SOCIETÀ ITALIANA
DI GERONTOLOGIA E GERIATRIA

**Simposio SIGG-SIE**
**L'Anemia e l'Unexplained Anemia nel Paziente Anziano**
**Sala Londra 29 Novembre 2013**

*Moderatori: Franco Aversa (Parma), Carlo Sabbà (Bari)*

# Il ruolo delle endocrinopatie nelle anemie non spiegate

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**Sezione di Geriatria**
***Università degli Studi di Parma***

# BACKGROUND:
## Prevalenza dell'anemia ed outcome clinici nel soggetto anziano

- ✓ L'anemia è classificata secondo l'OMS da livelli di Hb < 13 g/dL nei M e < 12 g/dL nelle F
  Nutritional anemias. WHO Tech Rep Set 1968;405:5-3

- ✓ La Prevalenza dell'anemia aumenta con l'età (dal 5 al 30%)
  20% soggetti >85 anni ("very very old")
  Guralnik JM et al. Blood 2004;104:2263-8.
  Kushang V et al. Sem Haemat 2008;45(4): 210-17

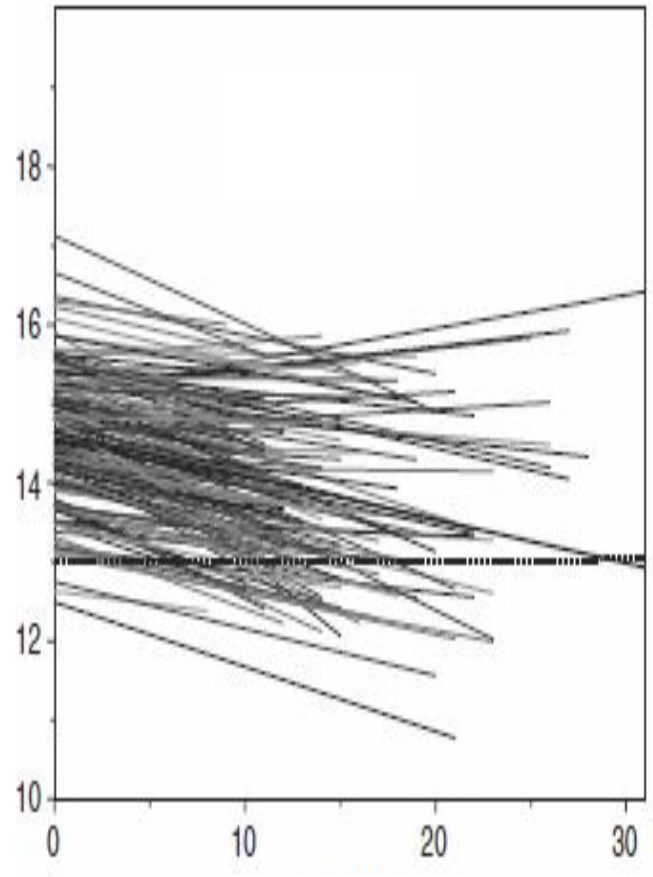
- ✓ L'anemia è un fattore predittore di fragilità, disabilità, ospedalizzazione e morte.
  Lipschitz D. J Am Ger Soc 2003;51:10-3.
  Penninx BW et al. J Am Ger Soc 2004;52:719-24

- ✓ 30-40% anemie nell'anziano sine causa ("unexplained anemia")

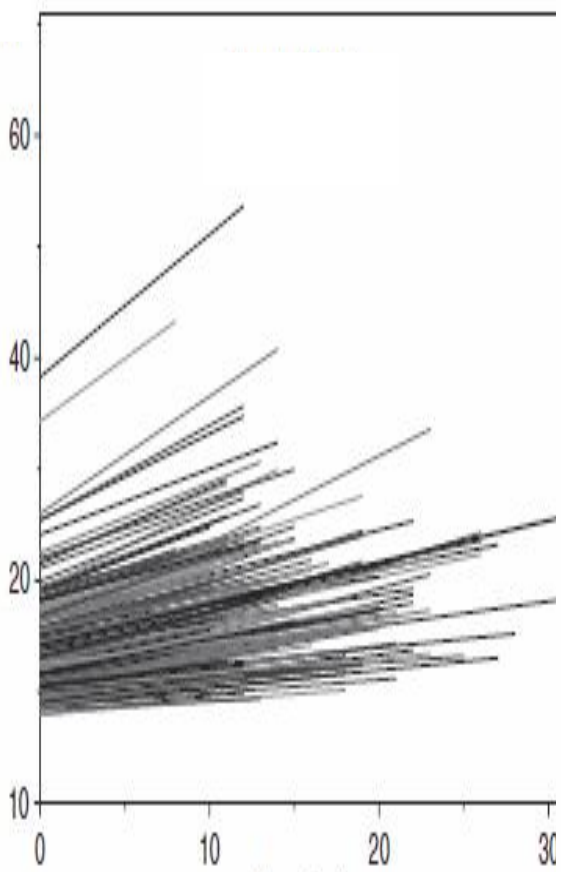
Guralnik JM et al. Blood 2004;104:2263-8

# Modificazioni longitudinali di emoglobina, Eritropoietina (EPO) nei due sessi e di testosterone nell'uomo: dati del BLSA

**Emoglobina (g/dL)**



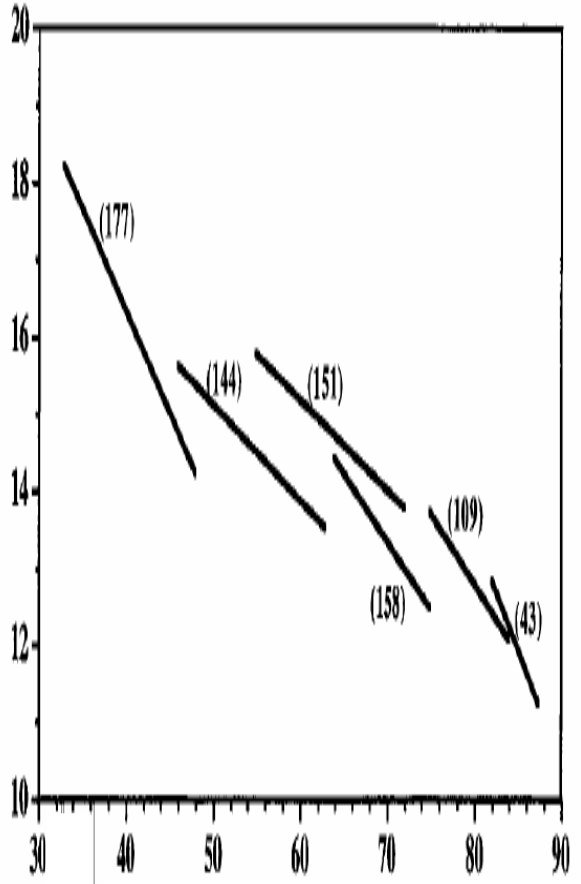

**EPO (mIU/mL)**




**Time (years of follow-up)**

Ershler et al. J Am Geriatr Soc 2005;53:1360-1365

**Testosterone (nmol/L)**




**Time (age-years )**

Harman et al. JCEM 2001;86:724-31

# Adverse Effects of Testosterone Therapy in Adult Men: A Systematic Review and Meta-Analysis

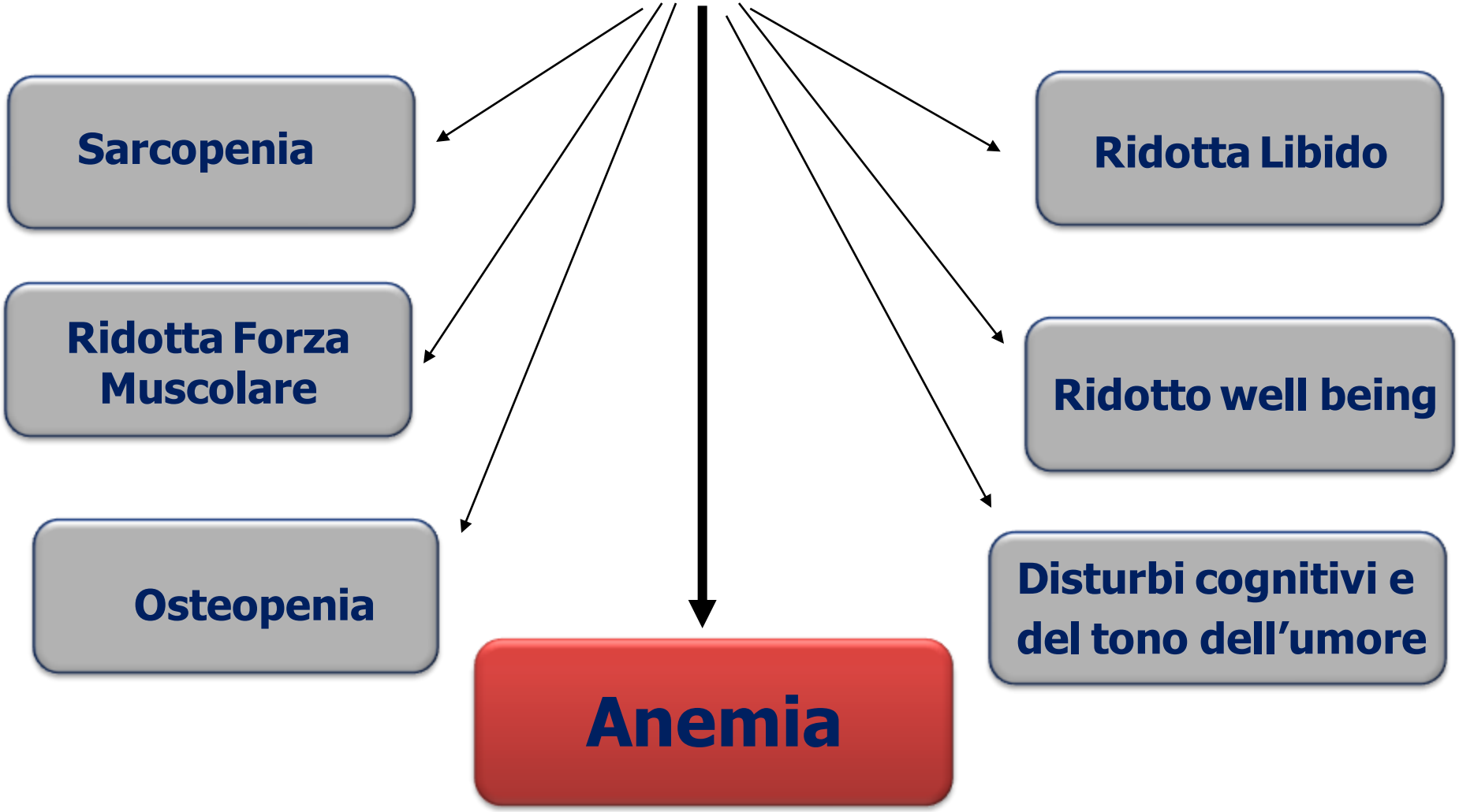
THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

**TABLE 4.**
**Random effects meta-analysis**

| First author, year (Ref.) | | 95% CI Lower boundary | 95% CI Upper boundary | $I^2$ |
|---|---|---|---|---|
| Hematocrit | 3.18 | 1.35 | 5.01 | 91.40 |
| Bhasin, 2007 (30) | 0.70 | −0.03 | 1.43 | |
| Snyder 1999a, 1999b, 2001 (58, 59, 19) | 3.40 | 1.99 | 4.81 | |
| Amory, 2004 (25); Page, 2005 (26) | 6.70 | 3.48 | 9.92 | |
| Emmelot-Vonk, 2008 (71) | 1.00 | 0.26 | 1.74 | |
| Morley, 1993 (54) | 6.00 | 4.17 | 7.83 | |
| Hemoglobin | 0.80 | 0.45 | 1.14 | 95.05 |
| Snyder 1999a, 1999b, 2001 (58, 59, 19) | 0.80 | 0.32 | 1.28 | |
| Amory, 2004 (25); Page, 2005 (26) | 2.20 | 1.37 | 3.03 | |
| Giannoulis, 2006 (43) | 0.50 | 0.37 | 0.63 | |
| Knapp, 2008 (51) | 1.10 | 0.97 | 1.23 | |
| Sih, 1997 (56) | 1.60 | 0.71 | 2.49 | |
| Emmelot-Vonk, 2008 (71) | 0.20 | 0.06 | 0.34 | |
| Allan, 2008 (17) | 0.20 | 0.10 | 0.30 | |
| Bhasin, 2000 (29) | 1.91 | −0.21 | 4.03 | |
| Clague, 1999 (36) | 0.50 | −0.50 | 1.50 | |
| Prostate symptom scales | 0.29 | −0.44 | 1.02 | 0.00 |
| Snyder 1999a, 1999b, 2001 (58, 59, 19) | 0.60 | −0.54 | 1.74 | |
| Amory, 2004 (25); Page, 2005 (26) | 2.00 | −0.60 | 4.60 | |
| Marks, 2006 (10) | −2.64 | −7.56 | 2.28 | |
| Wittert, 2003 (21) | −1.20 | −3.28 | 0.88 | |
| Emmelot-Vonk, 2008 (71) | 0.20 | −1.09 | 1.49 | |
| Chiang, 2007 (18) | 0.40 | −3.34 | 4.14 | |
| Kenny, 2004 (50) | 1.00 | −5.29 | 7.29 | |
| PSA change | 0.10 | −0.01 | 0.21 | 57.57 |
| Bhasin, 2007 (30) | 0.10 | 0.02 | 0.18 | |
| Malkin, 2006 (12) | 0.16 | −0.11 | 0.43 | |
| Snyder 1999a, 1999b, 2001 (58, 59, 19) | 0.40 | −0.14 | 0.94 | |
| Amory, 2004 (25); Page, 2005 (26) | 0.10 | −0.56 | 0.76 | |
| Katznelson, 2006 (48) | 0.30 | 0.11 | 0.49 | |
| Knapp, 2008 (51) | 0.16 | 0.10 | 0.22 | |
| Marks, 2006 (10) | 0.61 | −0.34 | 1.56 | |
| Sih, 1997 (56) | 0.40 | −0.31 | 1.11 | |
| Wittert, 2003 (21) | −0.30 | −0.76 | 0.16 | |
| Emmelot-Vonk, 2008 (71) | 0.00 | −0.30 | 0.30 | |
| Ferrando, 2002 (42) | 0.80 | 0.05 | 1.55 | |
| Morley, 1993 (54) | 0.60 | −0.25 | 1.45 | |
| Allan, 2008 (17) | −0.30 | −0.53 | −0.07 | |
| Sullivan, 2005 (60) | −0.49 | −1.64 | 0.66 | |
| Kenny, 2004 (50) | 0.73 | −0.19 | 1.65 | |
| Cavallini, 2004 (35) | −0.30 | −0.75 | 0.15 | |

Fernández-Balsells M M et al. JCEM 2010;95:2560-2575

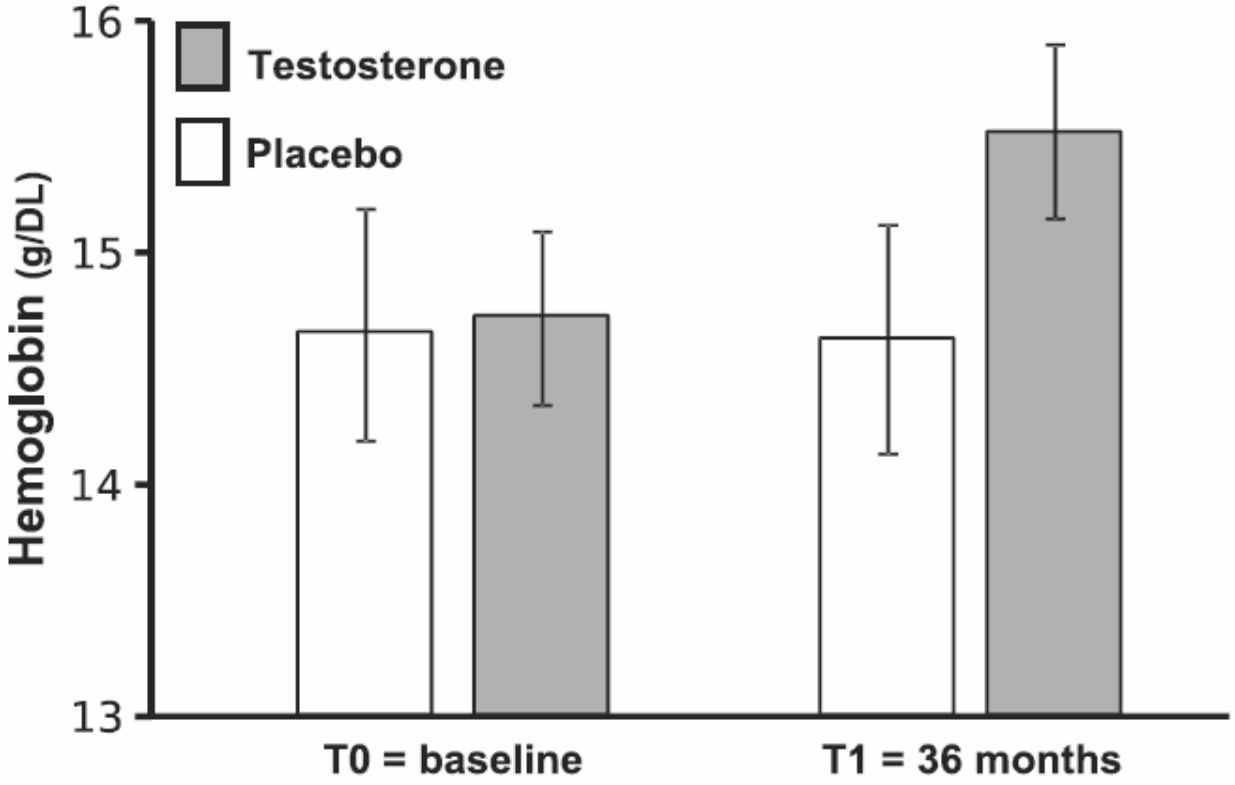
# Sintomi associati alla carenza di Testosterone nel soggetto di sesso maschile



# Is the haematopoietic effect of testosterone mediated by erythropoietin? The results of a clinical trial in older men

M. Maggio,*,† P. J. Snyder,‡ G. P. Ceda,*,† Y. Milaneschi,§,¶ M. Luci,*
C. Cattabiani,* S. Masoni,* A. Vignali,* R. Volpi,* F. Lauretani,†
H.Peachey,‡ G. Valenti,* A. R. Cappola,‡ D. Longo§ and L. Ferrucci¶

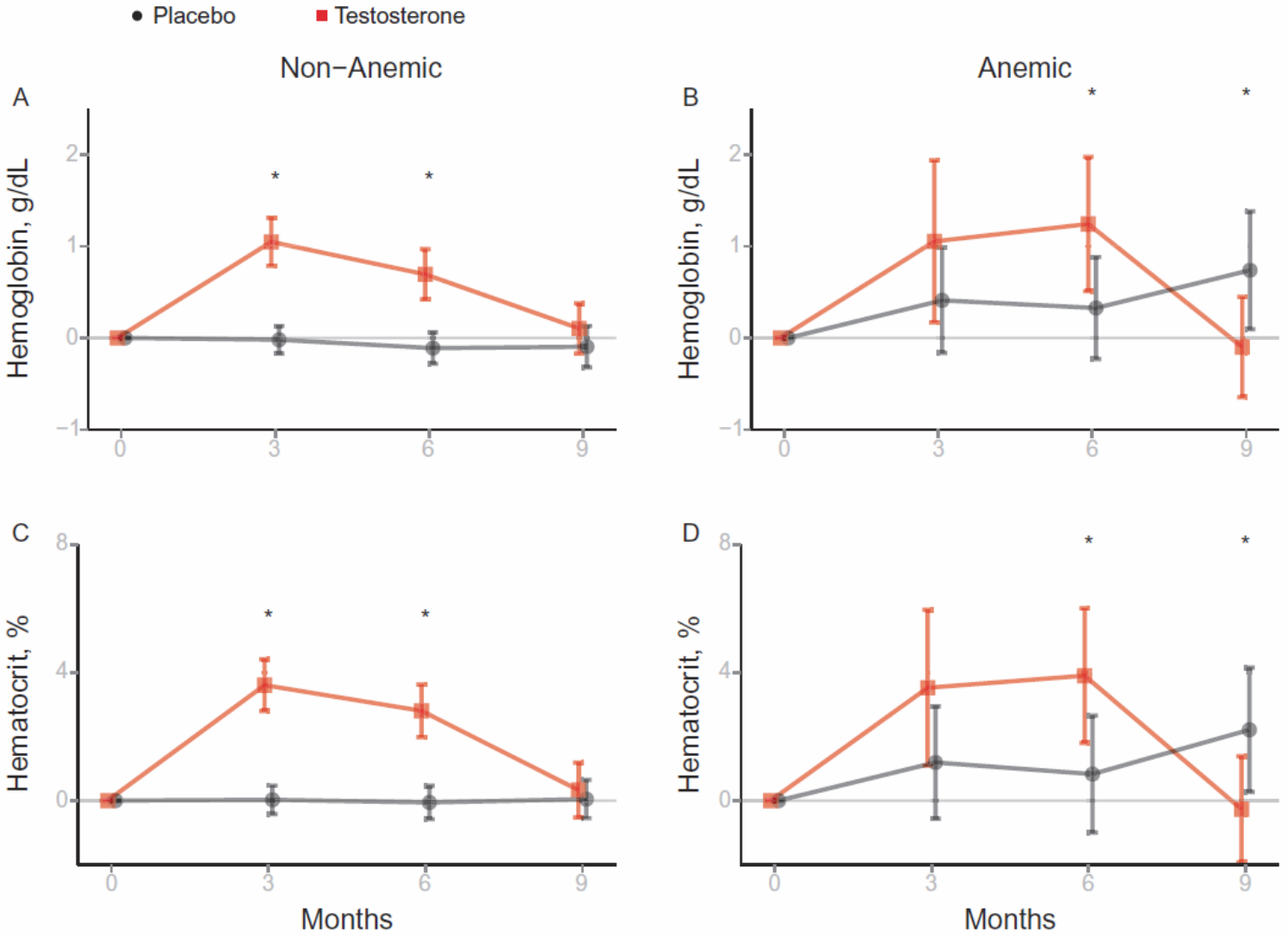
**Figure 2** Haemoglobin levels for treatment and placebo group at baseline and after 36 months of testosterone therapy.




Maggio M et al. Androl 2013; (1):24-8

the Journals of gerontology® Series A

# Testosterone Induces Erythrocytosis via Increased Erythropoietin and Suppressed Hepcidin: Evidence for a New Erythropoietin/Hemoglobin Set Point

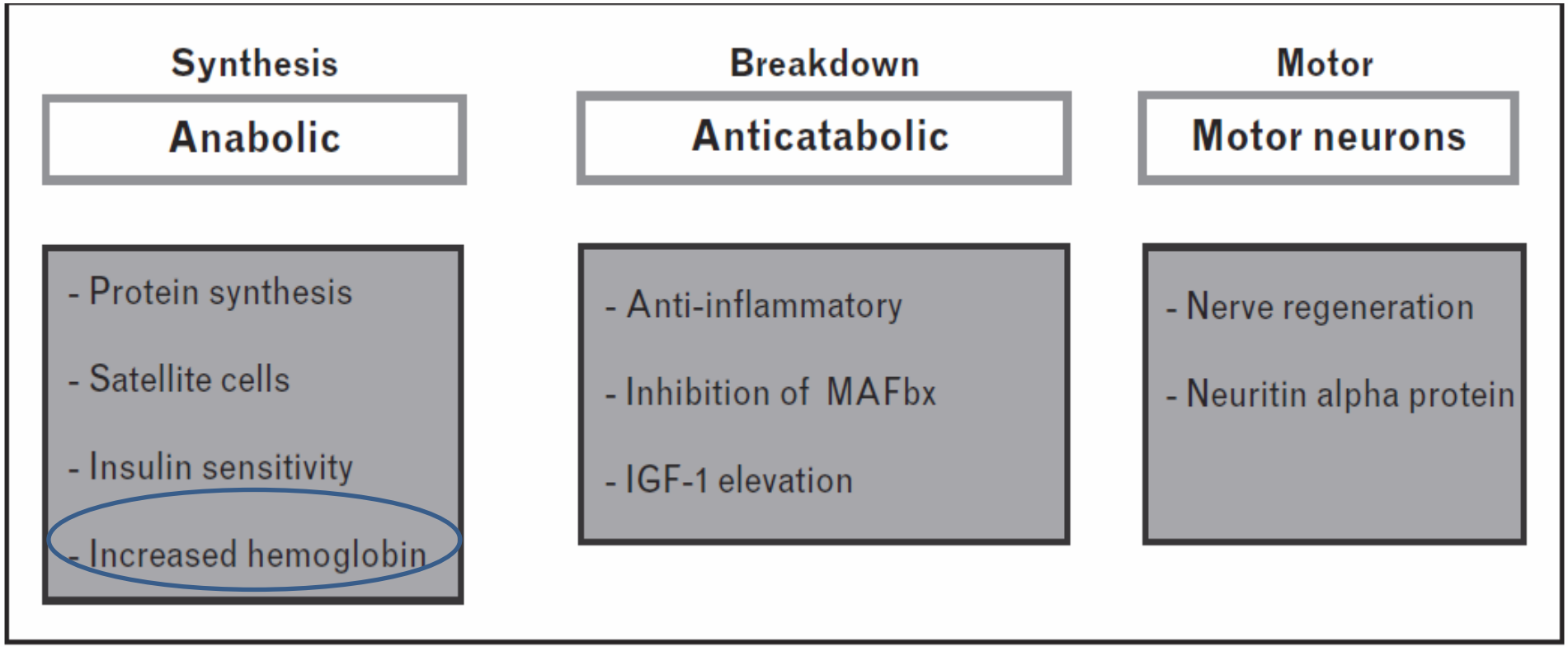



Bachman et al. J Gerontol 2013 in press

# Sex hormones and sarcopenia in older persons

*Marcello Maggio*[a,b], *Fulvio Lauretani*[b], *and Gian Paolo Ceda*[a,b]

**FIGURE 2.** Mechanisms by which testosterone improves muscle function. On the left column there are anabolic mechanisms, in the central column anticatabolic, and in the right column the hypothesized stimulatory action on motor neurons. IGF-1, insulin-like growth factor-1.




Maggio M et al. Curr Opin Clin Nutr Metab Care. 2013 Jan;16(1):3-13.

# Anemia in the elderly

*Wendy W. Pang and Stanley L. Schrier*

**Men with UAE had lower testosterone levels compared to non anemic controls, suggesting that hormonal deficiency may be a contributing factor to the development of UAE in men.**

Waalen et al. European Journal of Haematology 2001: 87:107–116

**Dysregulated growth hormone/insulin-like growth factor-1 (IGF-1) control of hepatic erythropoietin secretion**

Sohmya M et al. J Endocrin 2005; 184:199-207

**Low levels of IGF-1 have been associated with anemia in elderly individuals**

Succurro E et al. Thromb Haemost 2010:105:365-370

**Pang WW et al. Curr Opin Hemat 2012: 19:133-140**

# Erythropoietin, GDF15, IL6, hepcidin and testosterone levels in a large cohort of elderly individuals with anaemia of known and unknown cause

**Table 3** Mean cytokine/hormone levels

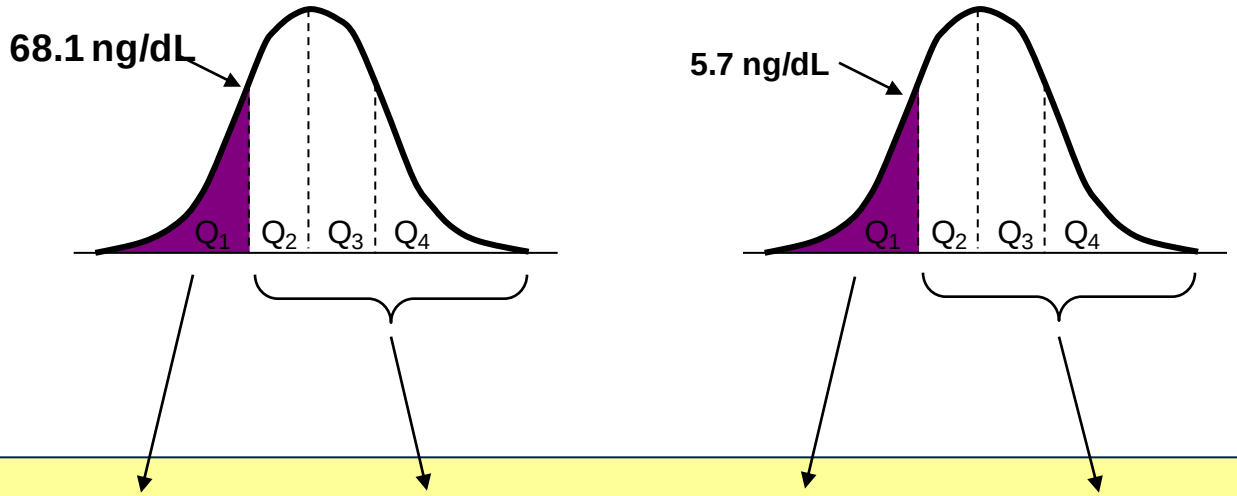
| | Control | | Anaemia of unknown aetiology (AUE) | | *P*-value | Iron deficiency anaemia (IDA) | | Anaemia associated with high creatinine | | Anaemia associated with haemodialysis | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | | *n* | | | *n* | | *n* | | *n* | |
| IL6 (pg/mL) | | | | | | | | | | | |
| Men | 24 | 1.4 ± 1.4 | 34 | 1.5 ± 1.3 | NS | 11 | 3.0 ± 2.8 | 5 | 1.2 ± 0.7 | 4 | 4.3 ± 2.5†† |
| Women | 23 | 1.7 ± 1.6 | 23 | 1.4 ± 1.4 | NS | 11 | 1.3 ± 1.3 | 4 | 2.0 ± 1.1 | | |
| EPO (mIU/mL) | | | | | | | | | | | |
| Men | 80 | 7.4 ± 2.9 | 72 | 10.0 ± 7.0** | 0.003 | 29 | 27.7 ± 25.7† | 10 | 8.5 ± 4.9 | 11 | 10.9 ± 10.6 |
| Women | 83 | 7.1 ± 2.7 | 80 | 8.6 ± 4.0** | 0.005 | 29 | 24.8 ± 18.3† | 13 | 25.0 ± 41.1†† | | |
| GDF15 (pg/mL) | | | | | | | | | | | |
| Men | 80 | 1117 ± 567 | 72 | 1299 ± 494** | 0.04 | 31 | 1460 ± 757 | 10 | 2859 ± 1034† | 11 | 4606 ± 3213† |
| Women | 83 | 943 ± 424 | 80 | 1181 ± 611** | 0.004 | 29 | 1066 ± 514 | 13 | 2772 ± 1694† | | |
| Testosterone (ng/mL) | | | | | | | | | | | |
| Men | 79 | 9.8 ± 7.7 | 72 | 7.6 ± 4.0** | 0.03 | 31 | 9.8 ± 4.3 | 10 | 7.9 ± 4.2 | 11 | 13.2 ± 6.3 |
| Hepcidin (ng/mL) | | | | | | | | | | | |
| Men | 25 | 132 ± 79 | 34 | 152 ± 69 | NS | 11 | 32 ± 25† | 5 | 257 ± 123** | 4 | 380 ± 240‡ |
| Women | 23 | 148 ± 74 | 23 | 192 ± 105 | NS | 11 | 37 ± 30†† | 4 | 92 ± 56 | | |

Waalen et al. European Journal of Haematology 2010 87:107–116.

# Bassi livelli di Testosterone biodisponibile e rischio di Anemia In soggetti non anemici dello Studio InCHIANTI

**Testosterone biodisponibile In Uomini senza Anemia** (N=274)

**Testosterone biodisponibile In Donne senza Anemia** (N=337)




**Baseline**

| | Uomini | | Donne | |
|---|---|---|---|---|
| **Incidenza di Anemia a 3 anni** | 21.0% | 4.7% | 16.1% | 3.9% |
| **Rischio Relativo*** | **4.7** (1.3-16.8) | | **4.4** (1.7-11.2) | |

* Aggiustato per età, BMI e molteplici confounders inclusa l'eritropoietina

**Ferrucci L, Maggio M et al. Arch Int Med 2006;166(13):1380-8**

# Prevalenza di anemia non spiegata (nero) in Uomini e Donne dello Studio InCHIANTI

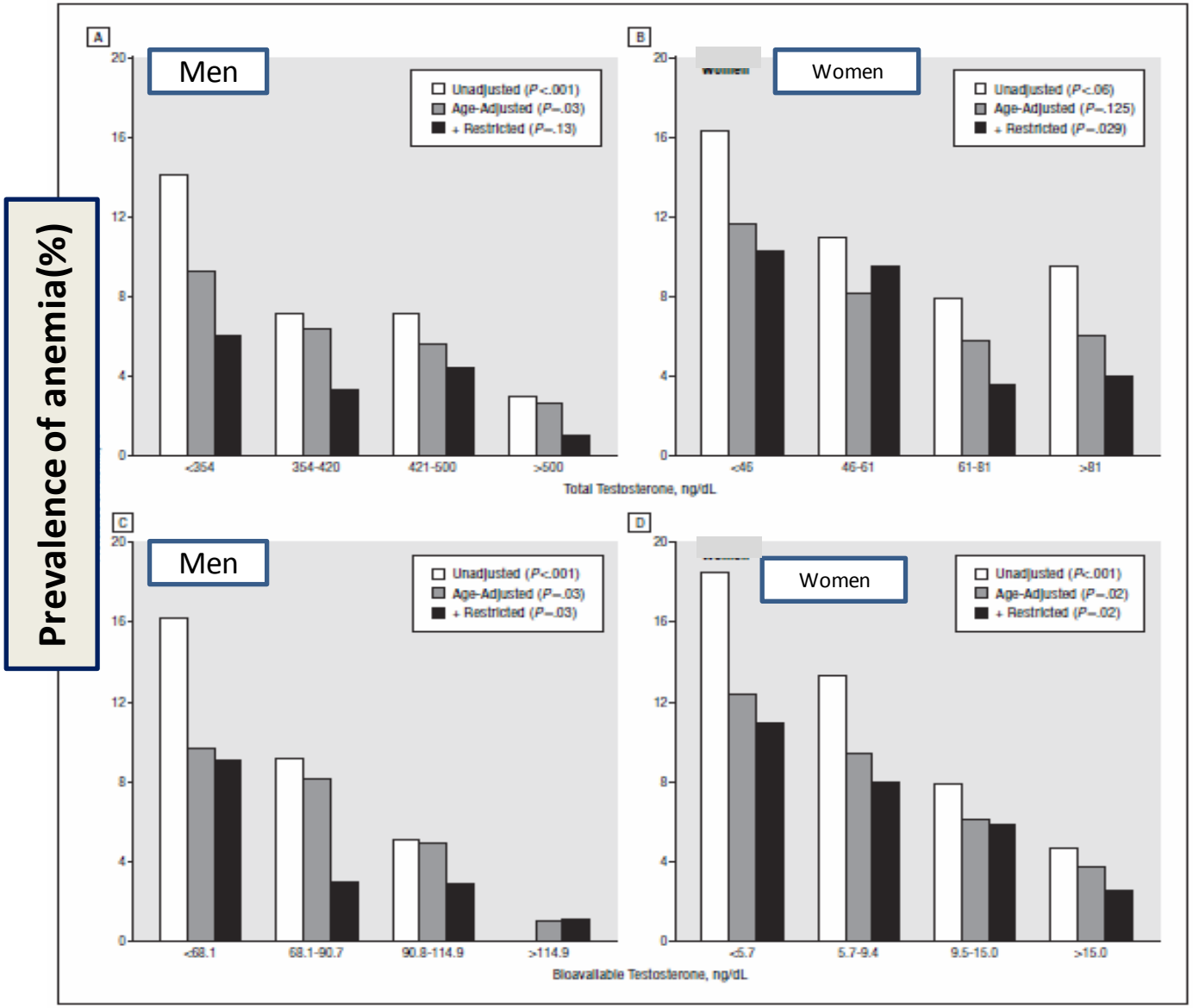



**Figure 2.** Crude and age-adjusted prevalence of anemia according to total and bioavailable testosterone level quartiles in all InCHIANTI[19] participants and restricted to cases of unexplained anemia (ie, normal serum iron levels and no deficiencies of iron, cyanocobalamin (vitamin $B_{12}$), or folate. To convert testosterone to nanomoles per liter, multiply by 0.0347.

Ferrucci L, Maggio M et al. Arch Int Med 2006;166(13):1380-8

# Anaemia associated with androgen deprivation in patients with prostate cancer receiving combined hormone blockade

S.B. STRUM, J.E. McDERMED, M.C. SCHOLZ, H. JOHNSON and G. TISMAN

*Daniel Freeman Marina Medical Centre, Marina del Rey, and The Institute for Prostate Cancer Research, California, USA*

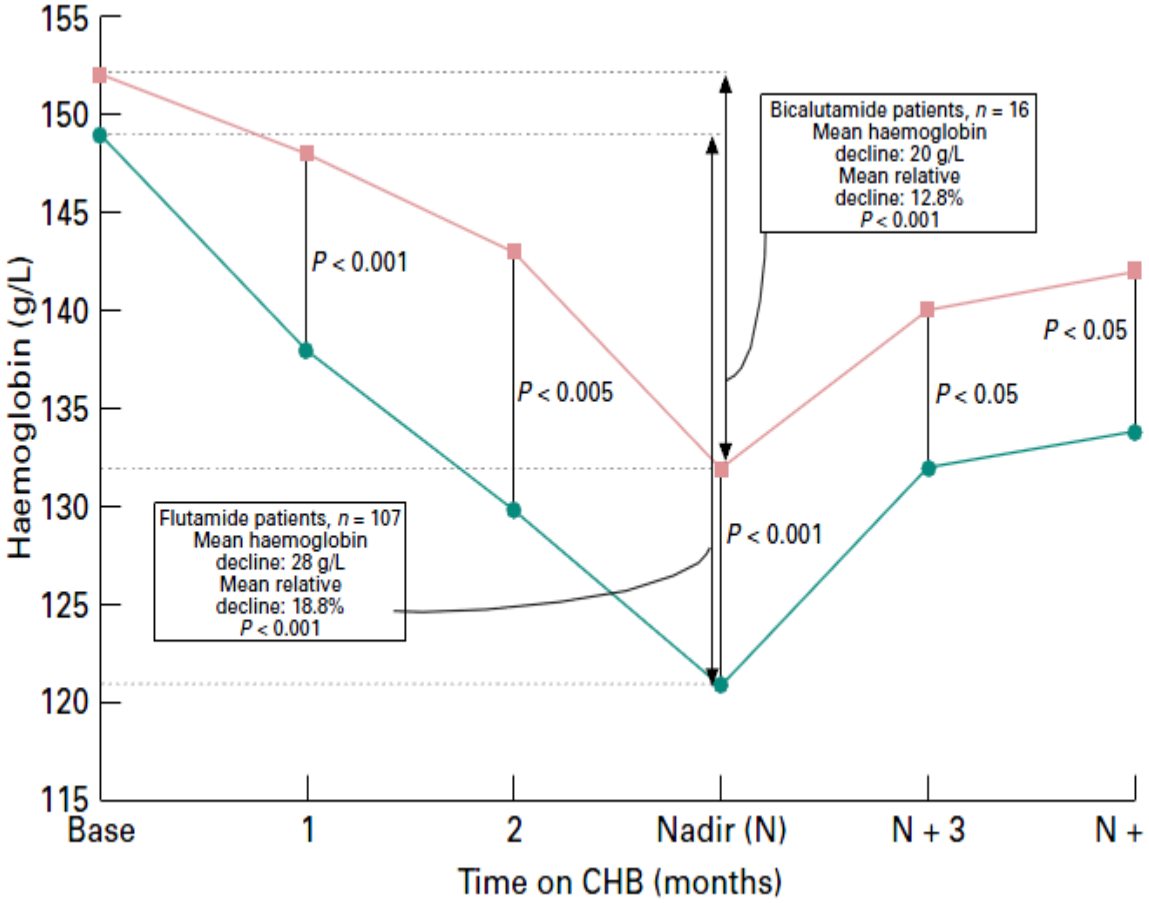



Fig. 3. There was no statistically significant difference in mean baseline haemoglobin levels between the 107 patients receiving flutamide (green) and the 16 patients receiving bicalutamide (red) ($P = 0.28$). Patients receiving CHB with flutamide had significantly lower mean haemoglobin levels at all measured times after CHB initiation when compared with patients receiving CHB with bicalutamide. The mean relative haemoglobin decline of each subset was significantly different (flutamide patients = 18.8 [1.1]%; bicalutamide patients = 12.8 [1.7]%, $P < 0.001$).

*British Journal of Urology* (1997), 79, 933–941

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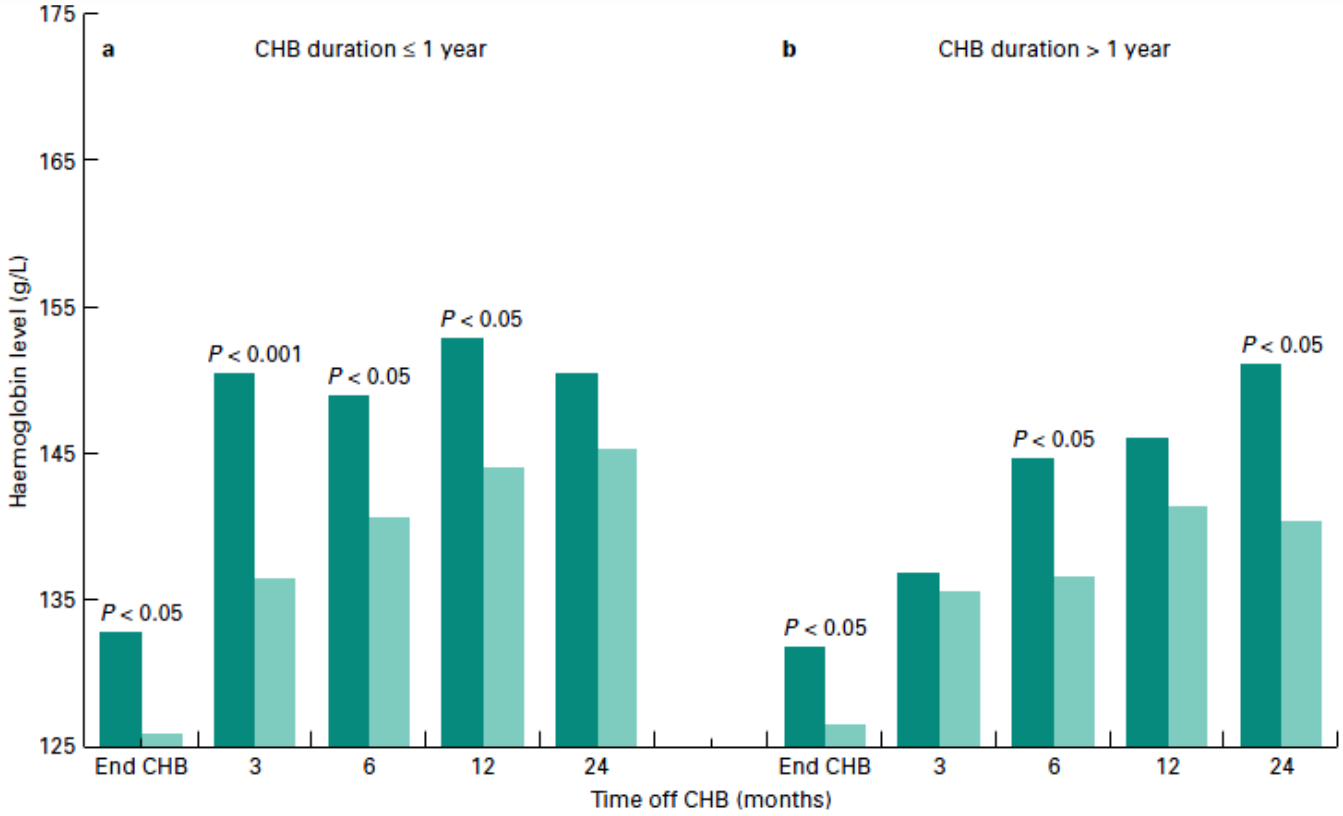


**Fig. 4.** Mean haemoglobin levels in patients aged ⩾68 years (light green) were significantly lower at the time CHB was discontinued than patients aged <68 years (green). Mean haemoglobin levels in the older subset remained significantly lower than baseline and lower compared with the younger subset until after androgen blockade for 24 months. The duration of CHB significantly affected haemoglobin recovery in the older subset, but had less impact upon the younger subset. Mean haemoglobin levels in patients aged <68 years receiving CHB for >1 year had normalized (>95% of baseline) by the sixth month off CHB, compared with 12 months in the older subset ($P < 0.05$).

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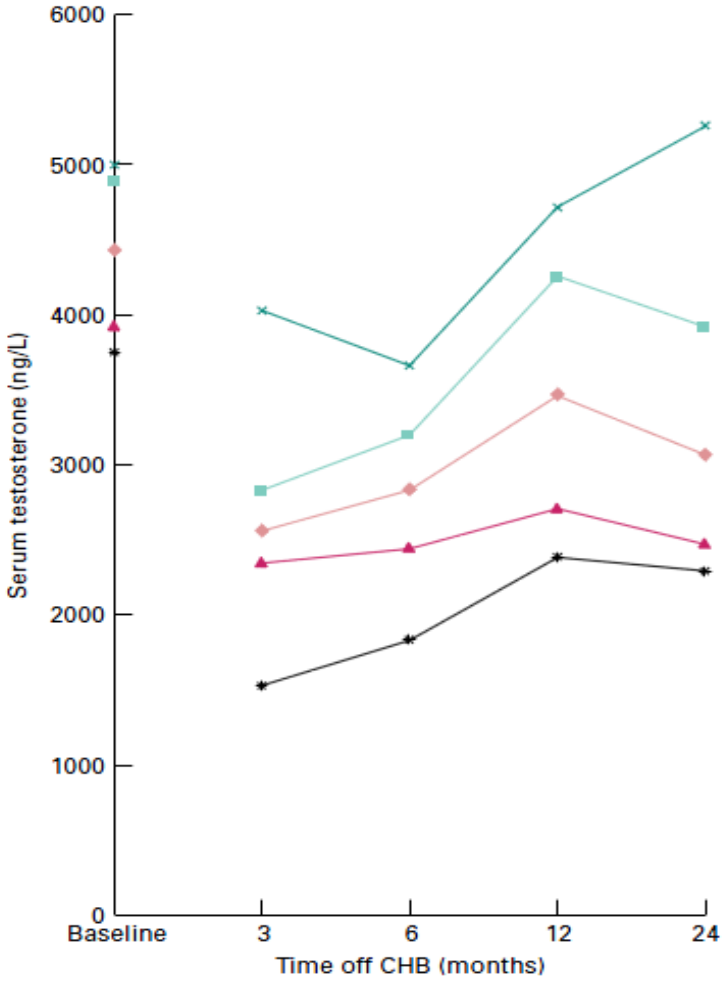


**Fig. 5.** The rate and extent of testosterone recovery varied with patient age at CHB initiation and the duration of CHB. Of the 14 patients aged $\geqslant 68$ years who had levels estimated at 24 months after CHB, eight had serum testosterone levels of $< 3000$ ng/L; in five of these eight, serum levels were $< 2000$ ng/L. Dark green, aged $< 68 +$ CHB $\leqslant 1$ year. Light green, aged $< 68$ (all). Light red, all patients. Dark red, aged $\geqslant 68$ (all). Black, aged $\geqslant 68 +$ CHB $> 1$ year.

*British Journal of Urology* (1997), 79, 933–941

# MECCANISMO D'AZIONE EMATOPOIETICO DEL TESTOSTERONE

## ✓ Azione diretta:

- aumenta attività del midollo osseo (stimolazione CFU-E)

  *Moriyama Y, Fisher JW. Blood. 1975; 45: 665-70.*

- stimola incorporazione del Ferro nei globuli rossi

  *Molinari PF, Rosenkrantz H. J Lab Clin Med. 1971; 78:399-410.*

- aumenta uptake del glucosio con attivazione glicolisi

  *Molinari PF, Esber HJ, Snyder LM. Exp Hematol. 1976; 4: 301-9.*

- potenzia l'effetto IGF-1 con maturazione e proliferazione dei proeritroblasti

  *Hagenfeldt Y, Linde K, Sjoberg HE, Zumkeller W, Arver. Int J Androl. 1992; 15: 93–102.*

- aumenta l' emivita dei globuli rossi

  *Solomon LR, Hendler ED. Acta Haematol. 1988; 79: 12–19*

## ✓ Azione indiretta:

- stimolazione di eritropoietina per aumento dell'RNA polimerasi con incremento della massa renale

  Paulo LG, Fink GD, Roh BL, Fisher JW .Blood. 1974; 43: 39-47.

**Basaria S, Maggio M. J Endocrinol Invest 2009; 32: 704-16**

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# Metodi: effetti del testosterone sull'EPO

**Dati Clinici sui Pazienti**

| Patients | Age | Sex | Weight | Diagnosis | Miscellaneous |
|---|---|---|---|---|---|
| M. N. | 75 | M | 58 kgm. | Multiple Myeloma | |
| L. H. | 39 | M | 55 kgm. | Multiple Myeloma | Chronic Renal Disease<br>BUN 40 mgm. percent<br>Creatinine 2.3 mgm. percent |
| K. K. | 3 | F | 10 kgm. | Aplastic Anemia | Secondary to choramphenicol toxicity |
| D. N. | 7 | M | 16 kgm. | Idiopathic Normochromic Normocytic Anemia | Idiopathic Mental Retardation |
| D. L. | 7 | M | 20 kgm. | Idiopathic Normochromic Normocytic Anemia | Idiopathic Mental Retardation |

Rishpon-Meyerstein et al. Blood 1968;31(4)

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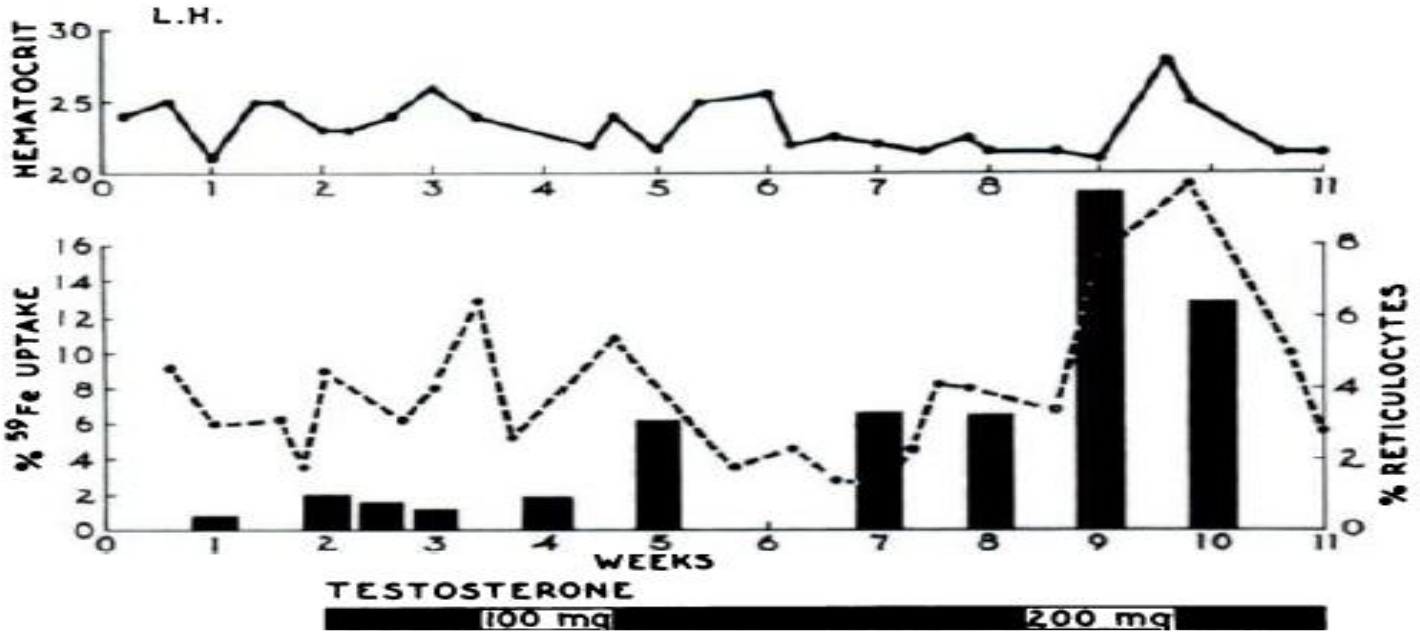
# Metodi: effetti del testosterone sull'EPO




Il contenuto plasmatico di EPO è stato misurato utilizzando un assay murino descritto da DeGowin et al. I livelli plasmatici di EPO sono espressi come la percentuale di intake di ferro nei GR formati de novo dopo iniezione di mezzo ml di plasma nell'assay murino.

**Rishpon-Meyerstein et al. Blood 1968;31(4)**

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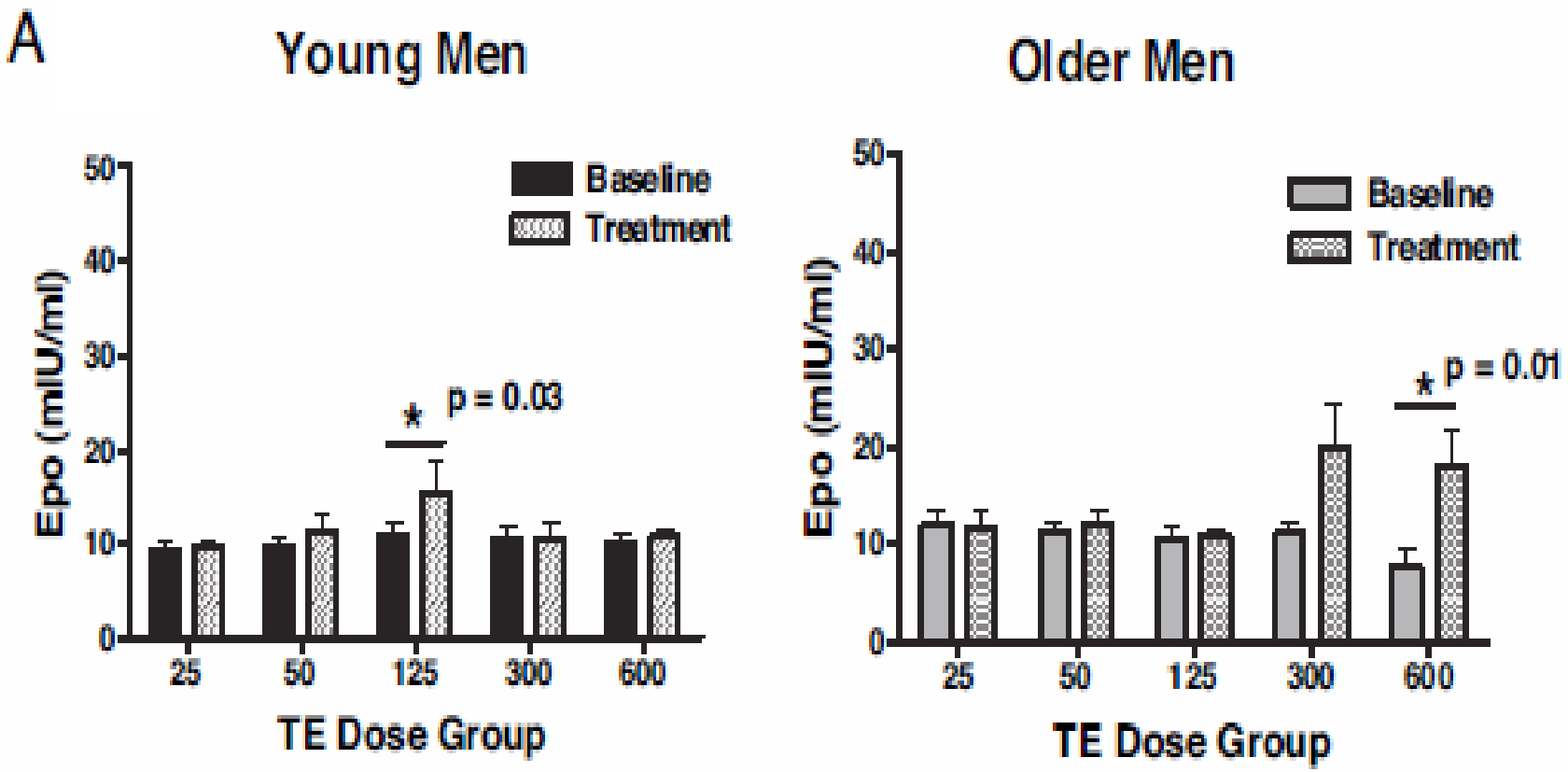
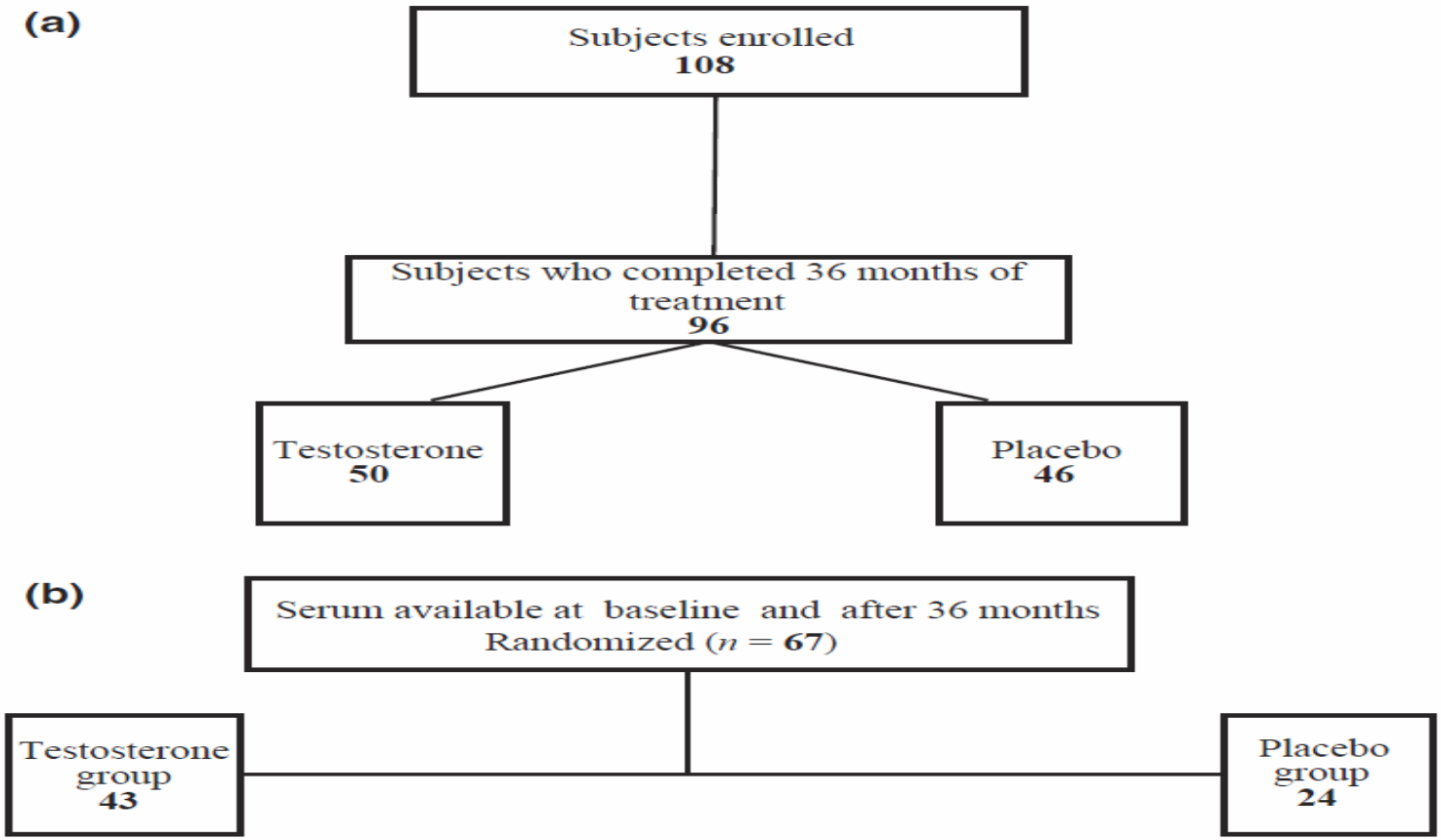
# Effetti del testosterone sull' EPO




Coviello A et al. J Clin Endocrinol Metab 2008;93(3):914-919

**Figure 1** Flow diagrams for the original RCT (a) and the post hoc data used in the current analysis of the RCT (b). Ten years after the original study had been completed, a proposal was submitted to National Institute on Aging and the University of Pennsylvania for access to serum available from the study to measure erythropoietin. Of the original 96 subjects, only 67 subjects (43 in the T group and 24 in the placebo group) had serum available from the baseline and 36 month visits. The study was performed on sera from these subjects.




Maggio M et al. Androl 2013; (1):24-8

# Scopo dello Studio

**Testare in soggetti ultrasessantacinquenni di sesso maschile con livelli circolanti di testosterone bassi-normali 1 sd o più al di sotto della media dei livelli considerati normali in soggetti giovani sani (475 ng/dL):**

**a) gli effetti della somministrazione di testosterone per via trans dermica sui livelli di emoglobina.**

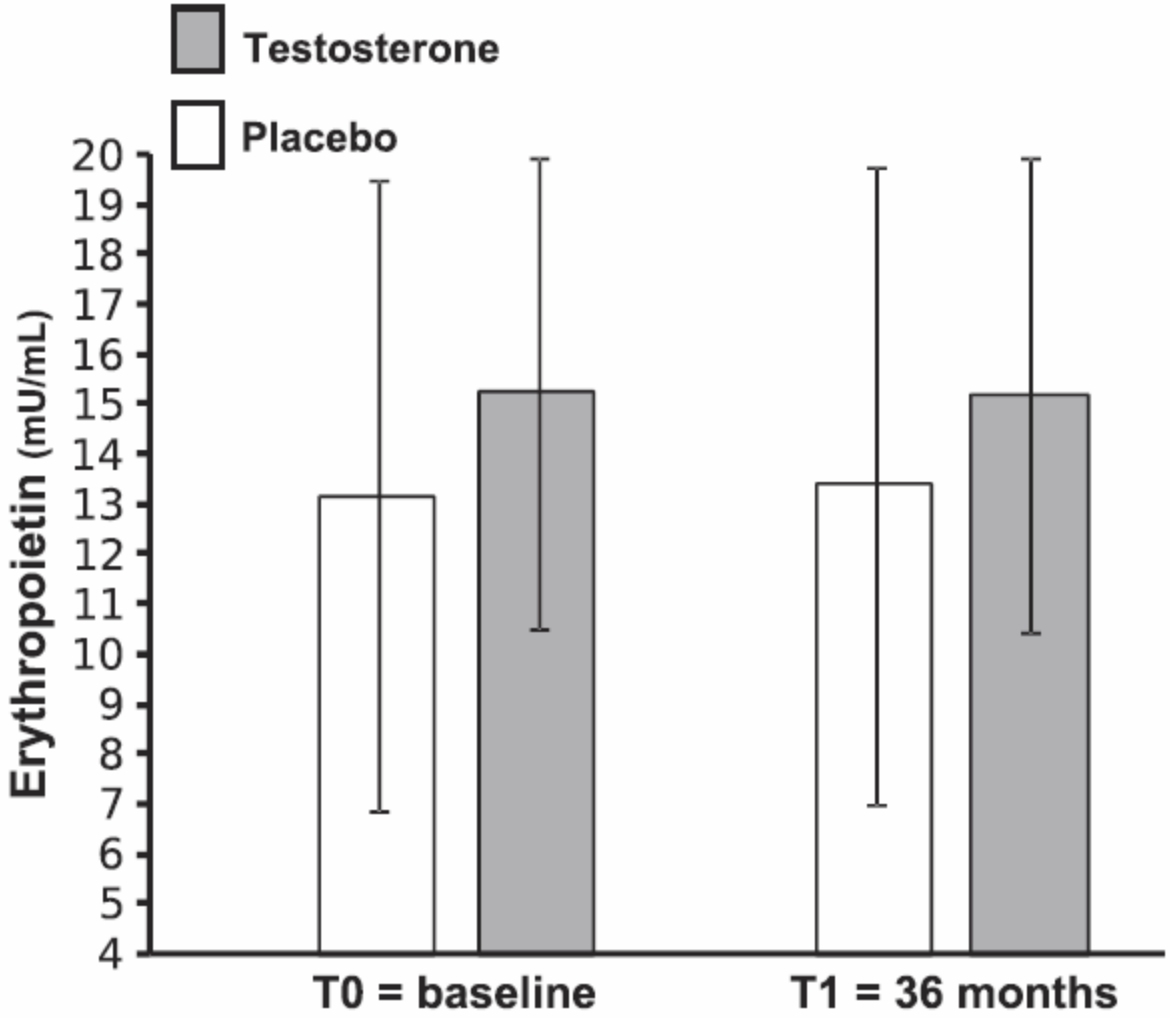
**b) se l'incremento dei livelli di emoglobina si accompagna ad una modificazione dei livelli circolanti di EPO.**

# Caratteristiche dei partecipanti allo studio al baseline

| | Treatment (n = 43) | Placebo (n = 24) | p |
|---|---|---|---|
| **Age (years)&** | 71.8 ± 4.7 | 71.8 ± 5.4 | 0.99 |
| **BMI (kg/m²)&** | 25.8 ± 3.3 | 24.8 ± 2.4 | 0.16 |
| **Testosterone (ng/dL) *** | 402.2 (245.6) | 372.1 (79.1) | 0.06 |
| **Creatinine (mg/dL) *** | 1.10 (0.20) | 1.20 (0.30) | 0.37 |
| **Hemoglobin (g/dL) *** | 14.9 (1.4) | 15.0 (1.7) | 0.84 |
| **Erythropoietin (mUI/mL)*** | 11.7 (7.8) | 11.9 (9.6) | 0.77 |

**& Means SD**
*** Medians Interquartile range**

**Figure 3** Erythropoietin levels for treatment and placebo group at baseline and after 36 months of testosterone therapy.




Maggio M et al. Androl 2013; (1):24-8

# Hemoglobin and erythropoietin concentrations (mean SD and change from baseline, delta) by treatment group

| | Baseline | | 36 months | | Delta | | P |
|---|---|---|---|---|---|---|---|
| **Hemoglobin (g/dL)** | | | | | | | |
| **Testosterone** | 14.7 | 1.02 | 15.5 | 1.36 | 0.80 | 1.24 | <0.001 |
| **Placebo** | 14.7 | 1.44 | 14.6 | 1.06 | -0.06 | 1.21 | 0.94 |
| **Erythropoietin (mUI/mL)** | | | | | | | |
| **Testosterone** | 15.2 | 19.32 | 15.4 | 17.5 | -0.08 | 9.1 | 0.58 |
| **Placebo** | 13.2 | 6.95 | 13.8 | 9.7 | 0.13 | 6.1 | 0.59 |

**The *P* values compares the mean change from 0–36 months between the two treatment groups.**

**Maggio M et al. Androl 2013; (1):24-8**

*Journals of Gerontology: MEDICAL SCIENCES*
*Cite journal as: J Gerontol A Biol Sci Med Sci*
doi:10.1093/gerona/glt154

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# Testosterone Induces Erythrocytosis via Increased Erythropoietin and Suppressed Hepcidin: Evidence for a New Erythropoietin/Hemoglobin Set Point

Eric Bachman,[1] Thomas G. Travison,[2] Shehzad Basaria,[1] Maithili N. Davda,[2] Wen Guo,[2] Michelle Li,[2] John Connor Westfall,[1] Harold Bae,[1] Victor Gordeuk,[2] and Shalender Bhasin[3]

Table 1. Baseline Characteristics of Study Subjects.

| Variable | Testosterone (82) | Placebo (84) |
|---|---|---|
| Age (y) | 74±6 | 74±5 |
| BMI (kg/m$^2$) | 29.8±4.1 | 30.1±4.4 |

**Bachman et al. J Gerontol 2013 in press**

# Testosterone Induces Erythrocytosis via Increased Erythropoietin and Suppressed Hepcidin: Evidence for a New Erythropoietin/Hemoglobin Set Point

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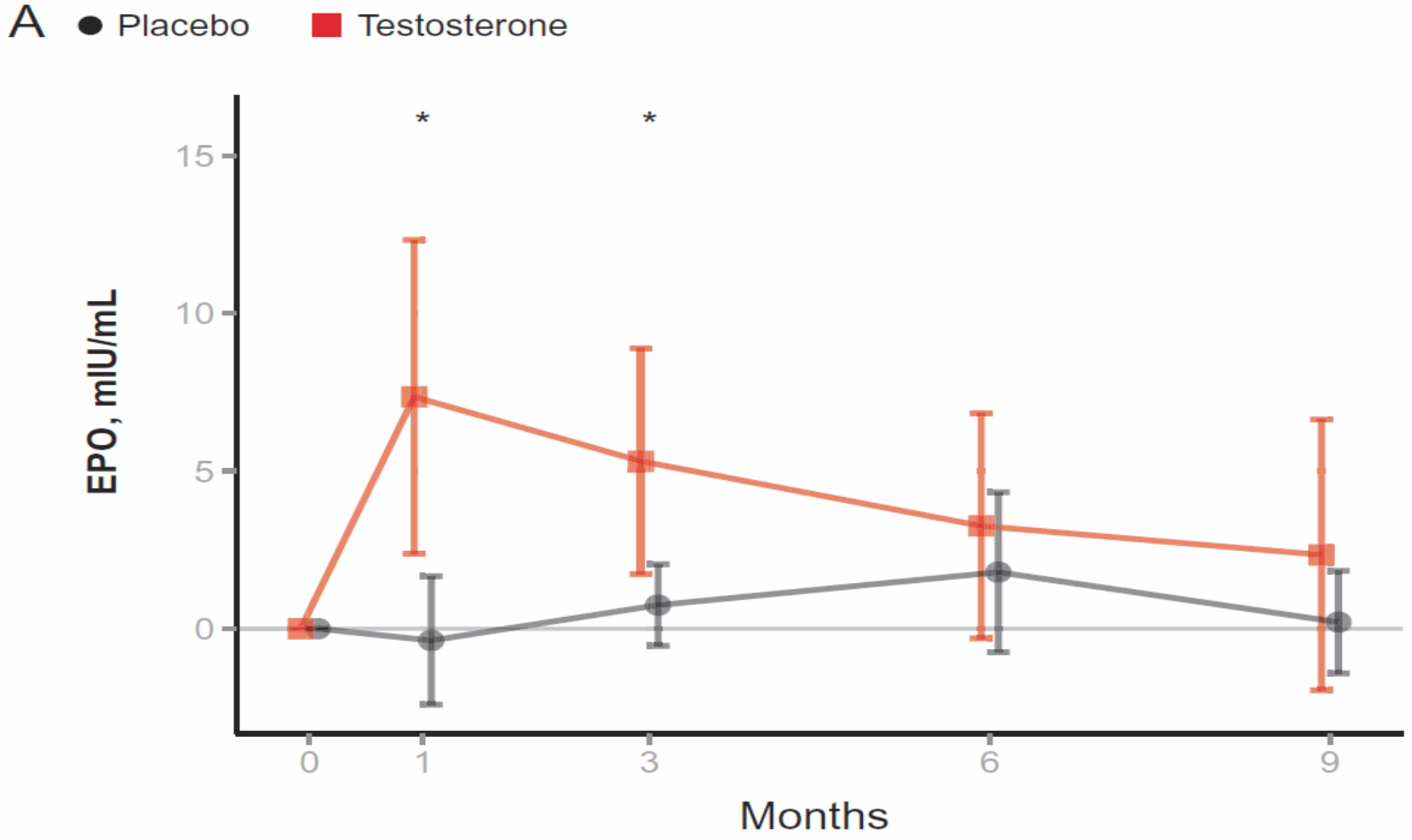


**Bachman et al. J Gerontol 2013 in press**

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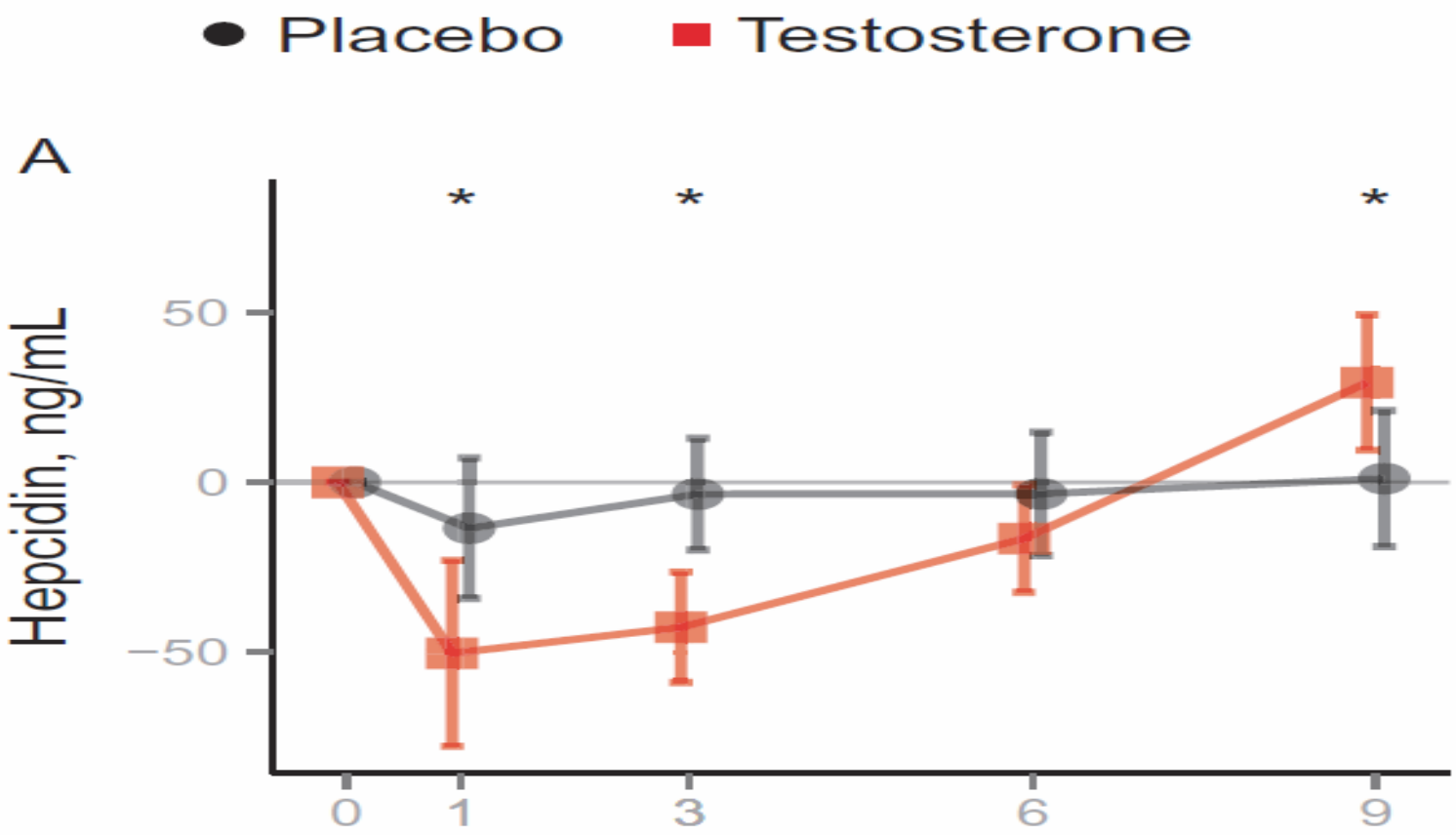
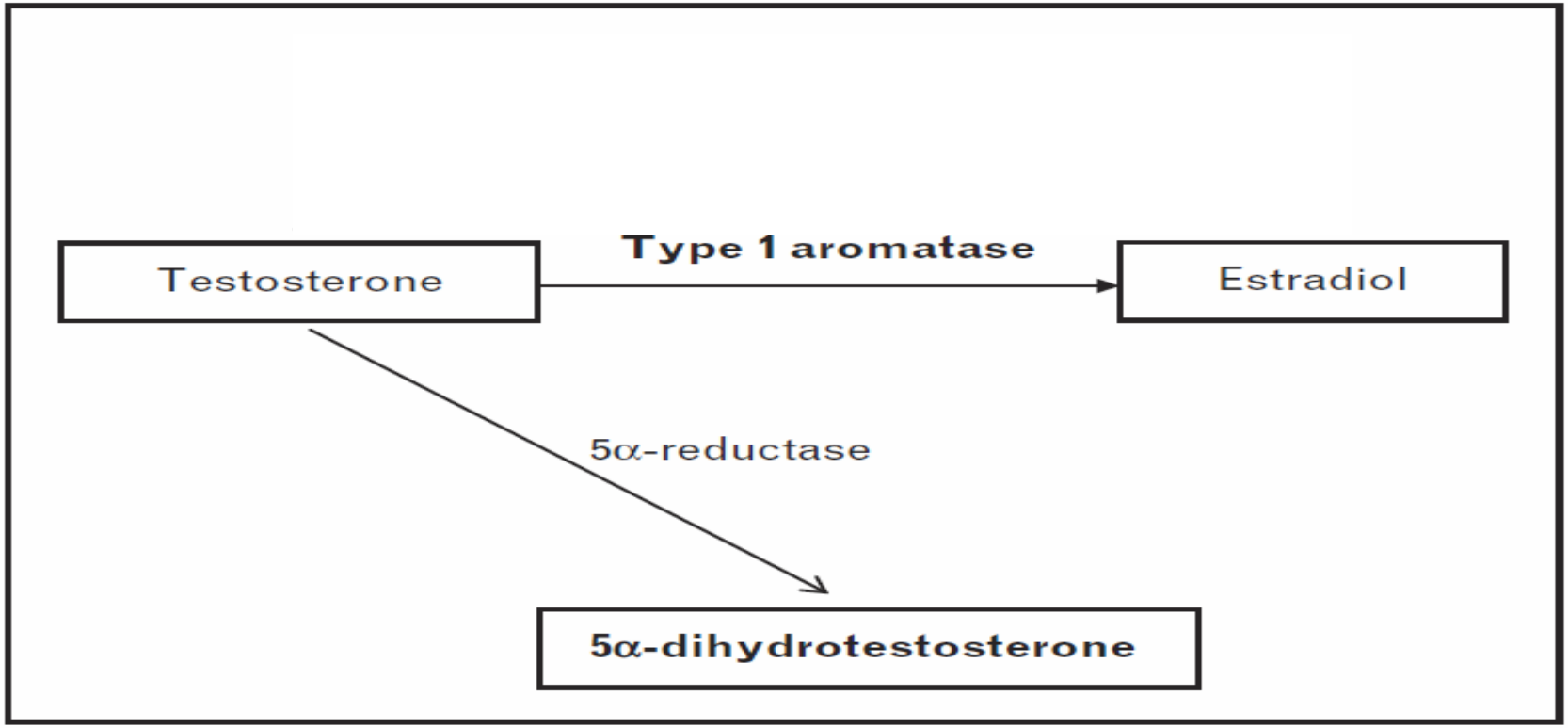



Bachman et al. J Gerontol 2013 in press

# Mediators of Erythropoietic effects of testosterone

CURRENT OPINION

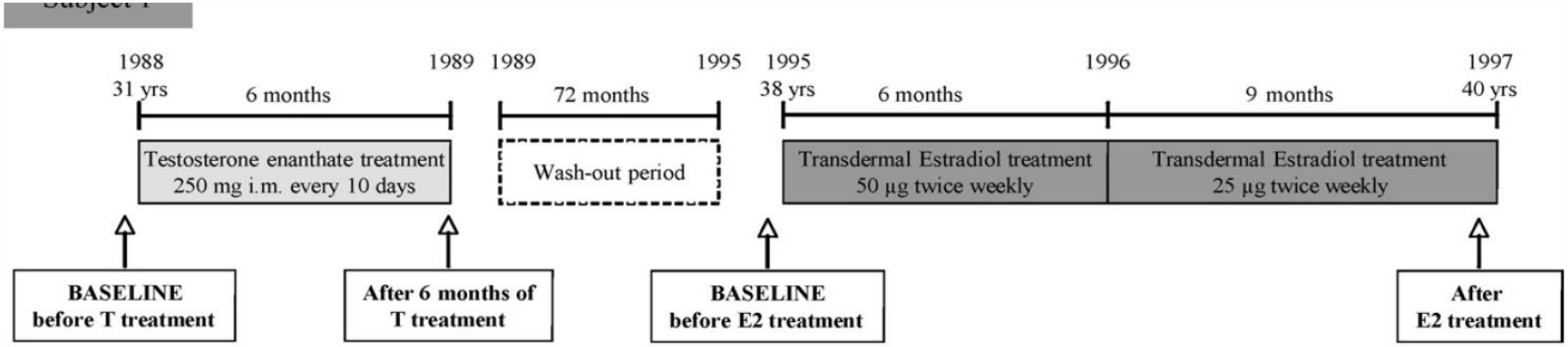
REVIEW

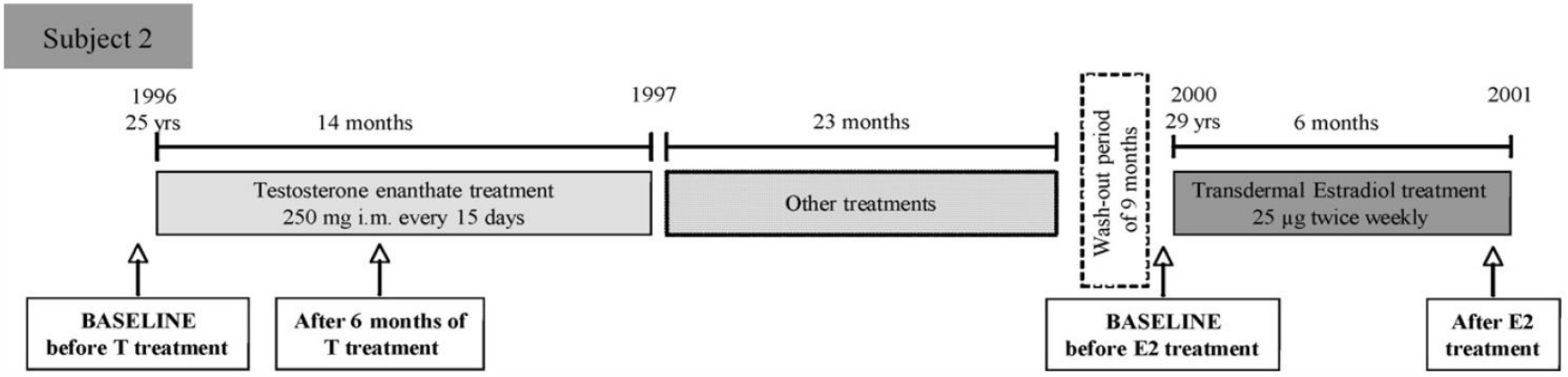



Maggio M, Lauretani F, Ceda GP. Curr Op Med Care Nutr 2013; 16:3-13

# Testosterone action on erythropoiesis does not require its aromatization to estrogen: Insights from the testosterone and estrogen treatment of two aromatase-deficient men☆

Vincenzo Rochira[a,*], Lucia Zirilli[a], Bruno Madeo[a], Laura Maffei[b], Cesare Carani[a]




Rochira V et al. Journal of Steroid Bioch and Mol Biol 2009;113:189-194

# Testosterone action on erythropoiesis does not require its aromatization to estrogen: Insights from the testosterone and estrogen treatment of two aromatase-deficient men☆

Vincenzo Rochira[a,*], Lucia Zirilli[a], Bruno Madeo[a], Laura Maffei[b], Cesare Carani[a]

**Table 1**

Biochemical and hormonal parameters of two aromatase-deficient men before and during testosterone (T) treatment at a supraphysiological dosage (testosterone enanthate 250 mg i.m. every 2 weeks), and before and during transdermal estradiol ($E_2$) replacement treatment (25 μg twice weekly). Both testosterone treatment and estrogen treatment lasted a minimum of six months, and the period of washout between the two treatments was longer than twelve months. All data are expressed in Conventional Units; S values are in parentheses.

| Parameter | Normal range | Subject | Before T | During T | Washout period (>12 months) | |
|---|---|---|---|---|---|---|
| | | | | | Before $E_2$ | During $E_2$ |
| Serum Testosterone ng/mL (nmol/L) | 3–10 (*10–35*) | Subject 1 | 3.9 (*13.5*)* | 11.86 (*41*)* | 5.2 (*18*)# | 4.2 (*14.5*)# |
| | | Subject 2 | 3.8 (*13.1*)§ | 9.1 (*31.5*)§ | 2.7 (*9.3*)§# | 1.45 (*5*)§# |
| Serum Estradiol pg/mL (pmol/L) | 10–40 (*36–146*) | Subject 1 | <1.5 (<*5.5*)* | <1.5 (<*5.5*)* | <1.5 (<*5.5*)# | 24 (*88*)# |
| | | Subject 2 | <1.5 (<*5.5*)§ | <1.5 (<*5.5*)§ | <1.5 (<*5.5*)§# | 23.5 (*86*)§# |
| Blood Hemoglobin g/dL (g/L) | 14–17.5 (*140–175*) | Subject 1 | 14.2 (*142*) | 16.3 (*163*) | 14.5 (*145*) | 14.7 (*147*) |
| | | Subject 2 | 14.8 (*148*) | 16.9 (*169*) | 14.5 (*145*) | 13.9 (*139*) |
| Hematocrit % (proportion of 1.0) | 42–54 (*0.42–0.54*) | Subject 1 | 40.5 (*0.405*) | 44.9 (*0.449*) | 40.7 (*0.407*) | 40.9 (*0.409*) |
| | | Subject 2 | 42.0 (*0.420*) | 49.2 (*0.492*) | 42.9 (*0.492*) | 39.8 (*0.398*) |

**Rochira V et al. Journal of Steroid Bioch and Mol Biol 2009;113:189-194**

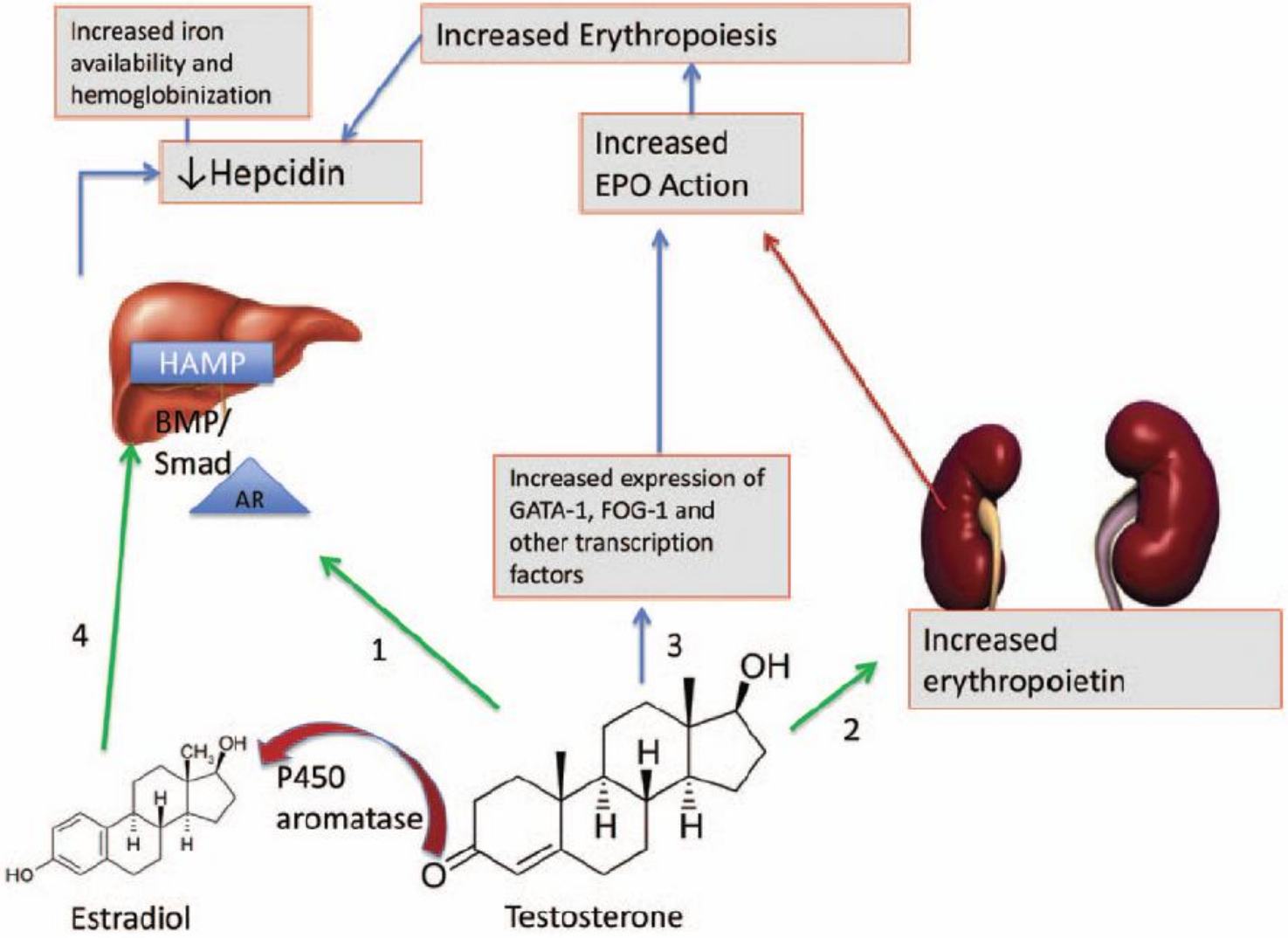
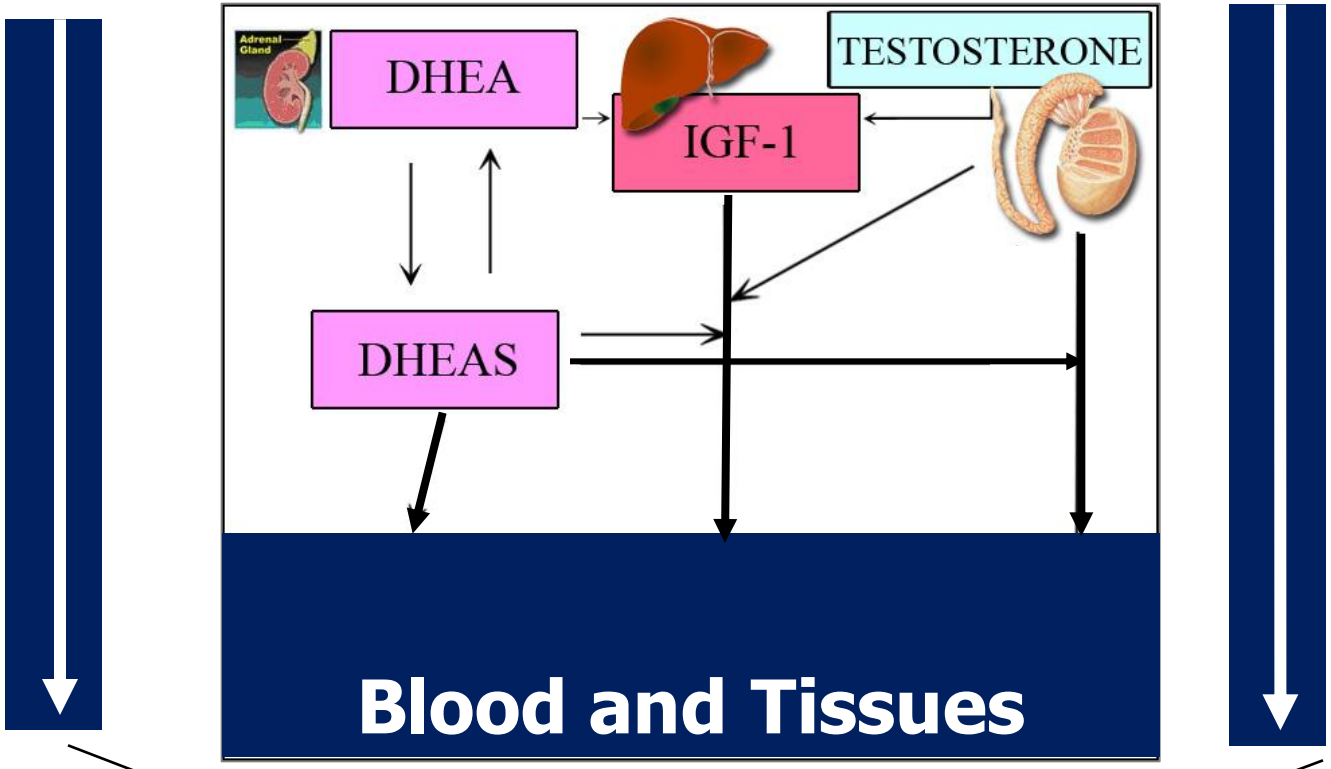



Figure 6. Model illustrating the currently established mechanisms by which testosterone increases red cell mass: (1) testosterone directly inhibits BMP-Smad signaling in hepatocytes leading to suppression of hepcidin transcription (26), (2) testosterone stimulates renal secretion of EPO through unknown mechanisms that stimulates erythropoiesis, which could suppress hepcidin (this manuscript), (3) testosterone upregulates the expression of GATA-1- and GATA-dependent genes, which could increase EPO sensitivity and stimulate stress erythropoiesis (38), and (4) testosterone is converted to estradiol (E2), which can regulate hepcidin transcription (35–37).

**Bachman et al. J Gerontol 2013 in press**

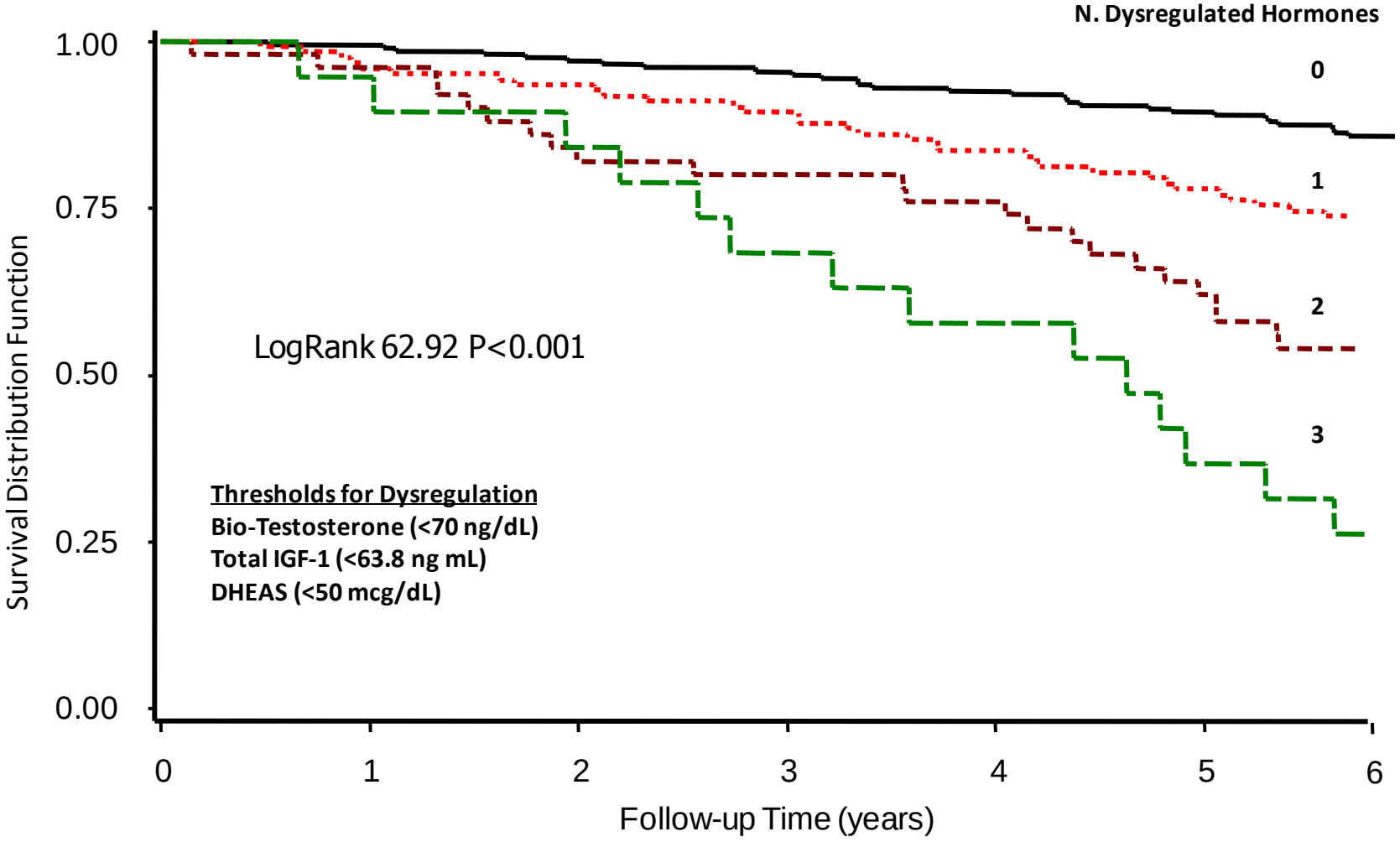
# Interrelation between Anabolic hormones




Unfavourable metabolic status

mortality

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




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

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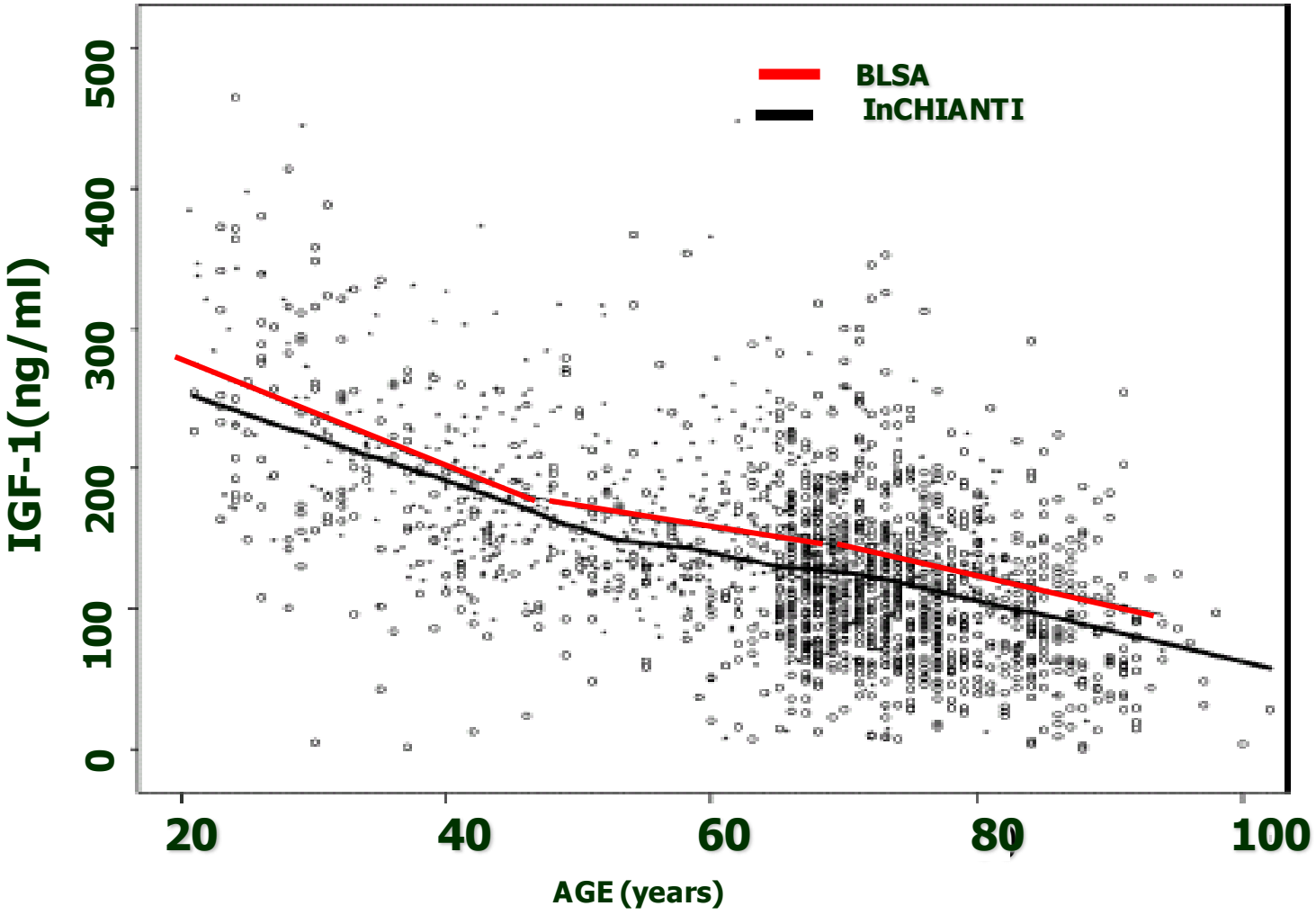
# Relationship between IGF-1 and age in men and women




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

# The Importance of Growth Hormone in the Regulation of Erythropoiesis, Red Cell Mass, and Plasma Volume in Adults with Growth Hormone Deficiency*

**In Soggetti affetti da deficit di ormone della crescita (GH), si registra un miglioramento della crasi ematica a seguito della somministrazione di GH, effetto verosimilmente relato all'aumento dei valori di IGF-1, ed in assenza di alterazioni dei livelli di EPO**

**Christ ER et al. J Clin Endocrinol Metab 1997 Sep;82(9):2985-90**

# Modelli sperimentali e dati di letteratura: IGF-1 e modulazione dell'eritropoiesi

- ✓ **IGF receptors are found in both erythrocyte precursors and mature erythrocytes.**
  Miyagawa S, et al. Br J Haematol 2000;109:555-562.

- ✓ **IGF-I administration to neonatal or hypophysectomized animals results in increased erythropoiesis in vivo.**
  Aron DC. Biofactors. 1992 Apr;3(4):211-6.

- ✓ **Serum IGF-I levels were significantly associated with the free erythrocyte protoporphyrin activities (FEP) blood hemoglobin and serum iron concentrations.**
  Choi JW, Kim SK. Ann Clin Lab Sci. 2004 Summer;34(3):324-8

- ✓ **IGF-I *In vitro* direct effects in the stimulation of the proliferation of primitive erythroid progenitor cells.**
  - Claustres M et al. JCEM 1987; 65: 78–82.
  - Correa PN,et al. Blood 1991; 78: 2823–2833.
  - Merchav S et al. Br J Haematol 1988; 70: 267–271.

# Modelli sperimentali e dati di letteratura: IGF-1 e modulazione dell'eritropoiesi

- **Concomitant increase in both IGF-1 serum concentrations and Hb levels after 4-wk low-dose recombinant human GH (rhGH) administration in malnourished older subjects**

  Chu LW, Lam KS, Tam SC, et al. A randomized controlled trial of low-dose recombinant human growth hormone in the treatment of malnourished elderly medical patients. J Clin Endocrinol Metab 2001; 86: 1913–1920.

- **Recombinant human GH (rhGH) administration, resulted in increased IGF-1 serum concentrations, Hb levels, red blood cell mass and red cell count in children with short stature and GH deficient adults.**

  Vihervuori E, Sipilä I, Siimes MA. Increases in hemoglobin concentration and iron needs in response to growth hormone treatment. J Pediatr. 1994 Aug;125(2):242-5.

- **Higher IGFBP-3 level is associated with a higher hemoglobin concentration among older people living in the community.**

  Landi F,et al. Insulin-like growth factor-binding protein 3 and hemoglobin concentration in older persons living in the community. Int J Hematol. 2007 May;85(4):294-9.

# Insulin-like growth factor-1 is a predictor of blood haemoglobin concentration in 70-yr-old subjects

Herman Nilsson-Ehle[1], Bengt-Åke Bengtsson[1], Göran Lindstedt[2], Dan Mellström[3]

EUROPEAN JOURNAL OF Haematology

GH and/or IGF-1 levels are significant determinants of Hb concentrations independent of erythropoietin and regardless of health status and sex in community-dwelling subjects aged >70 years.

Eur J Haematol. 2005 Feb;74(2):111-6.

JASN JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

# Insulin-Like Growth Factor I Plays a Role in Regulating Erythropoiesis in Patients with End-Stage Renal Disease and Erythrocytosis

LEE-YUNG SHIH,* JENG-YI HUANG,† and CHING-TAI LEE*

IGF-I plays an important role in the regulation of erythropoiesis in patients with patients with end-stage renal disease and erythrocytosis who did not have an increased EPO production.

J Am Soc Nephrol 10: 315–322, 1999

# Low insulin-like growth factor-1 levels are associated with anaemia in adult non-diabetic subjects

Elena Succurro; Franco Arturi; Vittoria Caruso; Stefania Rudi; Angela Sciacqua; Francesco Andreozzi; Marta L. Hribal; Francesco Perticone; Giorgio Sesti

| | Unadjusted correlations between Hb concentration and anthropo-metric and metabolic variables | | Age and gender adjusted correlations between Hb concentration and anthropo-metric and metabolic variables | |
|---|---|---|---|---|
| | r | P | r | P |
| Age (years) | 0.02 | 0.61 | 0.01 | 0.92* |
| BMI (kg/m$^2$) | 0.04 | 0.2 | 0.06 | 0.06 |
| Waist circumference (cm) | 0.15 | 0.0001 | 0.07 | 0.01 |
| SBP (mmHg) | 0.11 | 0.0001 | 0.04 | 0.17 |
| DBP (mmHg) | 0.14 | 0.0001 | 0.06 | 0.03 |
| Fasting glucose (mgl/dl) | 0.13 | 0.0001 | 0.02 | 0.70 |
| Fasting insulin (µU/ml) | 0.05 | 0.13 | 0.01 | 0.76 |
| IGF-1 (ng/ml) | 0.11 | 0.0001 | 0.10 | 0.005 |
| hsCRP (mg/l) | –0.12 | 0.0001 | –0.10 | 0.001 |
| Fibrinogen (mg/dl) | –0.13 | 0.0001 | –0.06 | 0.09 |
| Mean corpuscular volume (fl) | 0.26 | 0.0001 | 0.31 | 0.0001 |
| Mean corpuscular haemoglobin (pg) | 0.47 | 0.0001 | 0.49 | 0.0001 |
| Serum Iron (µg/dl) | 0.34 | 0.0001 | 0.27 | 0.0001 |
| eGFR (ml/min/1.73m$^2$) | –0.03 | 0.41 | –0.02 | 0.65 |

BMI=Body Mass Index SBP = systolic blood pressure; DBP = diastolic blood; ISI = insulin sensitivity index. *P-values refer to results after analysis with adjustment for gender.

| | 1st Quartile | 2nd Quartile | 3rd Quartile | 4th Quartile | P-value |
|---|---|---|---|---|---|
| Gender (M/F) | 107/149 | 123/139 | 137/120 | 124/140 | 0.07 |
| Age (years) | 55 ± 10 | 50 ± 11 | 46 ± 11 | 40 ± 14 | 0.0001* |
| BMI (kg/m$^2$) | 30.4 ± 5.2 | 30.9 ± 6.5 | 29.1 ± 5.4 | 28.1 ± 5.3 | 0.0001 |
| Waist circumference (cm) | 101 ± 12 | 102 ± 15 | 98 ± 12 | 94 ± 14 | 0.0001 |
| SBP (mmHg) | 137 ± 18 | 135 ± 18 | 133 ± 17 | 129 ± 17 | 0.24 |
| DBP (mmHg) | 84 ± 10 | 83 ± 10 | 83 ± 11 | 82 ± 10 | 0.52 |
| Fasting glucose (mgl/dl) | 94 ± 12 | 93 ± 10 | 91 ± 12 | 89 ± 10 | 0.11 |
| Fasting insulin (µU/ml) | 13 ± 9 | 13 ± 8 | 11 ± 7 | 12 ± 8 | 0.18 |
| IGF-1 (ng/ml) | 89 ± 16 | 129 ± 10 | 172 ± 13 | 267 ± 49 | 0.0001 |
| hsCRP (mg/l) | 3.4 ± 2.4 | 3.2 ± 2.5 | 2.6 ± 2.1 | 2.3 ± 1.9 | 0.0001 |
| Fibrinogen (mg/dl) | 334 ± 78 | 332 ± 79 | 319 ± 79 | 312 ± 75 | 0.63 |
| eGFR (ml/min/1.73m$^2$) | 93 ± 20 | 99 ± 23 | 102 ± 24 | 102 ± 22 | 0.01 |
| Haemoglobin (g/dl) | 13.8 ± 1.5 | 14.0 ± 1.3 | 14.2 ± 1.4 | 14.2 ± 1.4 | 0.005 |
| Mean corpuscular volume (fl) | 85.7 ± 7.3 | 85.6 ± 9.1 | 84.6 ± 7.4 | 85.3 ± 7.0 | 0.33 |
| Mean corpuscular haemoglobin (pg) | 28.8 ± 2.8 | 29.0 ± 3.1 | 29.0 ± 2.7 | 28.9 ± 2.7 | 0.83 |
| Serum Iron (µg/dl) | 85 ± 29 | 89 ± 31 | 94 ± 34 | 88 ± 31 | 0.09 |
| Subjects with anaemia (n) | 33 | 23 | 17 | 19 | 0.01** |

Data are means ± SD. IGF-1 levels were log transformed for statistical analysis, but values in the table represent a back transformation to the original scale. P values refer to results after analyses with adjustment for age, and gender. *P-values refer to results after analysis with adjustment for gender. **P for trend. Categorical variables were compared by Chi$^2$ test. M= male; F= female; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Succurro E et al, Thromb Haemost 2010, 105

# Characteristics of the older men (n = 402) and women (n = 536) according to the presence of anemia.

| | Men (n = 402) | | | Women (n = 536) | | |
|---|---|---|---|---|---|---|
| **Characteristics** | **Anemic** | **Not anemic** | **P^** | **Anemic** | **Not anemic** | **P^** |
| **N** | 45 | 357 | | 71 | 465 | |
| **Age (years)** | 80.07 8.44 | 74.06 6.46 | | 83.53 8.94 | 75.45 6.96 | |
| **BMI Kg/m²** | 26.02 3.44 | 27.18 3.24 | 0.01 | 25.48 4.35 | 27.90 4.50 | 0.02 |
| **IGF-1 (ng/mL)** | 100.26 54.19 | 129.67 55.88 | <0.001 | 89.07 48.02 | 109.60 51.73 | 0.001 |
| **Serum creatinine (mg/dL)** | 1.17 0.42 | 1.0 0.17 | <0.001 | 0.95 0.49 | 0.84 0.17 | 0.004 |
| **Energy Intake (Kcal/die)** | 1891.81 456.0 | 2184.04 568.6 | 0.01 | 1622.35 470.4 | 1716.36 468.3 | <0.001 |
| **Erythropoietin (mU/mL)** | 26.61 25.02 | 11.01 5.95 | 0.57 | 15.53 12.32 | 10.52 5.03 | <0.001 |
| **Total testosterone (ng/dL)** | 3.64 1.87 | 4.33 1.22 | 0.01 | 0.63 0.31 | 0.59 0.34 | 0.49 |
| **Vitamin B12 (pmol/L)** | 347.5 315.5 | 314.6 236.0 | *0.28* | 373.6 332.9 | 356.0 250.0 | 0.28 |
| **Folic acid (ng/mL)** | 3.10 2.10 | 3.05 1.95 | 0.13 | 3.45 2.87 | 3.38 1.87 | 0.01 |
| **Ferritin (ng/mL)** | 105.98 117.13 | 194.88 201.62 | 0.83 | 104.58 103.97 | 120.02 101.63 | 0.43 |
| **Iron (µg/dL)** | 54.23 28.50 | 87.66 25.73 | 0.04 | 65.95 26.46 | 83.30 23.22 | 0.08 |
| **C-reactive protein (µg/mL)** | 13.0 24.46 | 4.88 8.22 | 0.002 | 8.05 13.95 | 4.48 5.11 | 0.005 |
| **Interleukin-6 (pg/mL)** | 7.71 17.3 | 2.14 2.20 | 0.001 | 2.63 2.94 | 1.91 2.13 | <0.001 |
| **Insulin (mIU/L)** | 10.87 7.75 | 10.77 5.73 | 0.12 | 9.21 5.75 | 11.66 6.17 | 0.004 |

Legend: mean Standard Deviation

^ Differences in parameters among patients with anemia and without anemia defined according to WHO were tested by an age-adjusted linear regression model

**Maggio M et al. 2014; in press**

# Relationship between IGF-1 levels (predictor°) and anaemia (outcome) in older men and women

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | OR | CI | P value | OR | CI | P value |
| Model 1* | 4.75 | 1.41-16.10 | 0.01 | 0.81 | 0.32-2.06 | 0.66 |
| Model 2** | 8.72 | 1.23-61.89 | 0.03 | 0.68 | 0.19-2.43 | 0.55 |

°IGF-1 dicotomized as < 40 ng/mL and ≥ 40 ng/mL

* adjusted for age

** adjusted for multiple confounders: age, serum creatinine, C-reactive protein, Erythropoietin, Body mass Index, Caloric Intake, Vitamin B12, Folic acid, Iron, Ferritin.

**Maggio M et al. 2014; in press**

# Decline of the Red Blood Cell Count in Patients Receiving Androgen Deprivation Therapy for Localized Prostate Cancer: Impact of ADT on Insulin-like Growth Factor-1 and Erythropoiesis

Medical Oncology

**Table 2.** Comparison of GH, IGF-1, erythropoietin, and erythropoietic markers between before and after ADT

| | Before ADT Mean (SD) | After ADT Mean (SD) | *P* |
|---|---|---|---|
| GH (μg/L) | 1.5 (2.3) | 0.9 (0.9) | .691 |
| IGF-1 (nmol/L) | 18 (5) | 21 (6) | <.001 |
| Erythropoietin (mIU/mL) | 28.0 (13.9) | 27.8 (17.3) | .852 |
| IL-6 (pg/mL) | 2.10 (2.45) | 2.06 (3.68) | .208 |
| Hemoglobin (g/L) | 146 (15) | 131 (12) | <.001 |
| RBC count | 451 (44) | 408 (53) | <.001 |
| MCV (fL) | 95.6 (4.5) | 94.7 (4.7) | .002 |
| MCH (pg) | 32.3 (2.2) | 32.3 (2.0) | .676 |
| MCHC (g/dL) | 34.1 (1.1) | 33.8 (1.0) | .004 |
| Iron (μg/dL) | 94.0 (26.7) | 98.9 (30.1) | .234 |

GH = growth hormone; IGF-1 = insulin-like growth factor-1; ADT = androgen deprivation therapy; IL-6 = interleukin-6; RBC = red blood cell; MCV = mean corpuscular volume; MCH = mean cell hemoglobin; MCHC = mean cell hemoglobin concentration.

Hara,N et al. Urology. 2010 Jun;75(6):1441-5.

# Unexplained Anemia in the Elderly

**Sasan Makipour**, **Bindu Kanapuru**, and **William B. Ershler**
Clinical Research Branch, Intramural Research Program, National Institute on Aging, National Institutes of Health, Baltimore, MD

## Features of Unexplained Anemia

| | |
|---|---|
| Hemoglobin | 10.5–12 g/dL |
| Reticulocyte index | Low |
| Mean corpuscular volume (MCV) | 80–95 fL |
| Platelet and white blood cell counts | Normal |
| Peripheral smear | No dysplastic features |
| Serum iron | Mildly low or normal |
| Total iron binding capacity (TIBC) | Normal |
| % Iron saturation | Mildly low or normal |
| Serum levels of vitamin $B_{12}$ and folic acid | Normal |
| Serum level of thyroid-stimulating hormone (TSH) | Normal |
| Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) | Normal |
| Serum erythropoietin level | Not elevated |
| Creatinine clearance | >30 to <90 mL/min |

*Semin Hematol. 2008 October ; 45(4): 250–254.*

# Thyroid Hormones and hemoglobin

## Hypothyroidism is associated with normocytic anaemia

- ✓ **Thyroid hormones have regulatory functions in erythropoiesis**

*Perrin MC, et al Hematol Cell Ther 1997;39:19–26.*

*Sullivan PS et al. Proc Soc Exp Biol Med 1992;201:271–7.*

*Bauer A, et al . EMBO J 1998;17:4291–303.*

*Balzan S, et al Biomed Pharmacother 2007;61:463–7.*

*Dainiak N, et al Nature 1978;272:260–2.*

*Popovic WJ, et al. J Clin Invest 1977;60:907–13.*

*Kendrick TS, et al. Blood 2008;111:3245–8.*

- ✓ **In a population-based cohort of 1011 euthyroid older subjects, significant associations between free T4 and haemoglobin concentration,**
**erythrocyte count and haematocrit were found**

*Bremner AP, et al Clin Endocrinol (Oxf) 2012;76:304–11.*

Contents lists available at SciVerse ScienceDirect

European Journal of Internal Medicine

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

Original article

# Thyroid hormones and erythrocyte indices in a cohort of euthyroid older subjects ☆

Roger K. Schindhelm [a,b,*], Edwin ten Boekel [a,b], Nathalie E. Heima [c], Natasja M. van Schoor [d], Suat Simsek [c,e]

**Table 2**

Multivariable regression analyses of the association between free T4 (per 5 pmol/L) and erythrocyte parameters.

| Parameter | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | b (95% CI) | *P*-value | b (95% CI) | *P*-value | b (95% CI) | *P*-value |
| Haemoglobin, mmol/L | 0.096 (0.04; 0.19) | 0.04 | 0.12 (0.03; 0.20) | 0.009 | 0.12 (0.034; 0.21) | 0.007 |
| Haemoglobin, g/dL | 0.15 (0.06; 0.31) | 0.04 | 0.19 (0.048; 0.32) | 0.009 | 0.19 (0.055; 0.34) | 0.007 |
| Erythrocytes, $10^{12}$/L | 0.065 (0.017; 0.11) | 0.008 | 0.065 (0.017; 0.11) | 0.008 | 0.068 (0.02; 0.12) | 0.005 |
| Haematocrit, L/L | 0.006 (0.001; 0.01) | 0.008 | 0.006 (0.002; 0.01) | 0.002 | 0.006 (0.003; 0.01) | 0.001 |
| MCV, fL | −0.12 (−0.66; 0.42) | 0.66 | 0.048 (−0.46; 0.55) | 0.85 | 0.012 (−0.40; 0.52) | 0.96 |

Model 1: adjusted for age and sex; Model 2: Model 1 with additional adjustments for iron, vitamin B12 and folic acid; Model 3: Model 2 with additional adjustments for eGFR.

European Journal of Internal Medicine 24 (2013) 241–244

# Take Home messages

- ✓ **La anemie da causa non spiegata nel soggetto anziano possono riconoscere una causa endocrina.**
- ✓ **Il deficit di Testosterone specie nel soggetto di sesso maschile andrebbe indagato dopo esclusione di altre cause**
- ✓ **Studi ulteriori sono necessari per definire il ruolo dell' IGF-1 e degli ormoni tiroidei**