Hormone replacement therapy: Growth hormone

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Disclosure Statement of Financial Interest

I, Manfred Gogol DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Introduction I

- Age-related decline in activity of the hypothalamic growth hormone (GH)
- Which stimulates the insulin-like growth factor 1 (IGF-1)
- In various animal testing (yeasts, worms, flies, mice) GH – IGF-1 levels are associated with a longer lifespan
- Are these findings relevant for human life (throughout the evolution) ?

Introduction II

GH substitution **IN** GH-deficients patients improves

- Body composition
- Bone density (?)
- (Total) Cholesterol levels

may decrease

- Death

Functionally significant insulin-like growth factor I receptor mutations in centenarians

Yousin Suh*, Gil Atzmon†, Mi-Ook Cho*, David Hwang‡, Bingrong Liu‡, Daniel J. Leahy§, Nir Barzilai†¶, and Pinchas Cohen‡

PNAS 2008;105:438-42

Ashkenazi Jewish centenarians
Female n = 105, Male n = 92
Female: 35 % higher IGF-1 levels
→ maybe induced by mutations of IGF1R genes

Table 2. Height and IGFI levels among centenarian carriers of either the Ala-37–Thr or the Arg-407–His mutation in the *IGF1R* gene

Variable	Carriers, $n = 6$	Noncarriers, $n = 163$	P value
Height, cm	162 ± 2.8	165 ± 0.8	0.41
IGFI, ng/ml	165 ± 21	121 ± 6	0.04

Systematic Review: The Safety and Efficacy of Growth Hormone in the Healthy Elderly

Hau Liu, MD, MBA, MPH; Dena M. Bravata, MD, MS; Ingram Olkin, PhD; Smita Nayak, MD; Brian Roberts, MD; Alan M. Garber, MD, PhD; and Andrew R. Hoffman, MD

Ann Intern Med 2007;146:104-15

18 RCTs, 220 patients treated

Age	69 ± 6 a		
BMI	28 ± 2 kg/m^2		
Daily dosis of GH	14 µg ± 7 kg / body weight		
Treatment duration	27 ± 16 weeks		
Fat mass	-2,1 kg (95%CI	-2,8 – -1,35)	
Lean body mass	+2,1 kg (- " -	1,3 – 2,9)	p = 0,001
Weight	+0,1 kg (- " -	-0,7 – 0,8)	p = 0,87
Total cholesterol	-11,21 md/dl		p = 0,006
Other lipid levels			ns
Bone density			ns

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Side effects significant greater in the treatment group:

Soft tissue edema
Arthralgia
Carpal tunnel syndrome
Gynecomastia

New onset Diabetes mellitus
Impaired fasting glucose

Summary:
Small changes in body composition
Increased rates of adverse events

Ann Intern Med 2007;146: Editorial 202-4, Pro and Con 190-6 and 197-201

GH and Anti-Aging I

„Going to the gym is beneficial and certainly cheaper than growth hormone“

Vance ML. Can growth hormone prevent aging? N Engl J Med 2003;348:779-80

„However, clinically significant functional effects, prolongation of youth, and life extension have not been demonstrated“

Harman SM, Blackmann MR. Use of growth hormone for prevention or treatment of effects of aging. J Gerontol 2004;59A:652-8

„Transgenic mice that produce supraphysiological levels of GH have markedly reduced life spanns and … premature onset of … cognitive changes. Rats with adult-onset GHD … 30% decrease in tumor incidence and a 16% decrease in disease burden“

Perls TH et al. Provision or distribution of growth hormone for „Antiaging“. Clinical and legal issues. JAMA 2005;294:2086-90

GH and Anti-Aging II

American Academy for Anti-Aging Medicine

www.worldhealth.net

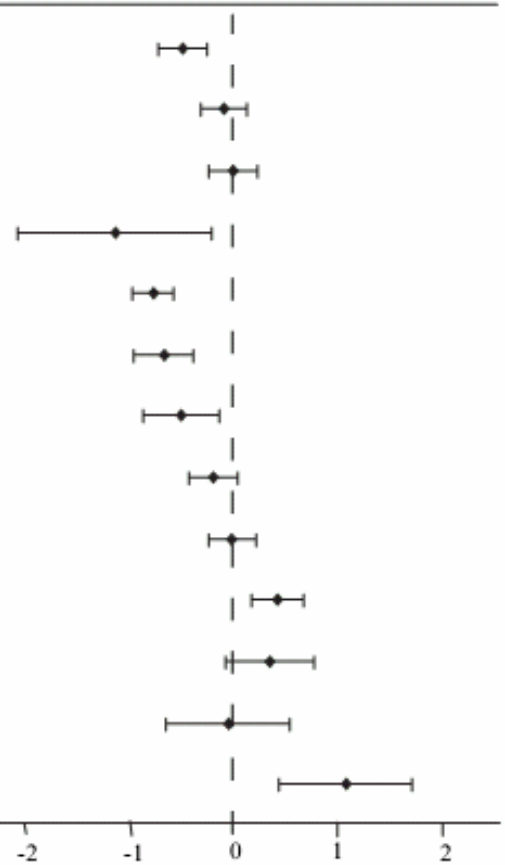
promote (?) GH as an anti-aging drug by selective reporting of scientific data

Impact of Somatostatin Analogs on the Heart in Acromegaly: A Metaanalysis

J Clin Endocrinol Metab 2007;92:1743-7

Patrick Maison, Anne-Isabelle Tropeano, Isabelle Macquin-Mavier, Andrea Giustina, and Philippe Chanson

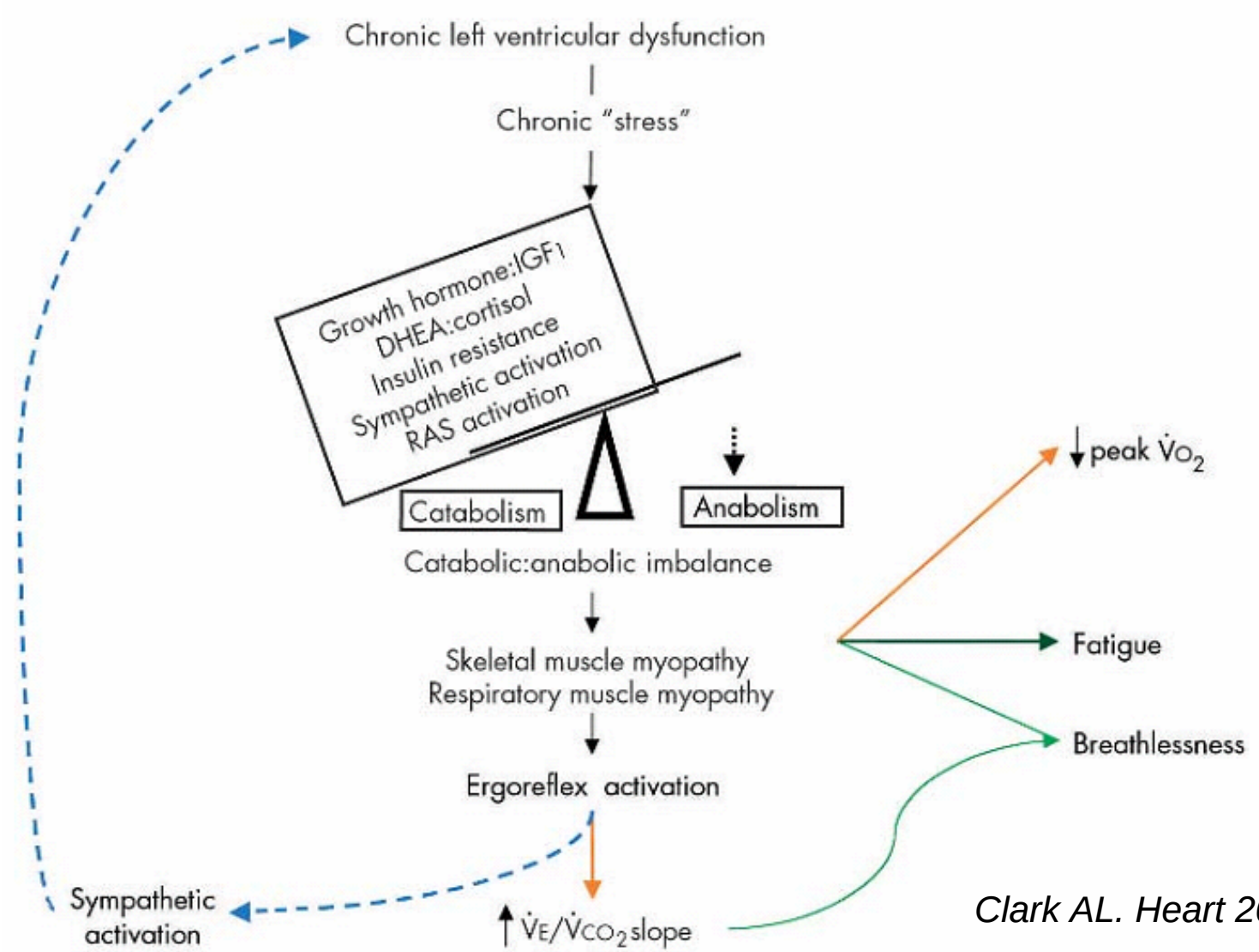
Factors	Number of trials	Number of Patients	Q test	Weighted mean (SD) change (before - after)
HR	16	199	<0.001	-5.8 (2.1) beats/min
SBP	16	199	<0.01	-2.5 (2.9) mmHg
DBP	15	180	<0.05	-1.7 (1.9) mmHg
LVM	7	51	<0.01	-50.3 (13.3) g
LVMi	14	143	ns	-22.3 (6.7) g/m^2
IVS	10	110	<0.05	-0.3 (0.2) mm
LVPW	9	91	<0.01	-0.8 (0.4) mm
LVEDD	8	71	ns	-1.5 (2.2) mm
LVESD	8	75	ns	0.4 (2.0) mm
E/A	5	61	ns	0.2 (0.1)
EF	15	188	<0.001	3.3 (1.7) %
FS	6	56	<0.01	-0.7 (2.0) %
Ex Dur	7	75	<0.01	1.6 (0.4) min



SBP, Systolic blood pressure; DBP, diastolic blood pressure; Ex Dur, exercise duration; ns, nonsignificant; CI, confidence interval.

Studies : 18
Design: open
Patients: 290

GH in Cardiology I



Clark AL. Heart 2006;92:12-6

GH in Cardiology II

…reduces circulating proinflammatory cytokines (TNF-α, sTNF-RI, sTNF-RII,IL-6, sIL-6R) and

…soluble Fas / soluble Fas ligand system (sFas, sFasL)

…improves Vo_2max

Adamopoulos S et al. Am Heart J 2002;144:359-64
Adamopoulos S et al. Eur Heart J 2003;24:2186-96

…Ghrelin reduces plasma norepinephrine and increases LV ejection fraction / LV mass and decreases LV end-systolic volume

Nagaya N et al. Circulation 2004;110:3674-9

…reduces C-reactive protein and IL-6

Sesmilo G et al. Ann Intern Med 2000;133:111-22

…improves endothelial dysfunction

Napoli R et al. J Am Coll Cardiol 2002;39:90-5
Thum T et al. Circ Res 2007;100:434-43

…increases exercise duration

Spallarossa P et al. Am J Cardiol 1999;84:430-3

Cardiac Effects of Growth Hormone in Adults With Growth Hormone Deficiency

A Meta-Analysis

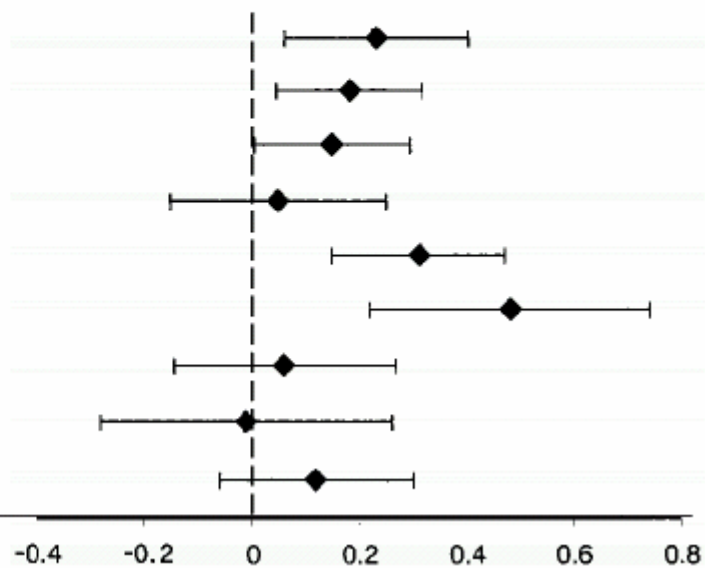
Patrick Maison, MD; Philippe Chanson, MD

Circulation 2003; 108:2649-52

16 trials 1991 – 2002 (9 blinded, 7 open)
n = 468, range 7 - 115

TABLE 2. Global Effect Sizes by Outcomes

Factors	No. of Trials	No. of Patients GH	No. of Patients Control	*Q* Test (*P*)	Weighted Mean Differences (SD)
LVM	11	210	211	NS	10.8 g (9.3)
IVS	15	292	294	<0.001	0.28 mm (0.38)
LVPW	14	255	256	<0.05	0.98 mm (0.22)
LVESD	10	153	151	NS	0.32 mm (1.06)
LVEDD	13	218	218	NS	1.34 mm (1.13)
Stroke volume	5	81	82	NS	10.3 mL (8.7)
E/A ratio	7	134	137	NS	0.05 (0.13)
IVRT	5	95	97	NS	−1.60 ms (7.36)
FS	9	148	158	NS	1.06 % (1.06)



GH in Cardiology IV

…improves exercise duration BUT NO cardiac structural or functional differences

Climent VE et al. Am J Cardiol 2006;97:1097-102

…no changes beside strain and strain rate of the septum

Cho G-Y et al. Am J Cardiol 2007;1000:1035-9

…no short- and long-term effects on the heart besides improved exercise capacity

Pérez-Berbel P et al. Int J Cardiology 2008;124:393-4

…improvement in decompensated congestive heart failure

Bocchi E et al. Int J Cardiology 2006;110:313-7

…no short-term effects

Acevedo M et al. Int J Cardiology 2003;87:185-91

GH in Cardiology V

…CHF in DCM patients is associated with a significant decrease in GH, IGF-1 and testosterone

Kontoleon PE et al. Int J Cardiology 2003;87:179-83

…low IGF-1 is an independent predictor for poor prognosis in CHF patients – deficiency of > 1 anabolic hormone predict higher mortality

Jankowska EA et al. Circulation 2006;114:1829-37

…low IGF-1 levels (combined with low testosterone and DHEA levels) predict high mortality in elderly men

Maggi M et al. Arch Intern Med 2007;167:2249-54

Conclusion

- Short-term effects ?
- Long-term effects ???

- Animal models and clinical studies show numerous positive effects → CAVE: surrogat parameters

- **Well-designed studies are needed**
- - CHF of what origin ?
- - which patients (sex, age, co-morbidities, level of CHF)
- - dosing regime ? duration of treatment ? onset of therapy ?
- - identify refractory patients (factors) for therapy

- - external validity ?

- **harms of GH therapy**
- - including oncogenic potential

GH and athletic performance

27 studies, 303 participants

Mean age 27 ± 3 y
Mean BMI 24 ± 2 kg/m^2
Mean GH 36 µg/kg per day
Mean treatment duration 20 ±18 days
Lean BMI +2,1 kg (95% CI 1,3 – 2,9)

No change
Strength
Exercise capacity

Lactat levels increases

ADR: soft tissue edema, fatique

Hau L et al. Systematic review: the effects of growth hormone on athletic Perfomance. Ann Intern Med 2008;148 – online 18.03.2008, print 20.05.2008