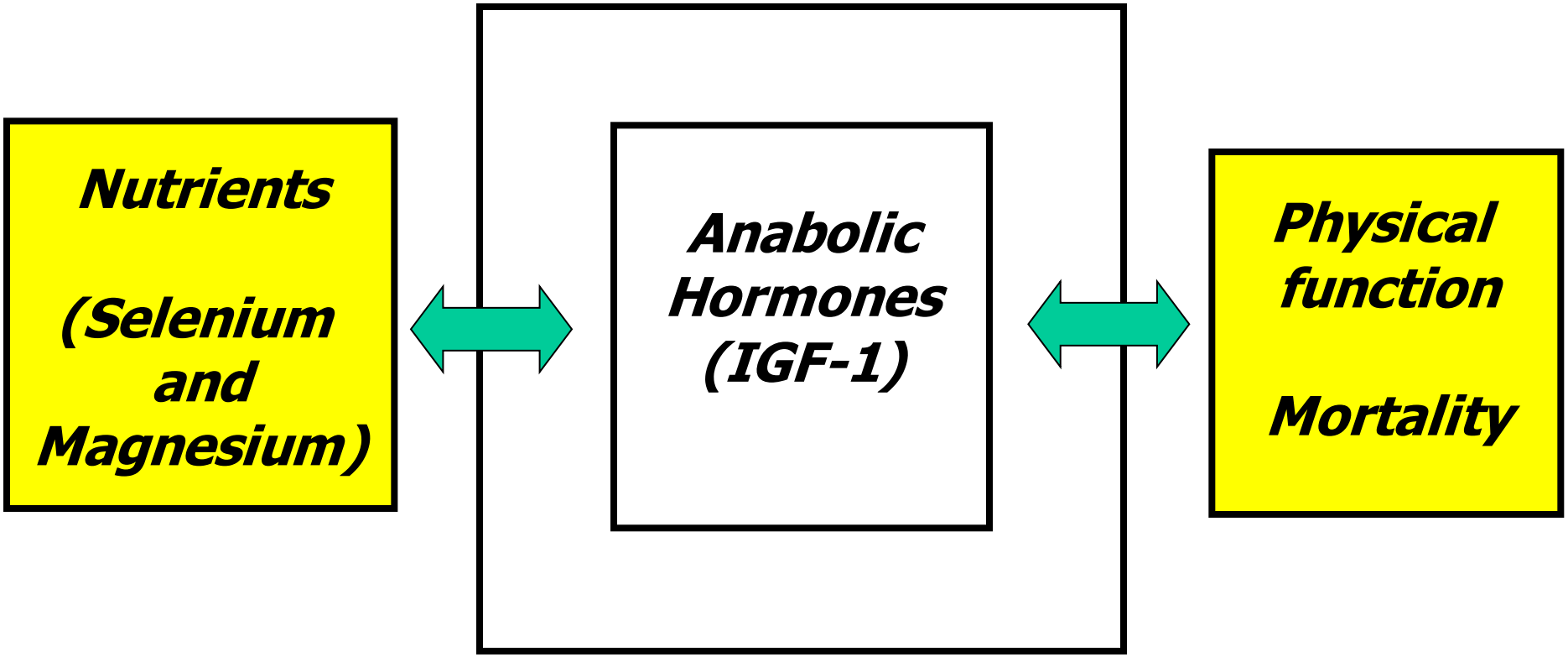
TABLE 4. Studies of combined GH and T replacement therapy in healthy older men

First author, year (Ref.)	Study protocol, active treatment, duration, no. of subjects	Main subject characteristics	Main findings and remarks
Brill, 2002 (429)	Crossover	Healthy older men	LBM increased in all treatment groups, with improvements also noticed in some measurements of physical performance; muscle strength and BF did not change
	GH, 6.25 μg/kg · d; T patch, 5 mg/d 1-month active treatment alternating with 3-month washout period n = 10	Age, 68 ± 2.5 yr T, <450 ng/dl; IGF-I, <200 ng/ml	
Giannoulis 2006 (48, 646); 2008 (597)	Parallel groups		Total, appendicular, and muscle CSA increased
	Duration, 6 months		VO_2max and one of six measurements of isokinetic muscle strength increased
	Act, n = 19; PL, n = 20 (dropouts, Act, n = 3; PL, n = 4)		Whole body protein turnover also increased
	T patch, 5 mg/d fixed dose		Total and appendicular BF decreased, abdominal fat area did not change; no changes in lipid profile and VLDL metabolism
	GH starting dose, 0.1 mg/d, increased gradually to a mean of 0.54 mg/d		No changes in insulin levels no glucose intolerance, diabetes or other adverse events
	Target IGF-I, 250 ng/ml		
Münzer, 2001 (576); Blackman, 2002 (49); Christmas, 2002 (583); Huang, 2005 (598); Münzer, 2009 (645)	Parallel groups		Total LBM increased and BF decreased; sc fat also decreased, but not VF
	Duration, 6 months		Muscle strength, VO_2max, WBPK increased
	Act, n = 19 to 21; PL, n = 17 (dropouts, Act, n = 1)		Markers of bone turnover increased whereas a marginal decline in BMD on proximal radius was found
	T enanthate, 100 mg/2 wk im		High incidence of adverse effects, mainly glucose intolerance and diabetes
	GH starting dose, 30 μg/kg, reduced to 20 μg/kg, 3 times/wk		
Sattler 2009 (602)	Not placebo controlled	Community-dwelling healthy older men	Total and appendicular LBM increased, total and trunk fat decreased
	T gel in two doses, 5 and 10 g/d, combined with three different GH doses (0, 0.3, 0.5 μg/kg · d)	Age, 70 ± 4.2 yr	All changes were dose-dependent, with the highest effects recorded when higher dose of combined GH and T was used
	Duration, 16 wk	IGF-I, <167 ng/ml	Muscle strength similarly increased only after higher doses of GH and T
	Act GH 0.3 + T 5, n = 21; Act GH 0.3 + T 10, n = 21; Act GH 0.5 + T 5, n = 19; Act GH 0.5 + T 10, n = 21(dropouts Act GH 0.3 + T 5, n = 2; Act GH 0.3 + T 10, n = 1; Act GH 0.5 + T 5, n = 2; Act GH 0.5 + T 10, n = 4)	T, <550 ng/dl	Increased incidence of glucose intolerance, diabetes, and high blood pressure

All studies included are randomized, placebo-controlled and double blind unless otherwise stated. Four trials were identified where GH+T was administered in healthy older men (aged >60 yr) and was reported on outcome measurements related to physical function. A total of 132 subjects received GH+T.

Giannoulis et al. Endocrine Reviews 2012; 33: 314–377

Modulation of anabolic status and impact on functional outcomes



Adapted from Ferrucci L et al. Inflammation: the fire of frailty? In Research and perspectives in Longevity. Springer ed 2005 Pag 91-98

Clinical Nutrition 29 (2010) 674–677

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Short Report

Association of plasma selenium concentrations with total IGF-1 among older community-dwelling adults: The InCHIANTI study

Marcello Maggio [a,b,*], Gian Paolo Ceda [a,b], Fulvio Lauretani [b], Stefania Bandinelli [c], Elisabetta Dall'Aglio [a], Jack M. Guralnik [d], Giuseppe Paolisso [e], Richard D. Semba [f], Antonio Nouvenne [g], Loris Borghi [g], Graziano Ceresini [a,b], Fabrizio Ablondi [a], Mario Benatti [h], Luigi Ferrucci [i]

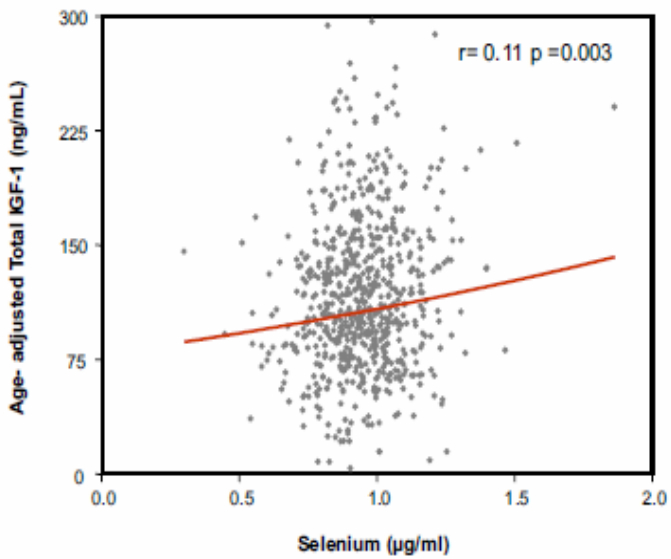


Fig. 1. Relationship between selenium levels expressed in µg/mL (horizontal axis) and age-adjusted total IGF-1 levels (ng/mL) (vertical axis). As shown, the relationship is statistically significant ($r = 0.11$, $p = 0.003$).

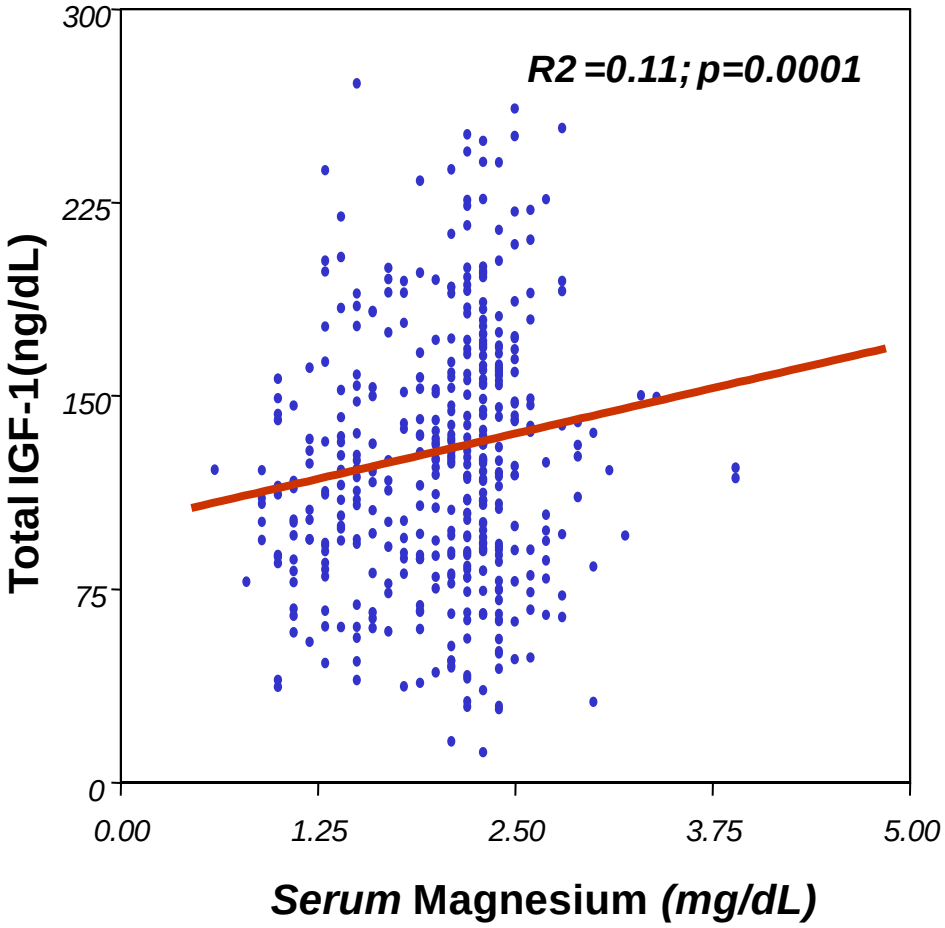
Table 3
Relationship between Selenium and IGF-1.

Characteristic	Total IGF-1 (ng/mL) (at enrollment, $n = 951$)		
	Beta	SE	p
Model 1			
Selenium (µmol/L)	43.76	11.25	0.0001
Model 2			
Selenium (µmol/L)	36.69	12.243	0.003
Model 3			
Selenium (µmol/L)	40.11	11.970	0.0008

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, energy intake, alcohol, GPT, congestive heart failure.
Model 3: adjusted for age, sex, energy intake, alcohol, GPT, congestive heart failure, log (IL-6).

Maggio M et al. Clinical Nutrition 2010 (29): 674-677

Relationship between Magnesium (predictor) and total IGF-1 (outcome)



Total IGF-1

	Beta* ± SE	P
Magnesium	16.4 ±4.9	0.001
Magnesium	14.4 ±4.9	0.01

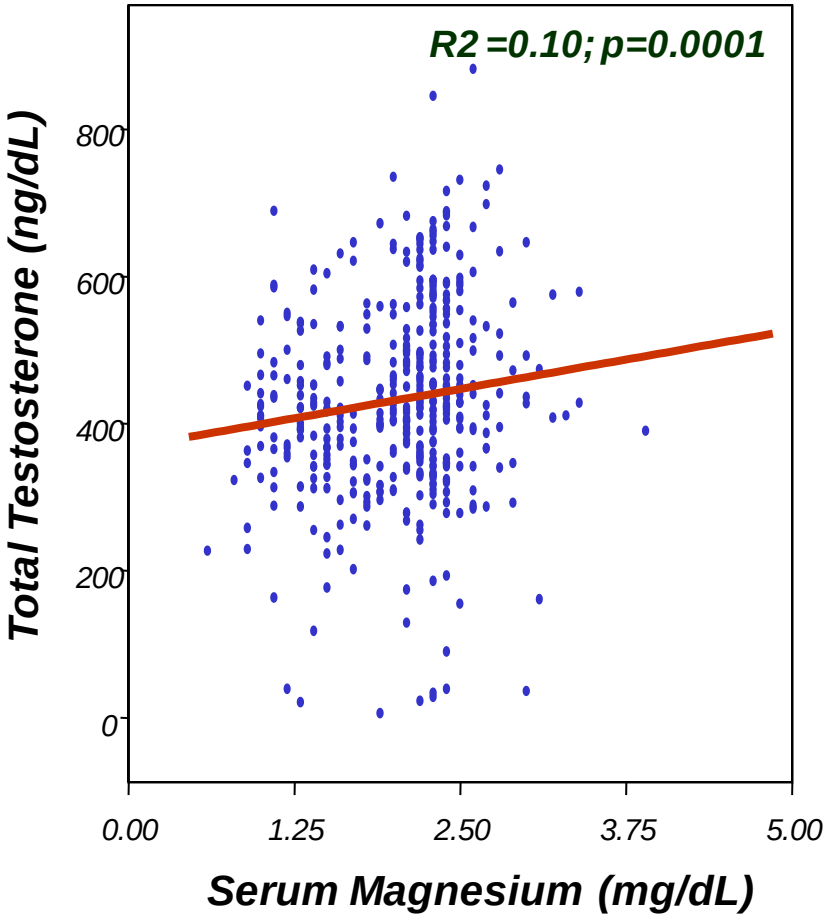
* Each line refers the results of a separate model adjusted for indicated covariates.

Model 1: adjusted for Age, BMI, GOT, GPT, Energy Intake, log (fasting insulin), log (DHEAS), log (IL-6), selenium.

Model 2: Model 1 plus testosterone.

Maggio M et al. Int J Andrology 2011

Relationship between magnesium (predictor) and total testosterone (outcome)



	Testosterone	
	Beta* ± SE	**p**
Magnesium	36.4 ± 10.7	0.008
Magnesium	48.7 +12.6	0.0001

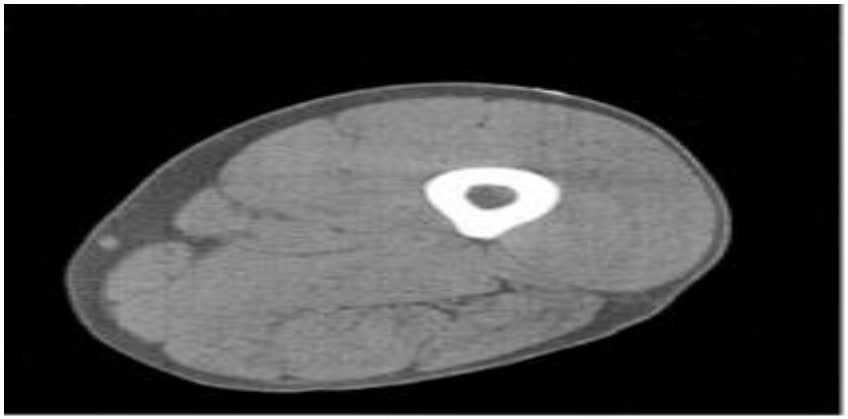
Model 1: adjusted for Age, BMI, log (DHEAS), log (SHBG), log (fasting insulin), Grip strength, Parkinson's Disease, Chronic Heart Failure.
Model 2: Model 1 plus total IGF-1.

*Each line refers the results of a separate model adjusted for indicated covariates.

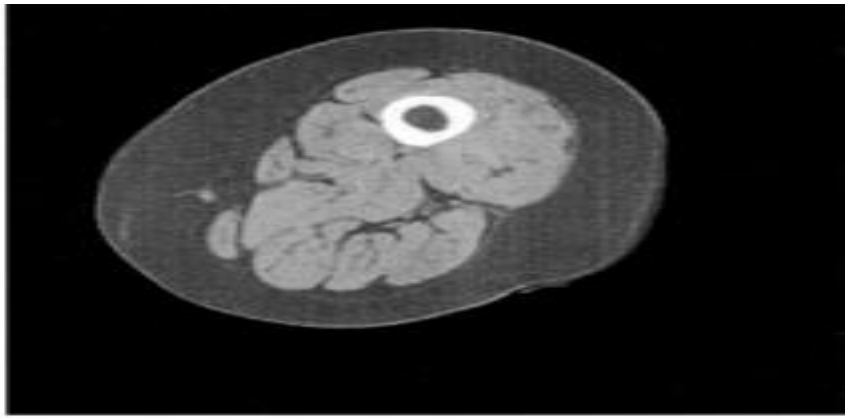
Maggio M et al. Int J Andrology 2011

Polipharmacotherapy and hormones

Positive	Negative
ACE-inibitors	Corticosteroids PPI



Young, active



Old, sedentary

+ IGF-1	- IGF-1

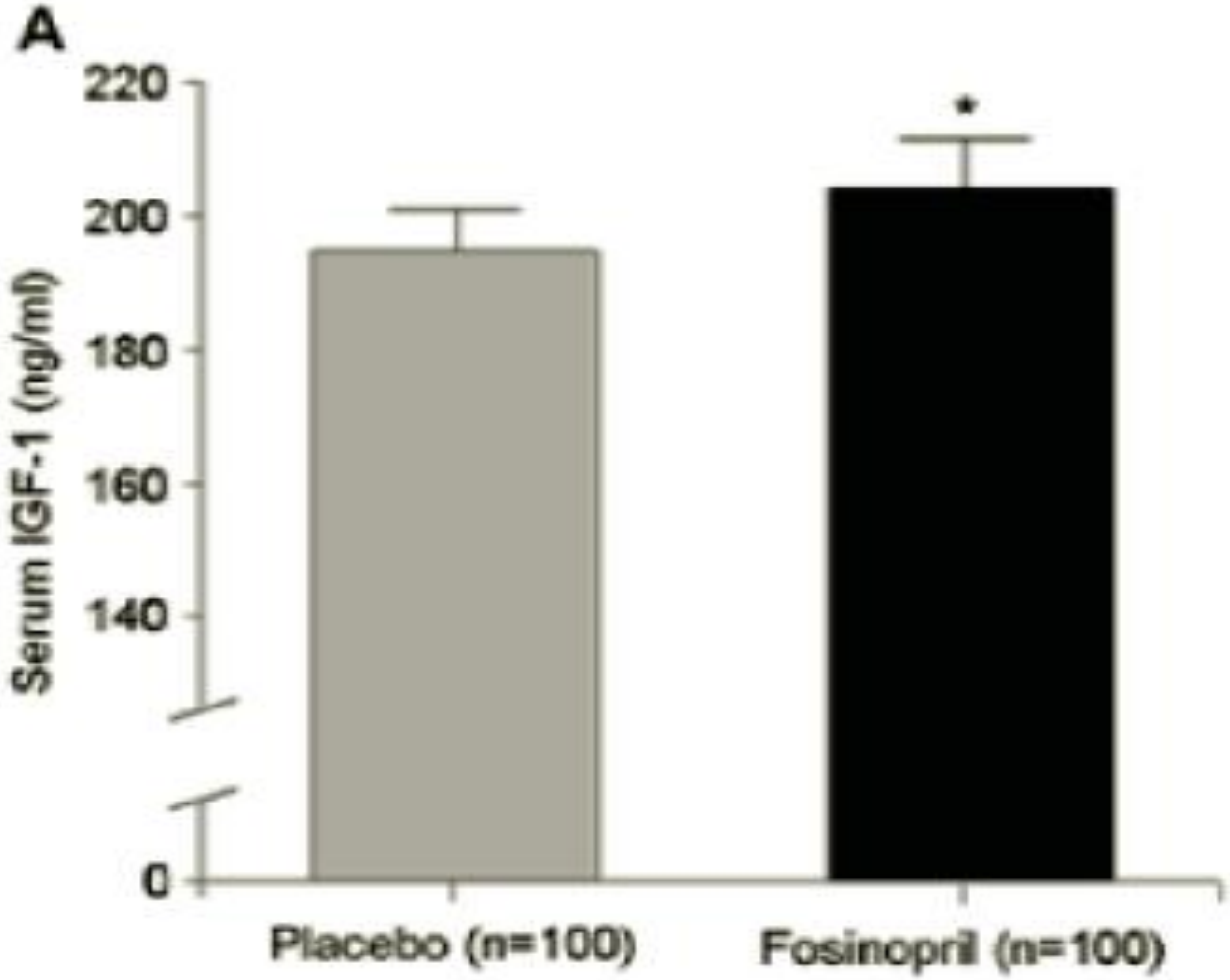
Use of ACE-inhibitors is positively associated with IGF-1 in older subjects

Multivariate linear regression model with total insulin-like growth factor-1 as the dependent variable*

Independent Variable	$\beta \pm$ SE	p Value
ACE inhibitors use	14.24 ± 4.49	<0.001
Age (yrs)	−1.37 ± 0.31	<0.001
Gender (women vs men)	−17.02 ± 8.58	0.05
Body mass index (kg/m^2)	0.12 ± 0.54	0.82
Caloric intake (kcal/d)	0.01 ± 0.00	0.06
Log interleukin-6 (pg/ml)	−0.95 ± 3.44	0.69
Hemoglobin (g/dl)	5.30 ± 2.04	0.007
Total testosterone (ng/ml)	3.13 ± 1.93	0.09
Alcohol (g/d)	−0.12 ± 0.09	0.26
Smoking (pack − yrs)	−0.12 ± 0.10	0.23
Creatinine clearance (ml/24 h)	0.04 ± 0.1	0.65
Diabetes mellitus	1.53 ± 6.06	0.98
Cancer	11.13 ± 7.06	0.12
Congestive heart failure	0.49 ± 2.28	0.91
Hypertension	7.57 ± 3.64	0.04
Stroke	−6.01 ± 9.70	0.45
Physical activity		
Light to moderate†	46.32 ± 15.20	0.002
High†	40.60 ± 14.51	0.005
No. of medications‡	−1.40 ± 1.07	0.18

Maggio M et al 2006 American Journal of Cardiology 2006;97(10):1525-9

Clinical Trial
Effects of ACE-inhibitors on IGF-1 levels in older subjects with high CV risk



Giovannini S, Cesari M,… Maggio M et al J Nutr Health Aging. 2010 Jun;14:457-60.

Overuse of proton pump inhibitors (PPI)

- ***Between 25% and 81% of patients taking PPI have no appropriate indication***

- ***In many cases physicians fail to provide specific instructions about how long to continue treatment***

Walker NM, et al . Pharm World Sci 2001;23:116–7

C.J. George, et al Am J Geriatr Pharmacother 6 (2008), pp. 249–254.

Hollingworth S et al Pharmacoepidemiol Drug Saf Oct 2010;19(10):1019–24

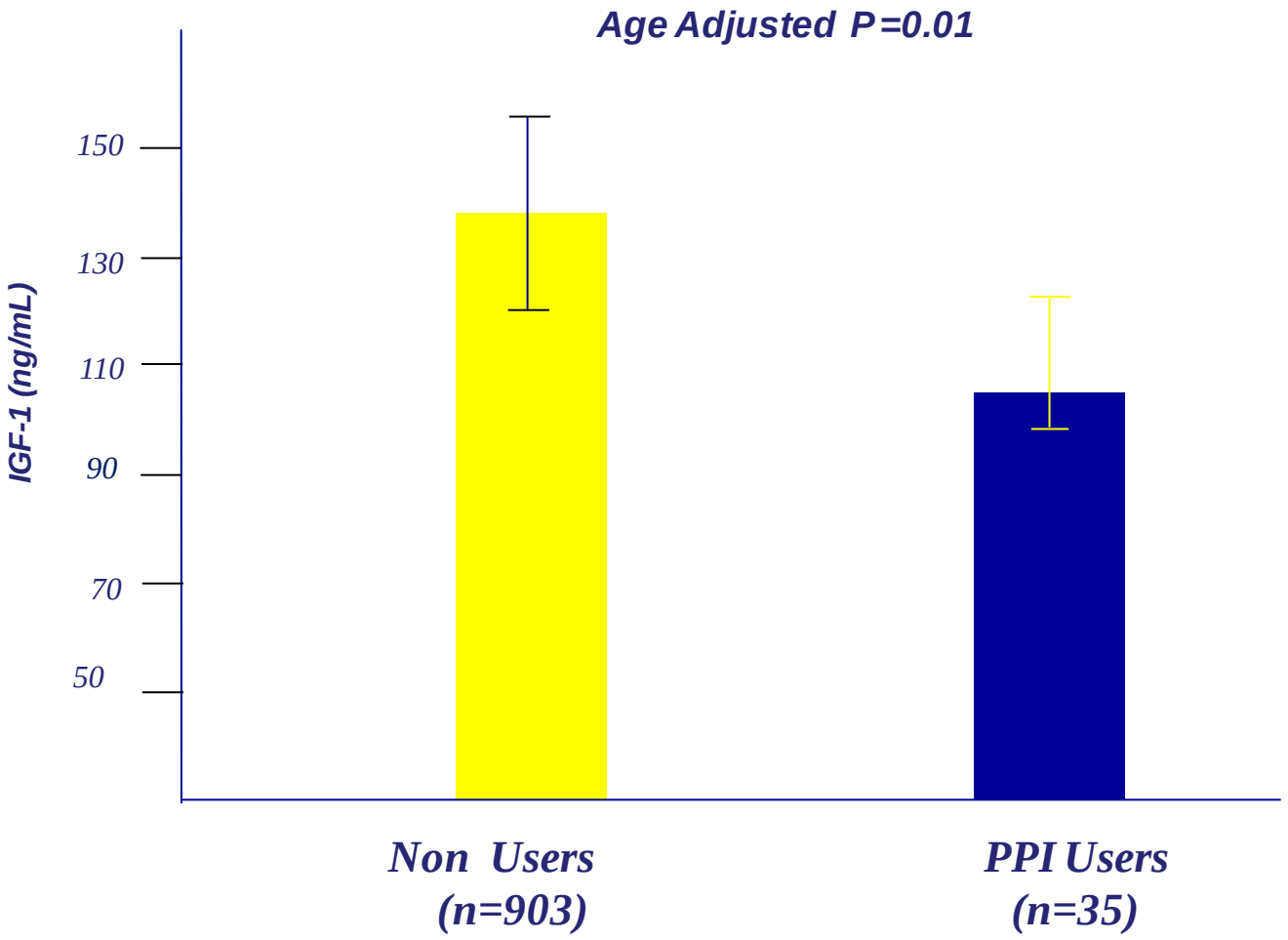
Relationship between 1-year PPI treatment and death and death or rehospitalization in older patients

	Incidence rates Person/years (95% CI)			Time-dependent Cox proportional hazard regression		
	Non users	Users	p	HR*	95% CI	p
Death	12.0 (5.2-18.8)	21.5 (11.8-31.2)	0.009	1.51	1.03-2.77	0.033
Death or rehospitalization	22.9 (13.5-32.3)	39.8 (27.4-52.2)	0.003	1.49	0.98-2.17	0.105

* Adjusted for age, gender, BMI, hypoalbuminemia, cognitive impairment, dependency in ADLs, CIRS comorbidity, cardiovascular diseases, gastroesophageal reflux disease, peptic ulcer, diarrhea, infectious disease, fracture, no. of drugs at discharge, antithrombotics, NSAIDs.

Maggio M et al. JAMA Internal Medicine 2013 in press

IGF-1 levels according to PPI use in older subjects of InCHIANTI Study



De Vita F, Maggio M , Ceda GP et al. 2012
57° Congresso Nazionale SIGG poster N° 199

CONCLUSIONI

La disregolazione ormonale multipla (soprattutto il deficit anabolico): impatto sfavorevole sugli outcome funzionali e clinici del soggetto anziano.

Aging=processo multifattoriale e multisistemico: un corretto approccio nell' aging male non dovrebbe incentrarsi su una singola modificazione endocrina

Tradizionale terapia ormonale sostitutiva (terapia combinata) ma anche fattori nutrizionali e farmacologici come possibili modulatori dello stato anabolico.

Acknowledgements

INTRODUCTION TEAM AT: *Parma*

The group of the Geriatric Clinic in the University Hospital of Parma, Italy, is led by Prof. Marcello Maggio, Medical Doctor with PhD. The other members of the staff include Professor Gian Paolo Ceda (the chief of the Geriatric Unit and Director of School in Geriatrics of Parma), Dr. Fulvio Lauretani (physician and specialist in Geriatrics also involved in the InCHIANTI Study), Dr. Chiara Cattabiani (a research fellowship with Specialization in Geriatrics) and Francesca De Vita (with Diploma in nutrition Sciences, dietician). Three medical doctors attending the School of Geriatrics, Dr. Giuliana Bondi, Dr. Giulia Schiavi and Dr. Eleonora Sutti collaborate in the study, performing tests and collecting data under the supervision of PI. The group focuses on investigating the impact of the "Hormonal dysregulation during aging" on age-related phenomena including sarcopenia and physical function.

Novel strategies to counteract the side effects associated with testosterone treatment in older men

Who? *What preparation?*	*population to treat* *older with low androgens with signs and symptoms*	*correct formulation (transdermal) dosage (5g 10g)* *individually adjusted dosage*
How long?	*Continuous versus intermittent*	
Testosterone alone?	*Plus 5α-reductase inhibitor* *Plus physical exercise*	*Plus nutrients*
Targeting *Skeletal muscle and bone*	*Selective Androgens Receptor Modulators (SARMS)*	

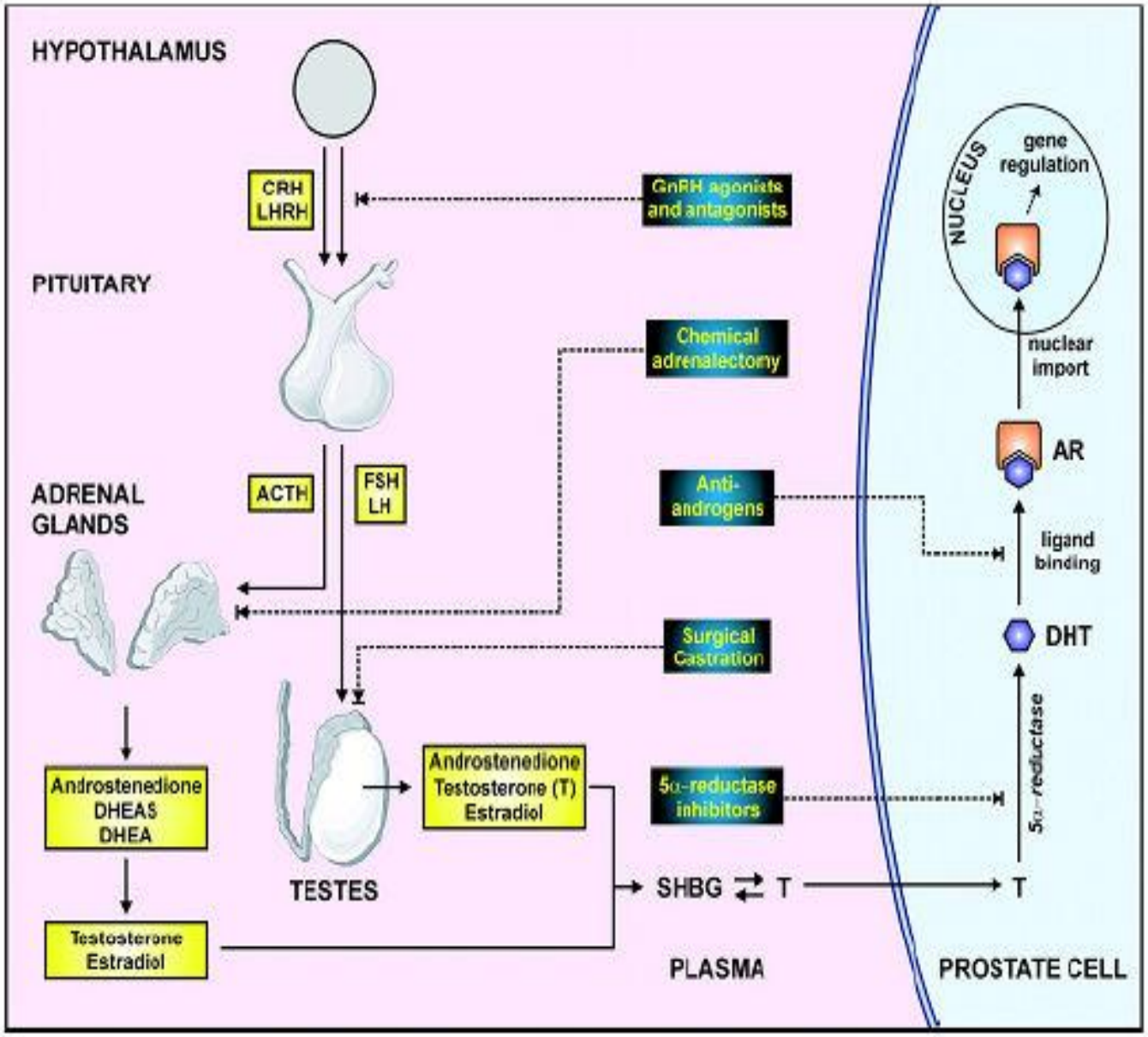
Maggio M et al. Curr Opin in Clin Nutr and Med Care 2013 in press

Relationship between testosterone and cognitive function in elderly

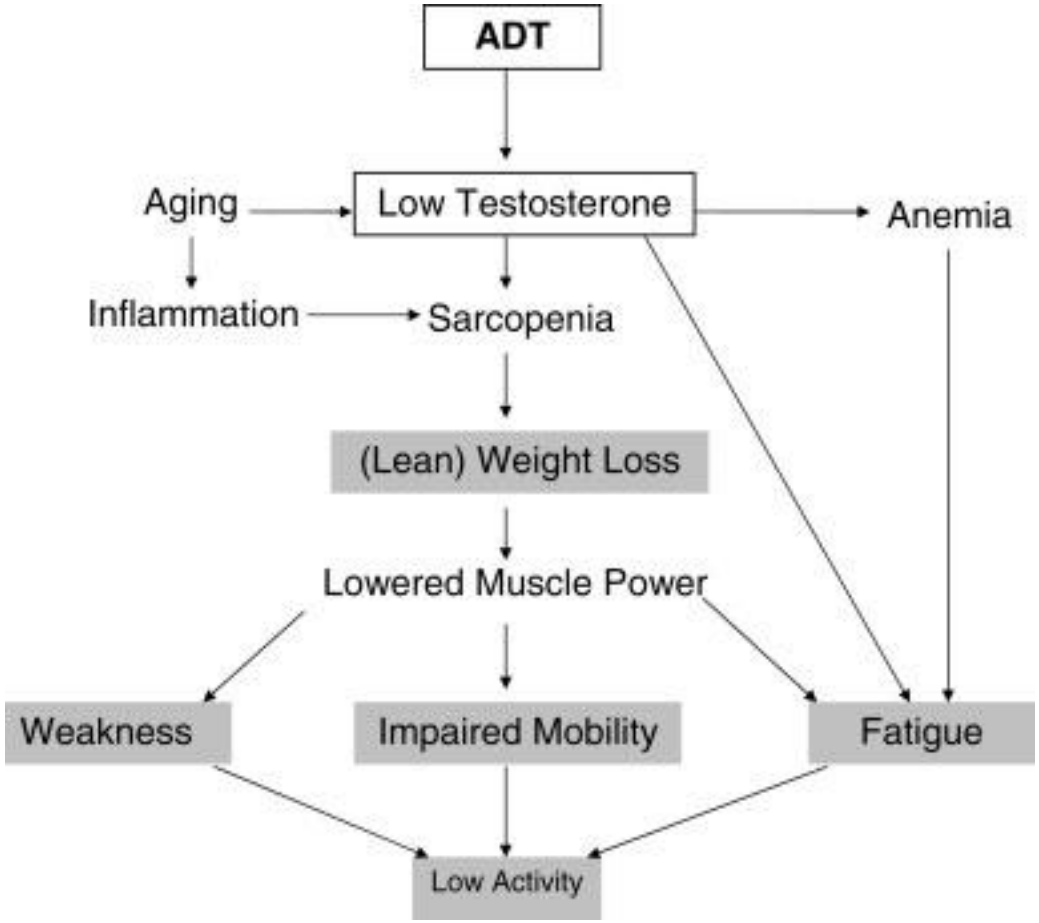
Author/Reference	Type of survey	Population	Follow up	Results
		Observational studies		
Morley J.E. et al. 27	Cross-sectional	56 healthy men aged 20-84 years	--	Positive association between bioavailable testosterone levels and the cognitive measurements.
Barrett-Connor E et al 101	Cross-sectional Longitudinal	547 community-dwelling men 59–89 yr of age	7 yr	Low estradiol levels were associated with better performance on two standard cognitive function tests, whereas high TT or BioT levels predicted better performance on tests of verbal memory and mental control.
Moffat SD, et al 77	Longitudinal	407 volunteers from the Baltimore Longitudinal Study of Aging, aged 50–91 yr	10 yr	Higher FTI was associated with better scores on visual and verbal memory, visuospatial functioning, and visuomotor scanning and a reduced rate of longitudinal decline in visual memory.
Yaffe K, et al 76	Longitudinal	310 men mean age 73.0±7.1	6,5 yr	BioT but not TT level was positively associated with cognitive scores in older men. Testosterone improves cognitive function in older men and this association is not an indirect effect via aromatization to estradiol.
Wolf OT, & Kirschbaum C. 86	Cross-sectional	38 older women (mean age 68 years) and 30 older men (mean age 69 years).	--	In men no positive association between sex steroids and cognition could be detected. Only higher testosterone (TT and FT) levels were negatively associated with verbal fluency.
Muller M, et al. 75	Cross-sectional	400 men ages 40 and 80	--	Higher T levels are associated with better cognitive performance in the oldest age category. Men with lower T levels performed significantly worse than men with higher T levels.
Lessov-Schlaggar CN et al. 87	Longitudinal	514 pairs of twins selected by the National Heart Lung and Blood Institute (the NHLBI Twin Study)	10- to 16-yr	No significant associations between sex hormone or SHBG levels and performance on a series of cognitive tasks measuring global and executive function, visual and verbal learning and memory.

Maggio M et al. J Nutr Health Aging. 2012 Jan;16(1):40-54. Review

Androgen deprivation therapy: site of blockage



LINK TRA ADT E RIDOTTA MOBILITA' NEL SOGGETTO ANZIANO



Bylow K et al. 2007 Dec 15;110(12):2604-13

Relationship between IGF-1 and cognitive function in elderly

Author/Reference	Type of survey	Population	Follow up	Results
Paolisso G et al. 121	Cross sectional	Three groups of subjects: 1) 30 adults (50 yr), 2) 30 aged men (75–99 yr), 3) 19 centenarians (100 yr).	--	In centenarians, the plasma IGF-I/IGFBP-3 molar ratio correlated with Mini Mental State Examination (r 0.53; P<0.0.03).
Aleman A, et al. 122	Cross sectional	Twenty five healthy older men with well-preserved functional ability aged 65–76 yr	--	Subjects with higher IGF-I levels performed better on these tests
Rollero A et al. 123	Cross sectional	22 subjects (7 females, 15 males) aged 65-86 yr.	--	IGF-I levels were directly correlated with MMSE scores, being lowered in patients with more advanced cognitive deterioration.
Deijen JB et al. 126	Cross sectional	89 subjects 31 men with multiple pituitary hormone deficiencies MPDH 17 men with isolated growth hormone deficiency (IGHD). 41 controls (healthy). aged 19-37 yr	--	IGHD patients only showed subnormal memory performance. Cognitive impairment in both MPHD and IGHD was related to GH deficiency.
Kalmijn S et al. 127	Longitudinal	186 healthy participants from the population based Rotterdam Study, aged 55–80 yr.	4 yr	In elderly subjects, total IGF-I and the total IGF-I to IGFBP-3 ratio were both inversely related to cognitive decline in the next 2 yr. These results were independent of differences in age, sex, insulin levels, body mass index, or other major confounders. No association between free IGF-I and cognitive decline.

Maggio M et al. J Nutr Health Aging. 2012 Jan;16(1):40-54. Review

AD determinants for IGF-1 in older men

	Men	
	OR (95% CI)	*P*
ApoE ε4 allele		
No	1.0 (ref)	
Yes	2.99 (1.13–7.93)	0.02
Educational level		
Primary school	9.16 (1.06–78.84)	0.04
High school	2.68 (0.90–7.96)	0.08
College diploma	1.11 (0.22–5.61)	0.90
University diploma	1.0 (ref)	
Age	1.07 (0.99–1.16)	0.08
BMI	1.00 (0.84–1.18)	0.98
Diabetes	0.45 (0.14–1.40)	0.17
IGF-I (100*ng/ml)	0.48 (0.26–0.88)	0.02

Duron E et al. JCEM. 2012 in press

IF HORMONAL ANABOLIC DEFICIENCY RATHER THAN SINGLE HORMONAL DERANGEMENT HAS AN IMPORTANT ROLE IN AGE-RELATED PHENOMENA

↓

Strategies to attenuate the impact of this deficit in older male population ?