Proposed diagnostic algorithm of adult GH Deficiency

Is it time to amend the GHRS Consensus Guidelines for the diagnosis of adult GHD ?

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Consensus Guidelines for the Diagnosis and Treatment of Adults with GHD: Summary Statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency

Adult GHD should be suspected within an appropriate clinical context …

i.e.

Adult patients with evidence of hypothalamic or pituitary disease or cranial irradiation (likelyhood of deficiency increases with number of pituitary hormone deficits)

Adults patients with childhood-onset GHD (all patients should be retested as adults before continuing treatment with GHD)

JCEM 1998;83: 379-81.

Consensus Guidelines for the Diagnosis and Treatment of Adults with GHD: Summary Statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency

- **Within an appropriate clinical context, severe GH deficiency should be defined biochemically by provocative testing of GH secretion. (measurement of IGF-I, IGFBP-3 as well as of 24h mGHc do not distinguish GHD from normal subjects)**

- **The Insulin Tolerance Test is the diagnostic test of choice (ITT distinguishes GHD from the reduced GH secretion which accompanies ageing and obesity) and severe GH deficiency is defined by a peak GH response to hypoglycaemia of < 3 µg/L. (notice that the 3rd centile limit of GH response to ITT in normals is 5 µg/L).**

- **Alternative provocative tests of GH secretion must be used with appropriate cut-offs. (among classical alternatives: clonidine test is not reliable; arginine or glucagon alone can be used but they are stimuli less potent than ITT and thus have less established diagnostic value).**

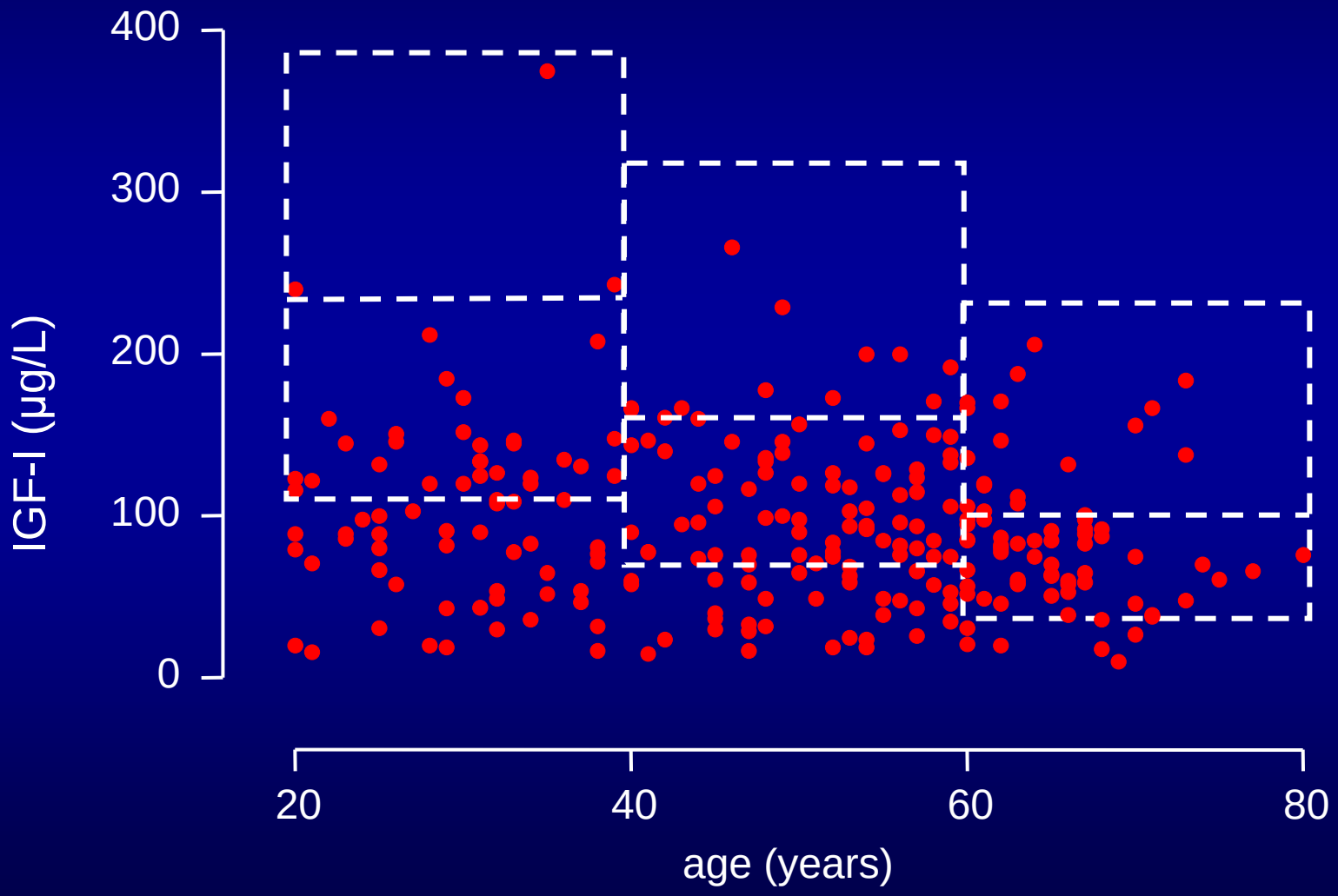
- **At present, the combined administration of GHRH and arginine is the most promising alternative to ITT.**

Is it time to amend the GHRS Consensus Guidelines for the diagnosis of adult GHD ?

- diagnostic value of IGF-I measurement
* provocative tests as alternative to ITT
*diagnosis of GHD in obesity
*diagnosis of GHD in brain injured patients
i.e. to widen the appropriate clinical context

Individual total IGF-I levels in adults with severe GHD

(areas represents age-related normal values)



Consensus Guidelines for the Diagnosis and Treatment of Adults with GHD: Summary Statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency

Biochemical markers of GH action.

Several biochemical markers of GH action have been studied to determine their diagnostic potential in adult GH deficiency.

Serum IGF-I concentrations are only useful when age-adjusted normal ranges are available.

In adults, a normal serum IGF-I does not exclude the diagnosis of GH deficiency.

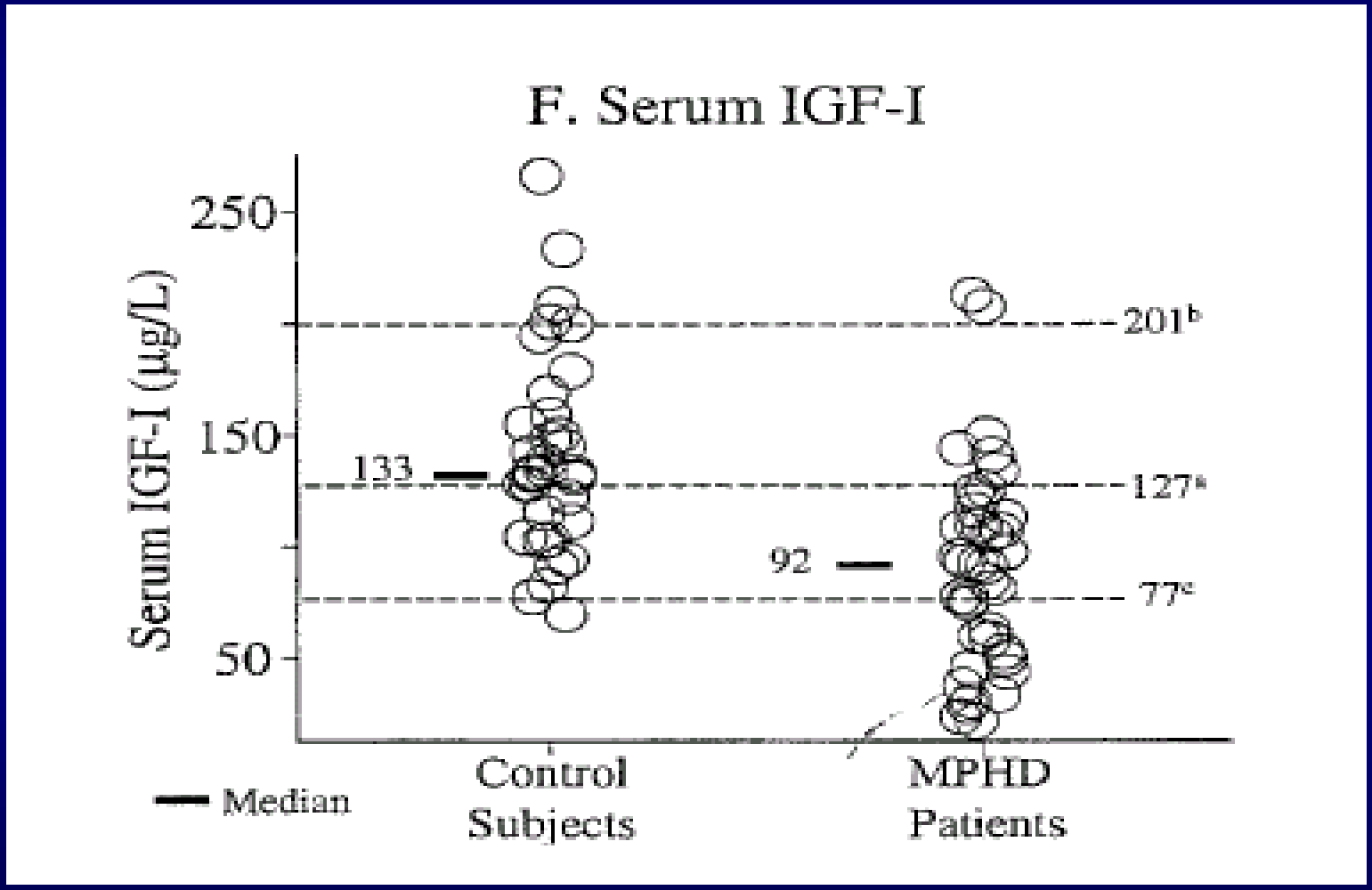
A serum IGF-I below the normal range is suggestive of GH deficiency in the absence of other conditions known to lower serum IGF-I levels; for example, malnutrition, hepatic disease, poorly controlled diabetes mellitus, and hypothyroidism.

In the presence of multiple (two or more) pituitary hormone deficiencies, a low serum IGF-I level indicates a high probability of GH deficiency. However, it is recommended that the diagnosis of adult GH deficiency be confirmed by a provocative test of GH release.

Measurement of serum IGF-binding protein-3 or acid labile sub-unit has to date not proven to offer any advantage over the measurement of serum IGF-I.

JCEM 1998;83: 379-81.

Sensitivity and specificity of six tests for the diagnosis of adult GHD



Serum IGF-I levels measured at the screening visit in the two groups

Biller BMK, et al. *JCEM* 2002;87:2067-79.

Which Patients Do Not Require a GH Stimulation Test for the Diagnosis of Adult GH Deficiency?

MARK L. HARTMAN, BRENDA J. CROWE, BEVERLY M. K. BILLER, KEN K. Y. HO, DAVID R. CLEMMONS, AND JOHN J. CHIPMAN, ON BEHALF OF THE HYPOCCS ADVISORY BOARD AND THE U.S. HYPOCCS STUDY GROUP

Lilly Research Laboratories (M.L.H., B.J.C., J.J.C.), Eli Lilly & Co., Indianapolis, Indiana 46285; Massachusetts General Hospital (B.M.K.B.), Boston, Massachusetts 02114; Garvan Institute of Medical Research, St. Vincent's Hospital of Sydney (K.K.Y.H.), Sydney, NSW 2064, Australia; and University of North Carolina (D.R.C.), Chapel Hill, North Carolina 27599

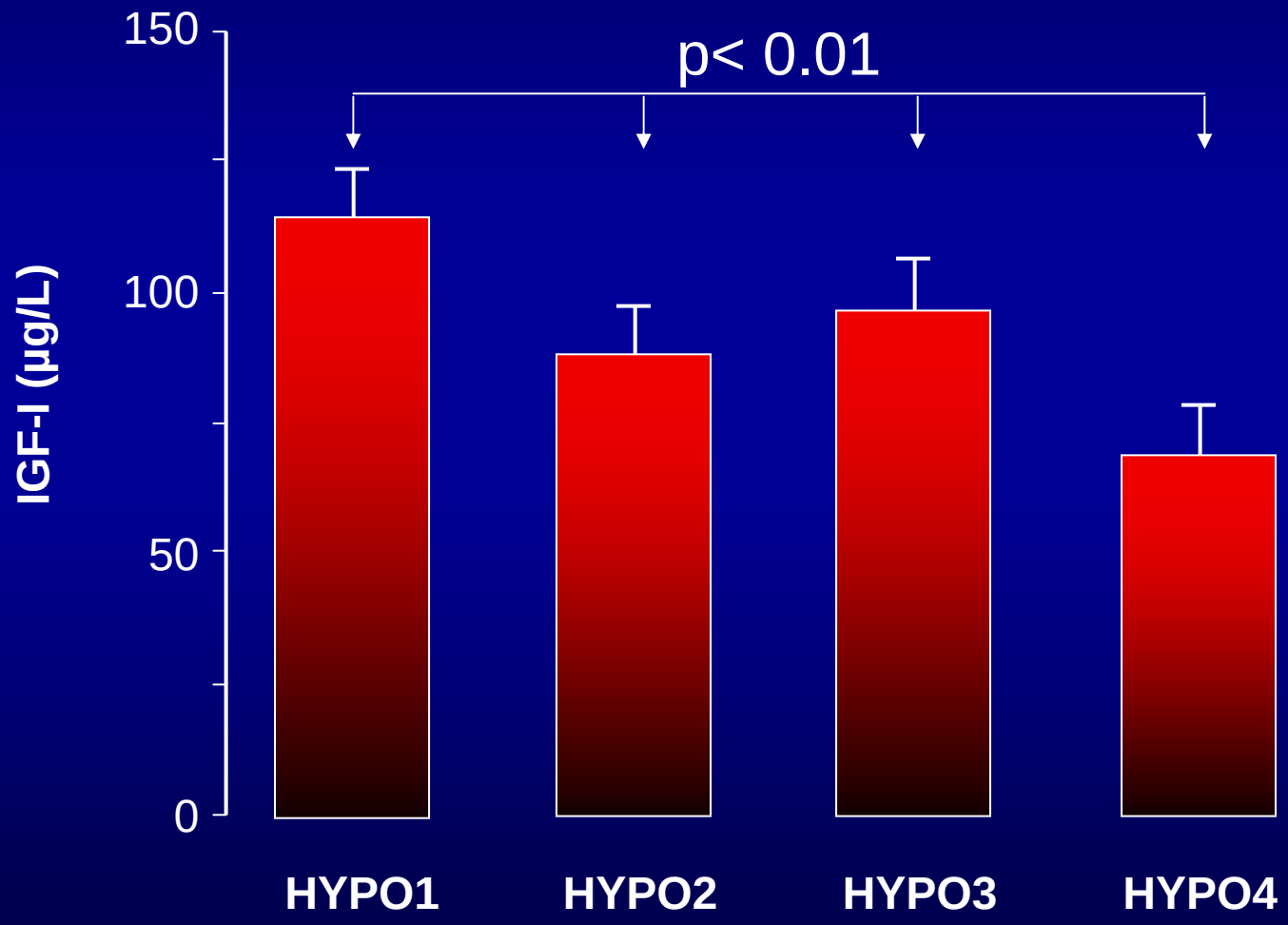
- **Patients with an appropriate clinical history and the presence of three or four additional PHDs or serum IGF-I less 84 µg/L (measured in the Exoterix assay) do not require GH stimulation testing for the diagnosis of adult GHD.**

- **In clinical practice, other causes of low serum IGF-I should be excluded before applying these diagnostic criteria.**

1.4), 0.06 (0.025, 0.295), and 0.025 (0.025, 0.07), respectively. The 477–485, 2002)

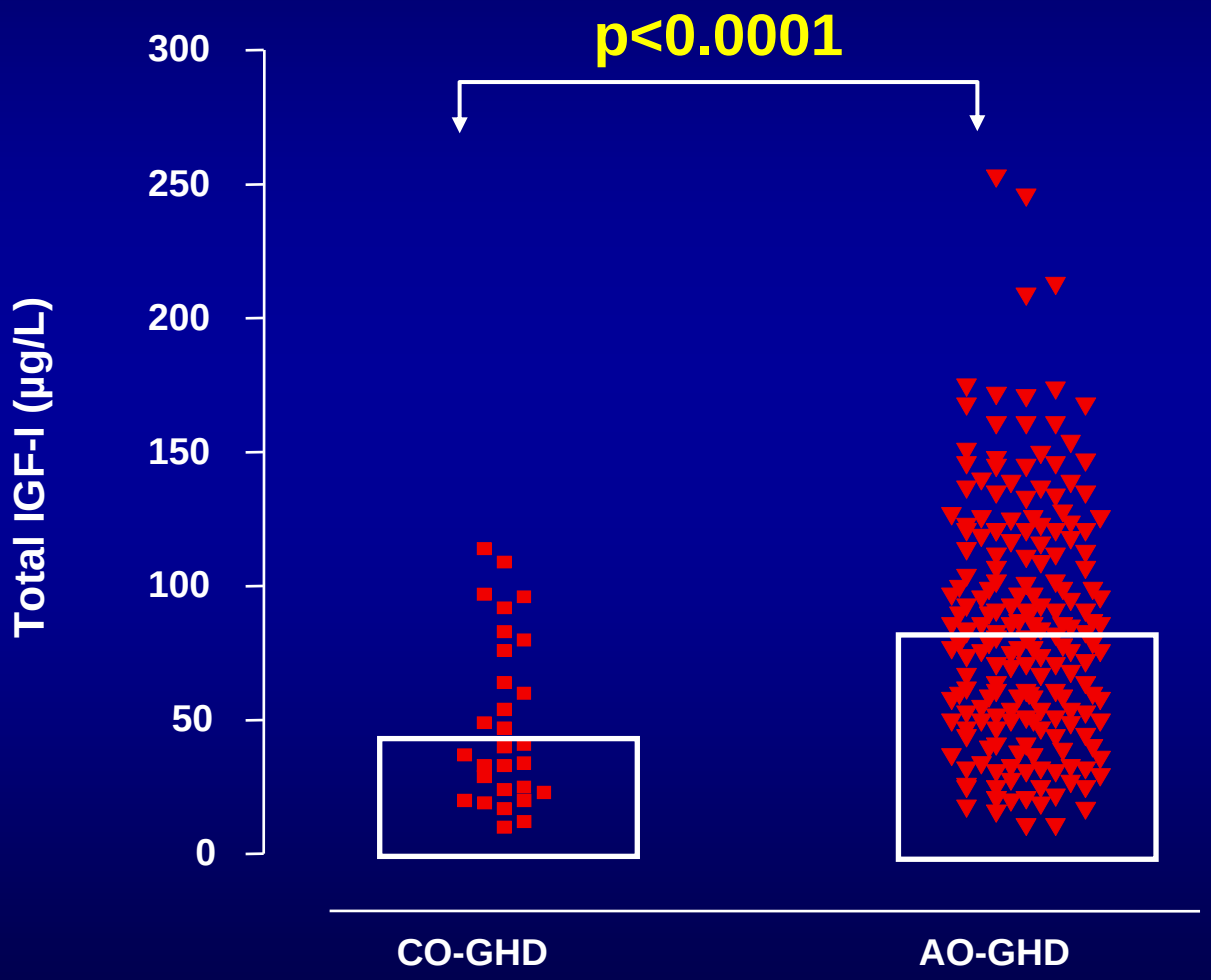
Hartman ML, et al. *JCEM* 2002;87:477-85.

MeanIGF-I levels in adult patients with isolated GHD (HYPO1) or GHD plus one, two or three other pituitary hormone deficiencies (HYPO2, HYPO3, HYPO4)

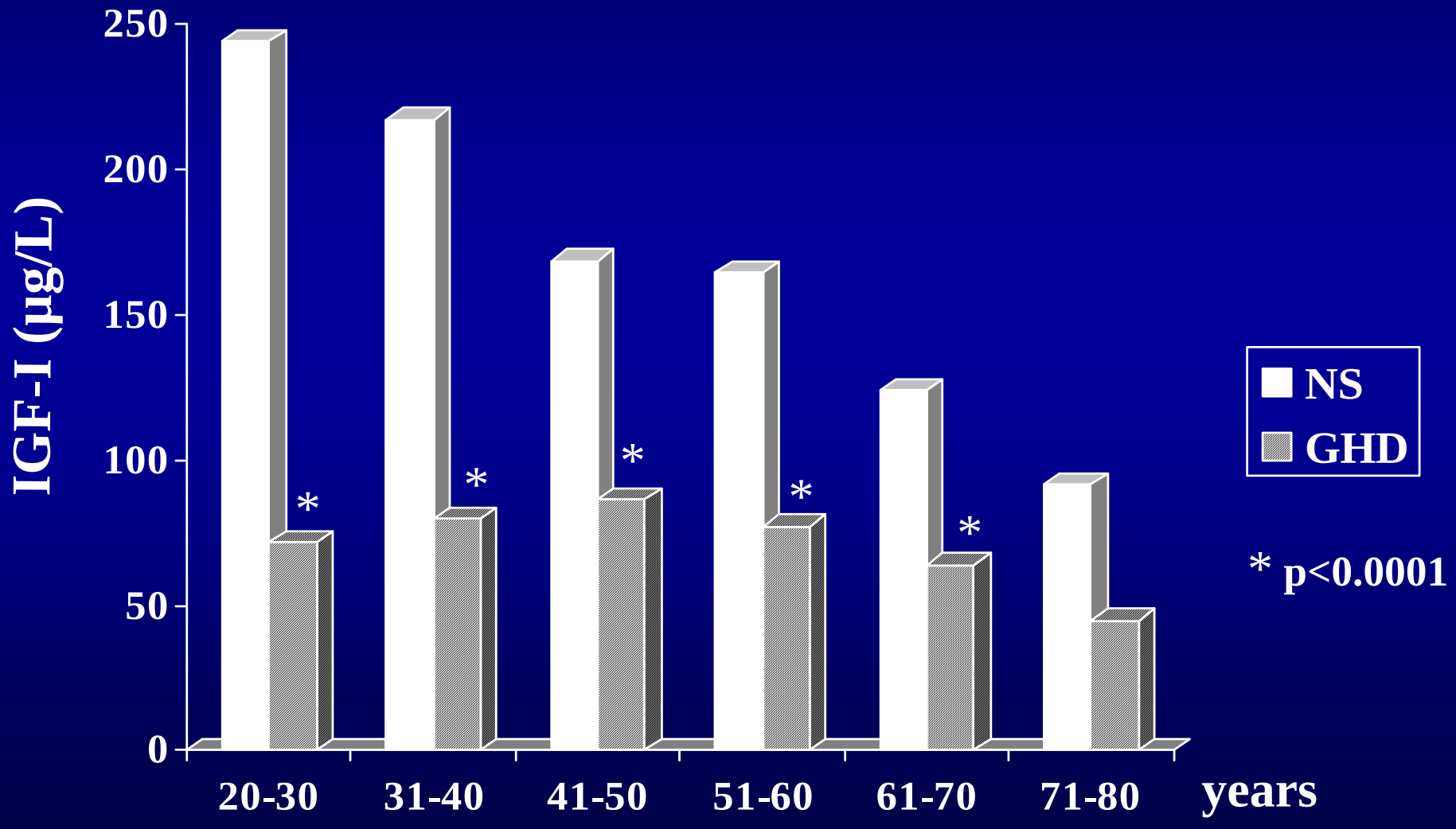


Aimaretti G, et al. *JEI* 2005;28:247-52.

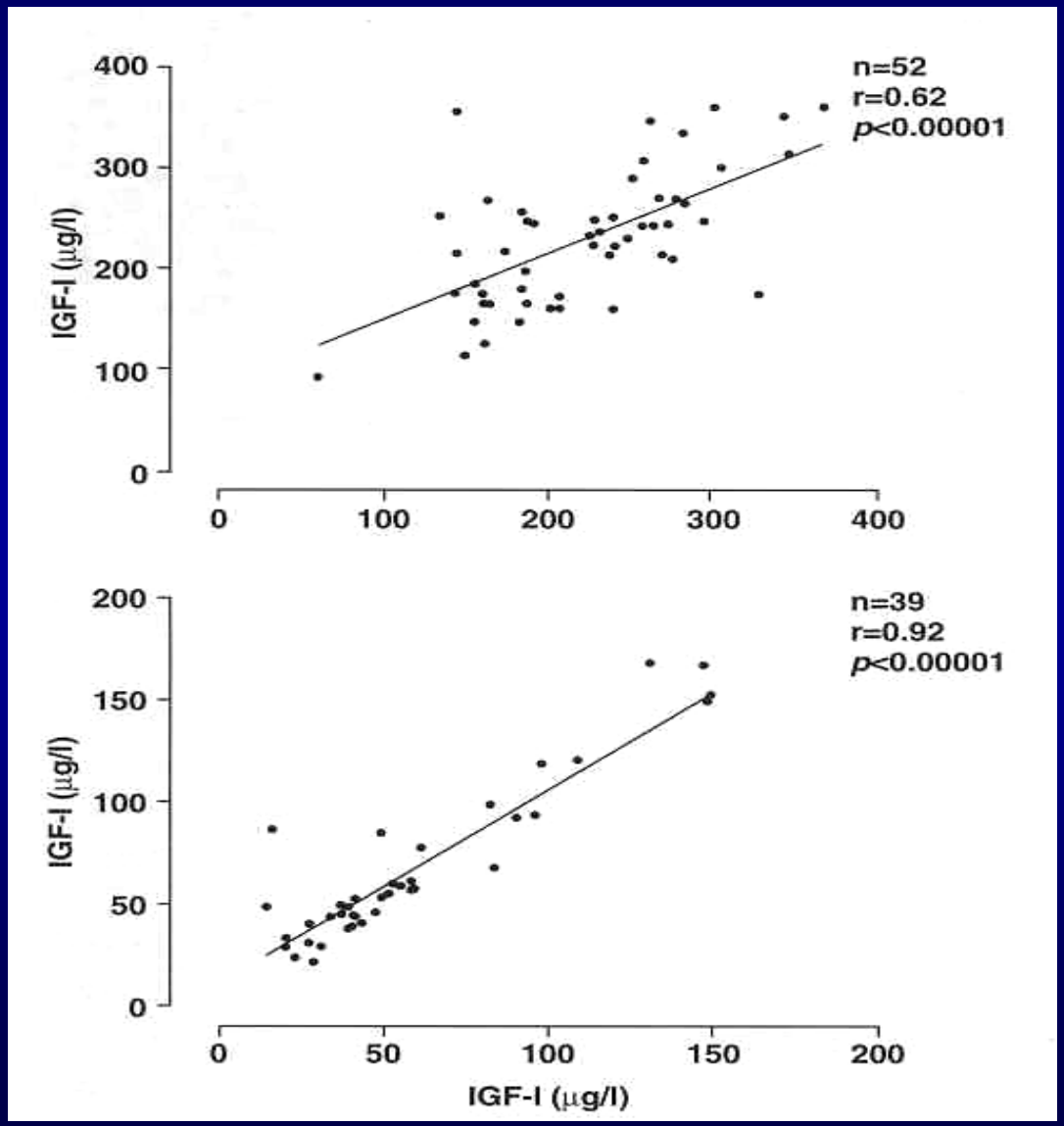
Mean and individual total IGF-I levels in patients with CO-GHD or AO-GHD



Mean IGF-I levels in normal subjects (NS) and Panhypopituitaric adults with severe GH deficiency (GHD) in each decade of life



Within-subject reproducibility of total IGF-I levels in normal and GHD adults



Normal adults

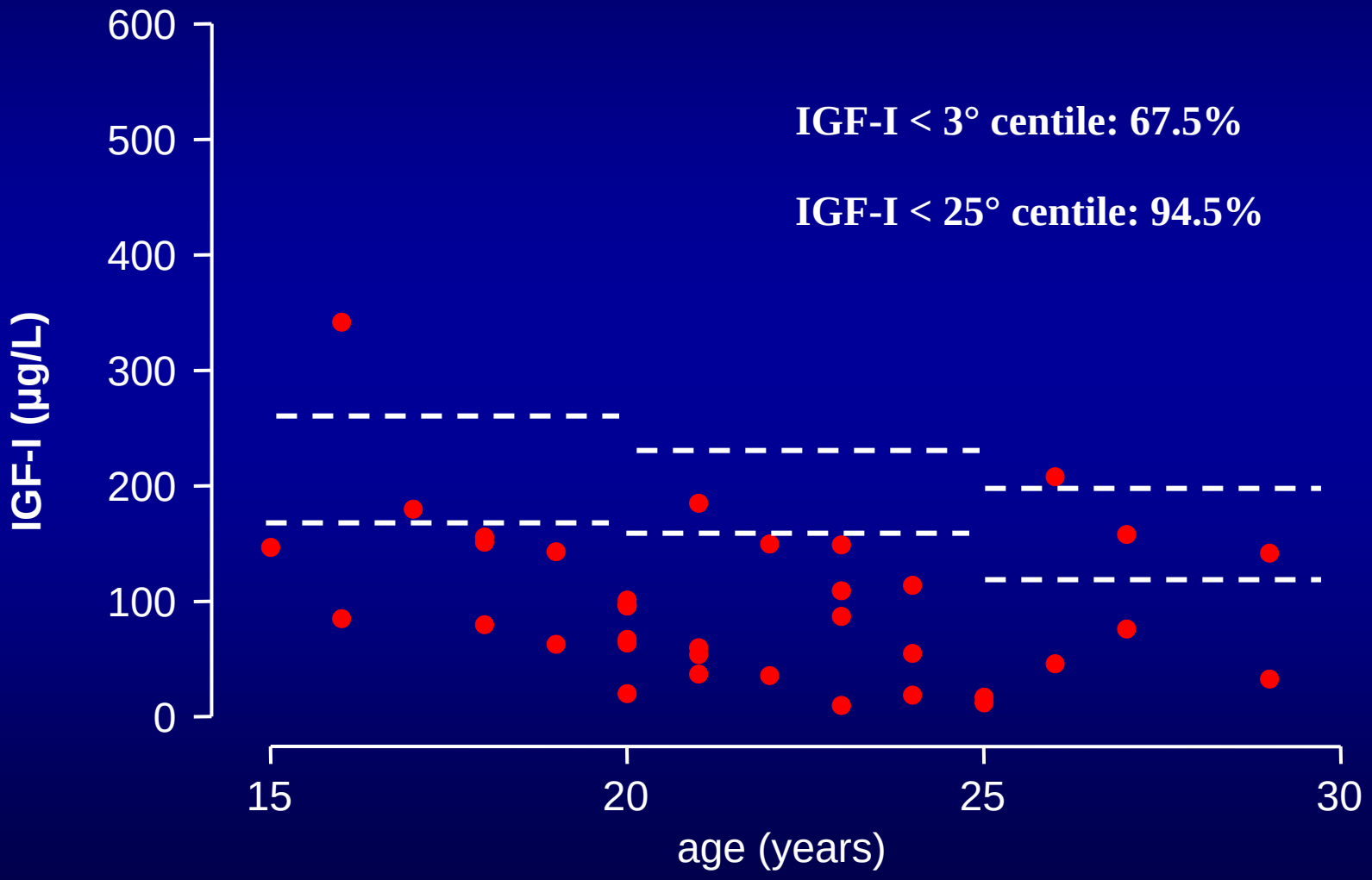
GHD adults

Aimaretti et al,

J. Endocrinol. Invest. 21: 506, 1998

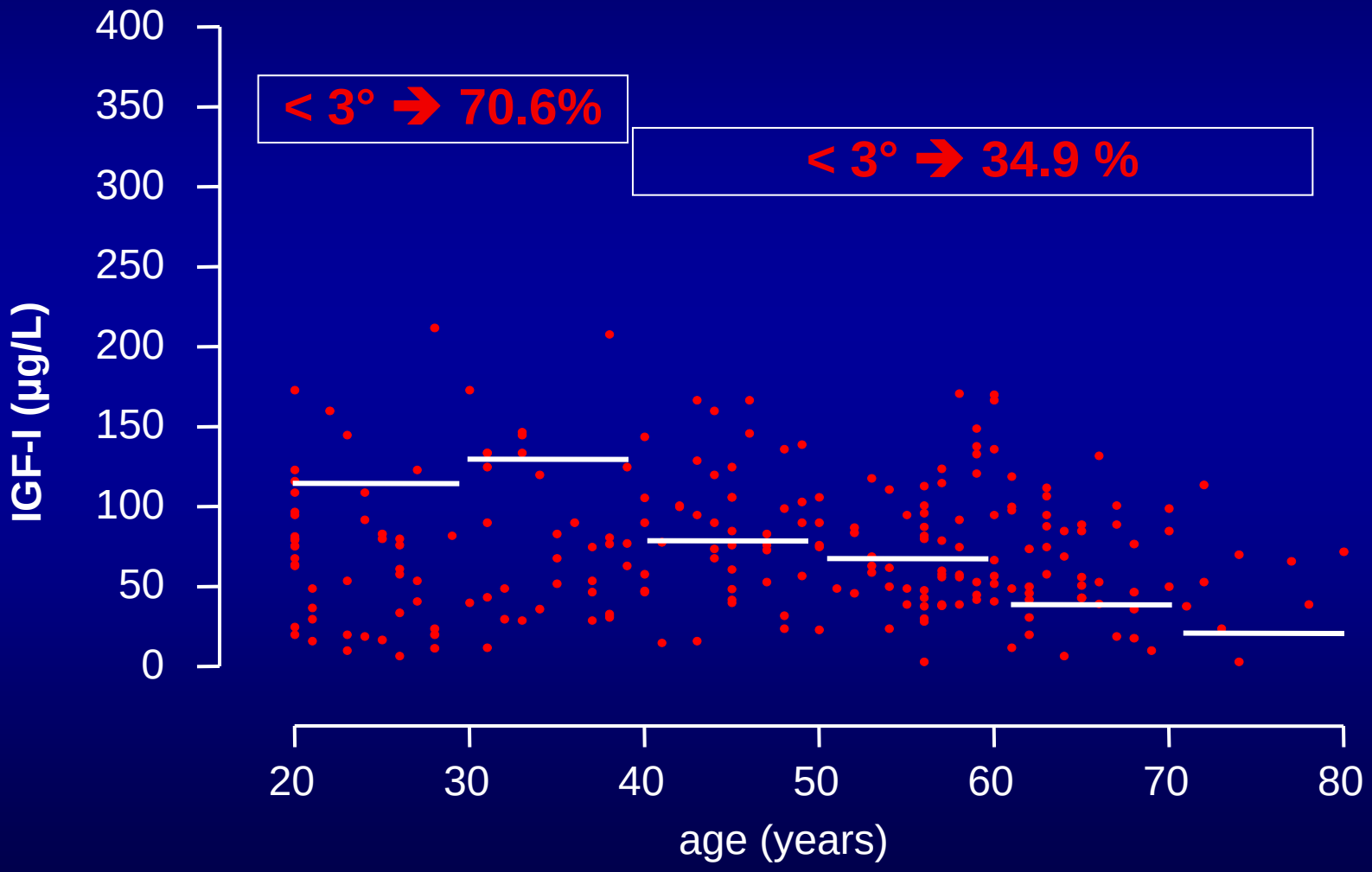
Retesting transition adolescents with severe GHD by total IGF-I levels

(severe GHD confirmed by peak GH response to GHRH+ARG test < 9 µg/L)
(lines represent 3rd and 25th age-related centile limits)



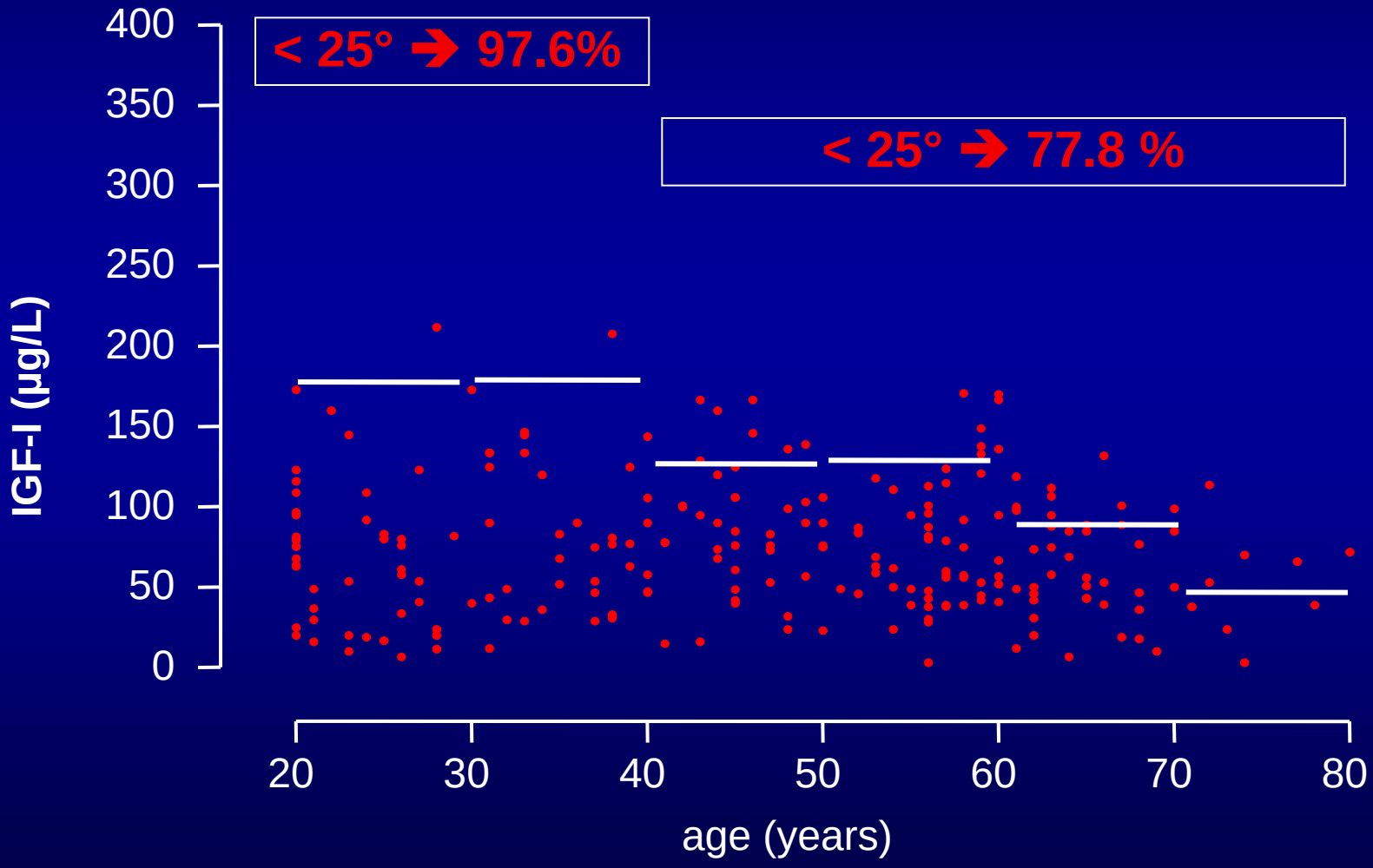
Individual total IGF-I levels (●) in 237 adult panhypopituitary patients

(lines represent the **3rd centiles** of age-related normal limits)



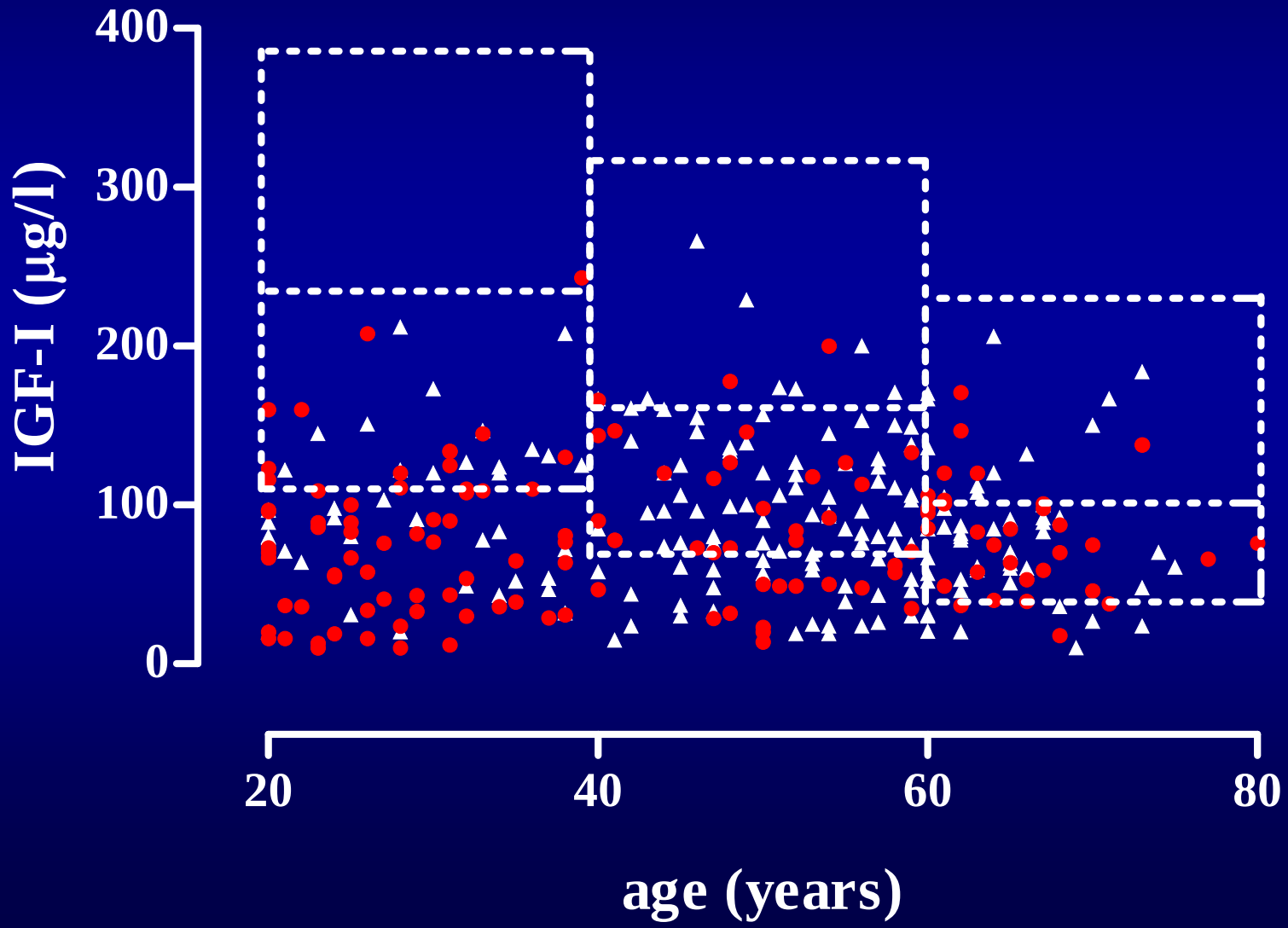
Individual IGF-I levels (●) in 237 adult panhypopituitary patients

(lines represent the **25th centiles** of age-related normal limits)

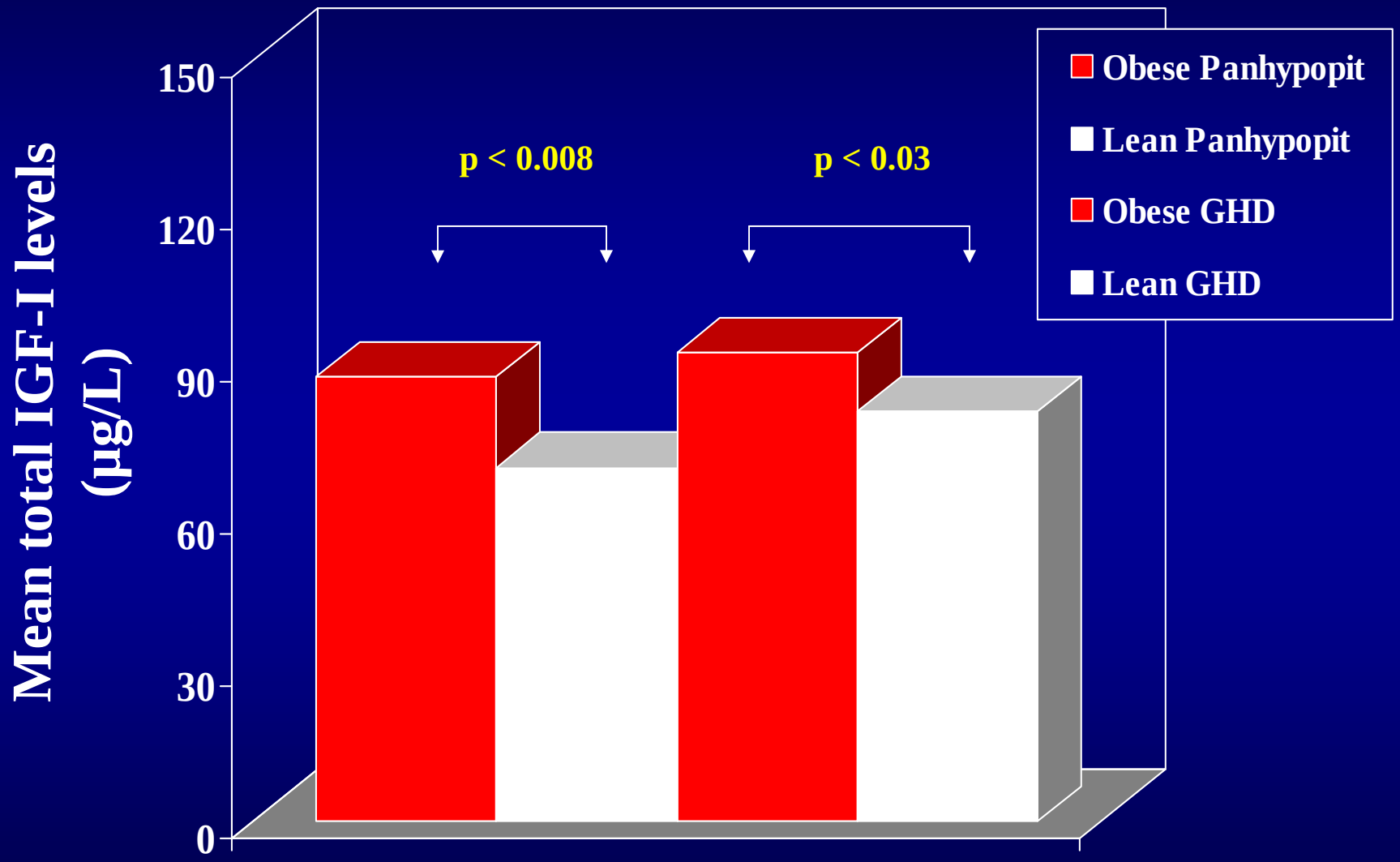


Individual, total IGF-I levels in hypopituitaric adults (n=316) with severe GHD as function of BMI

(red circles = GHD with normal BMI; white triangles = GHD with BMI > 25)



Mean total IGF-I levels in patients with panhypopituitarism or isolated GHD as function of BMI



Body weight and hyperinsulinism are associated to enhanced sensitivity to GH and probably this applies also to patients with severe GHD

Very low IGF-I levels (below 2 SD ?)

in patients highly suspected for adult GHD

(without malnutrition, liver disease or hypothyroidism)

could be considered definite evidence of severe GHD;

thus, provocative tests could be omitted in these patients.

This assumption particularly applies to patients with:

- **childhood-onset, isolated severe GHD or multiple hypopituitarism**
- **adult-onset multiple and total hypopituitarism**

However …

Normal IGF-I levels do not definitely rule out severe GHD;

thus,
patients suspected for adult GHD showing normal IGF-I levels must be investigated by provocative tests.

CLINICAL PRACTICE GUIDELINE

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

Mark E. Molitch, David R. Clemmons, Saul Malozowski, George R. Merriam, Stephen M. Shalet, and Mary Lee Vance, for The Endocrine Society's Clinical Guidelines Subcommittee

Suggestions on IGF-I

• A normal IGF-I level does not exclude the diagnosis of GHD but makes provocative testing mandatory to make the diagnosis of GHD (level of evidence, high).

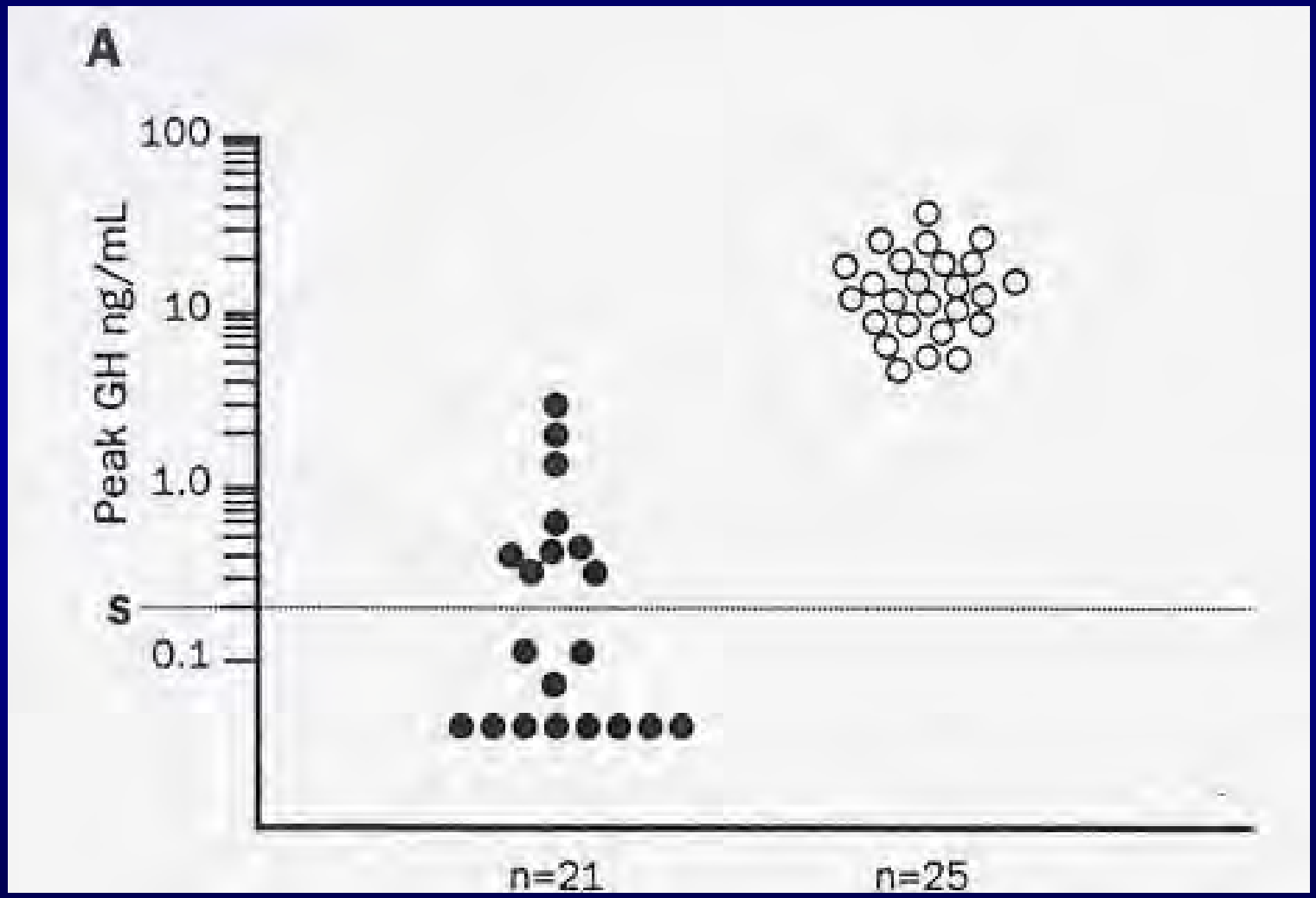
• A low IGF-I level, in the absence of catabolic conditions and liver disease, indicates severe GHD and may be useful in identifying patients who may benefit from treatment (level of evidence, moderate).

• The presence of deficiencies in three or more pituitary axes strongly suggests the presence of GHD, and in this context provocative testing is optional (level of evidence, moderate).

JCE&M 91: 1621, 2006

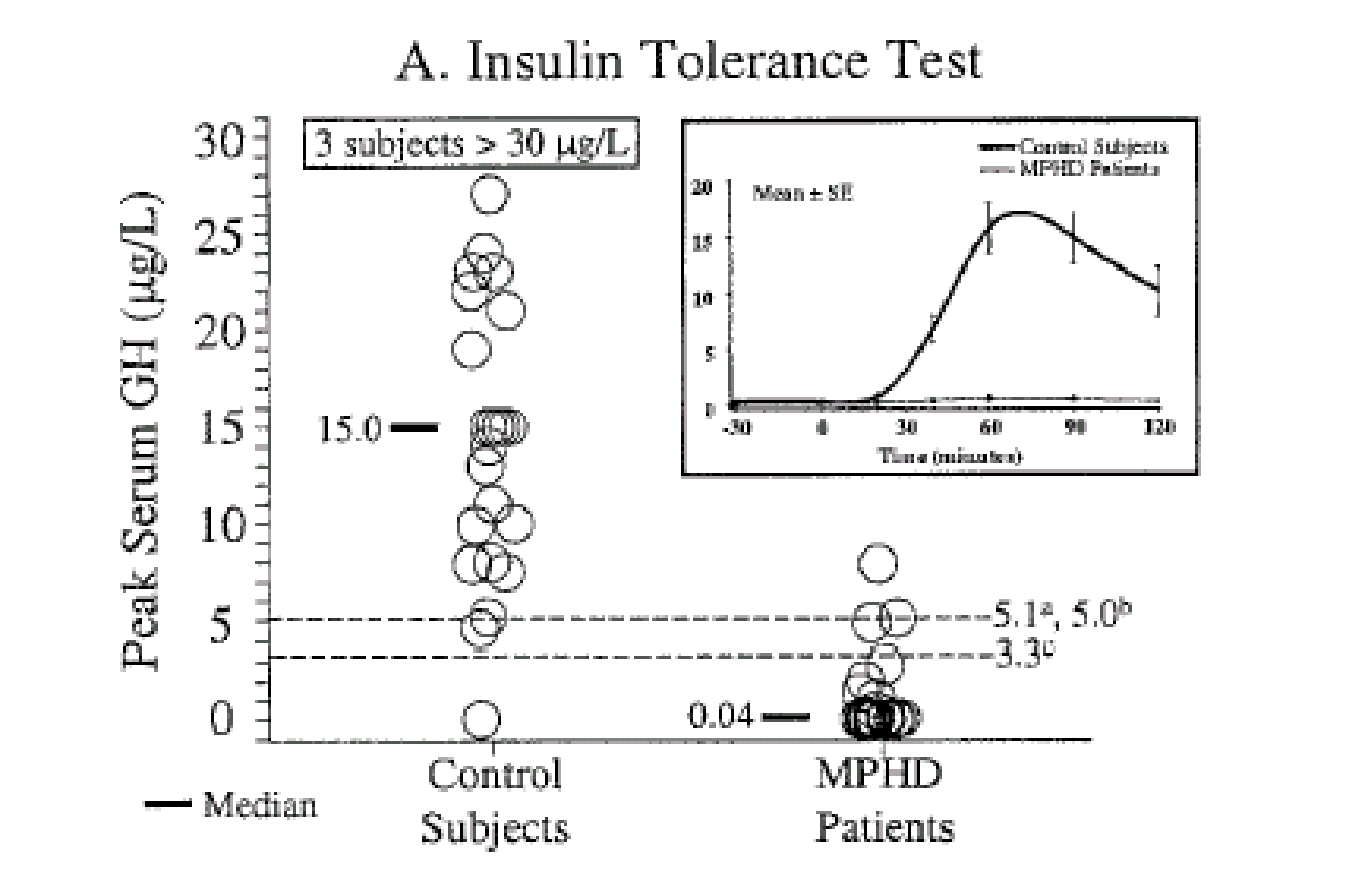
Diagnosis of GH Deficiency in adults

Hoffman DM, O'Sullivan AJ, Baxter RC, Ho KKY, Lancet 1994; 343: 1064-68



Results of ITT test in normal (o) and hypopituitary (•) subjects

Sensitivity and specificity of six tests for the diagnosis of adult GH Deficiency



Individual peak serum GH concentrations in control subjects and in patients with MPHD

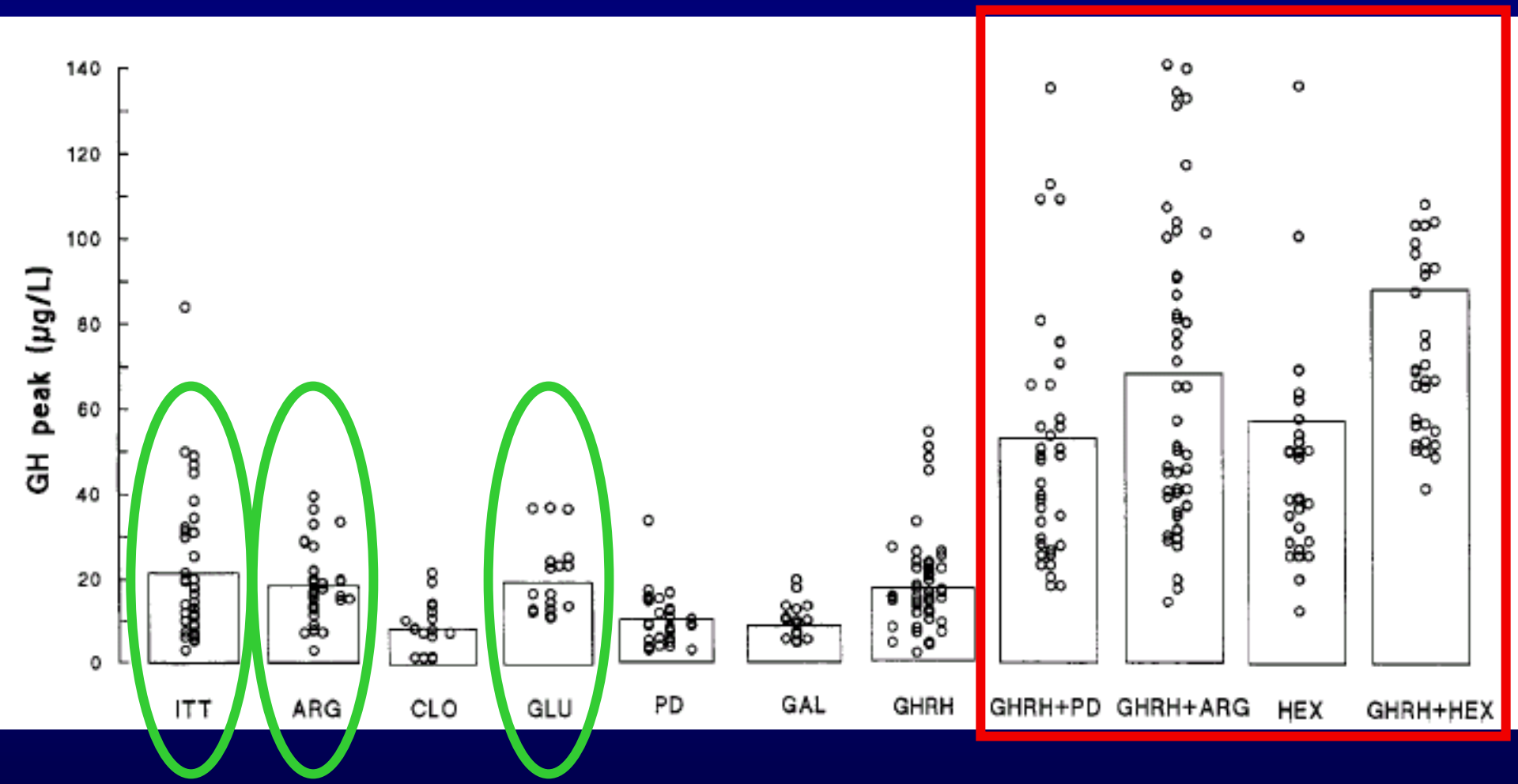
Biller BMK, et al. *JCEM* 2002;87:2067-79.

Consensus Guidelines for the Diagnosis and Treatment of Adults with GDH: Summary Statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency

- **Poor within-subject reproducibility of the GH response to ITT has been reported**
- **Testing with ITT is contraindicated in patients with ECG evidence or history of ischemic heart disease or in patients with seizure disorders**
- **Alternative provocative tests have therefore to be often used but it is recommended that appropriate cut-off limits are considered**

JCEM 1998;83: 379-81.

Mean and individual peak GH responses to provocative tests in normal lean subjects

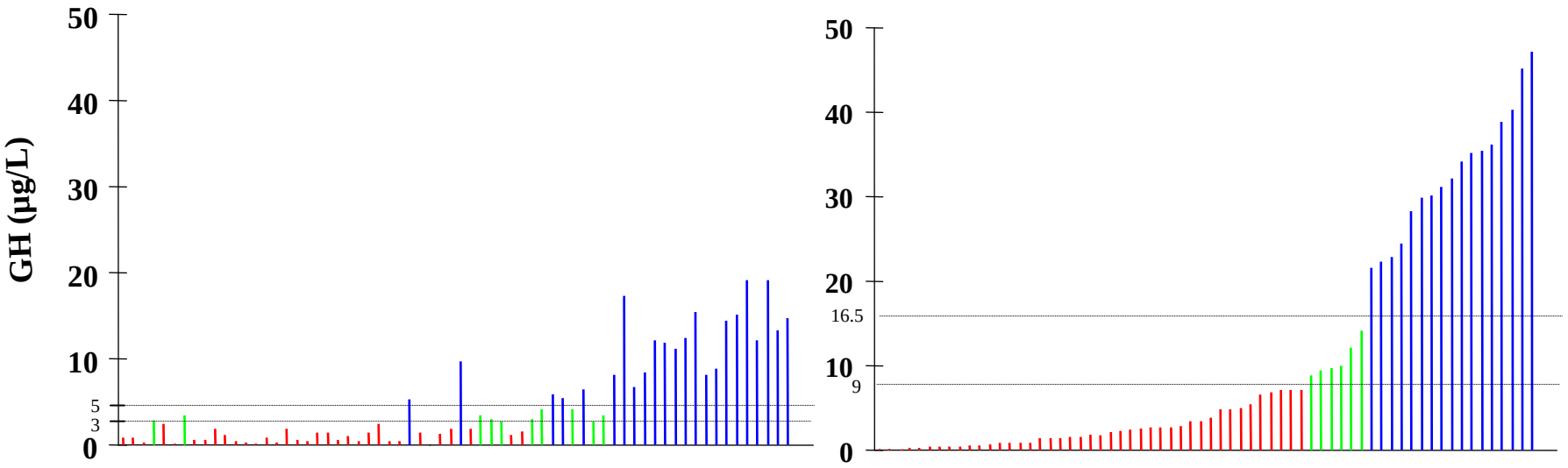


Diagnosis of GH Deficiency

The GH response to either GHRH + arginine or GHRH + GHRP-6

- **shows good within-subject reproducibility**
- **does not undergo significant age-related variations**
- **is refractory to the inhibitory effect of rhGH, rhIGF-I, glucose load, free fatty acid load**

Individual peak GH responses to ITT (left panel) and GHRH+ARG (right panel) in the same 66 adults with appropriate clinical context to suspect GHD



ITT

normal GH response: 36.4 %

partial GHD: 9 %

severe GHD: 54.6 %

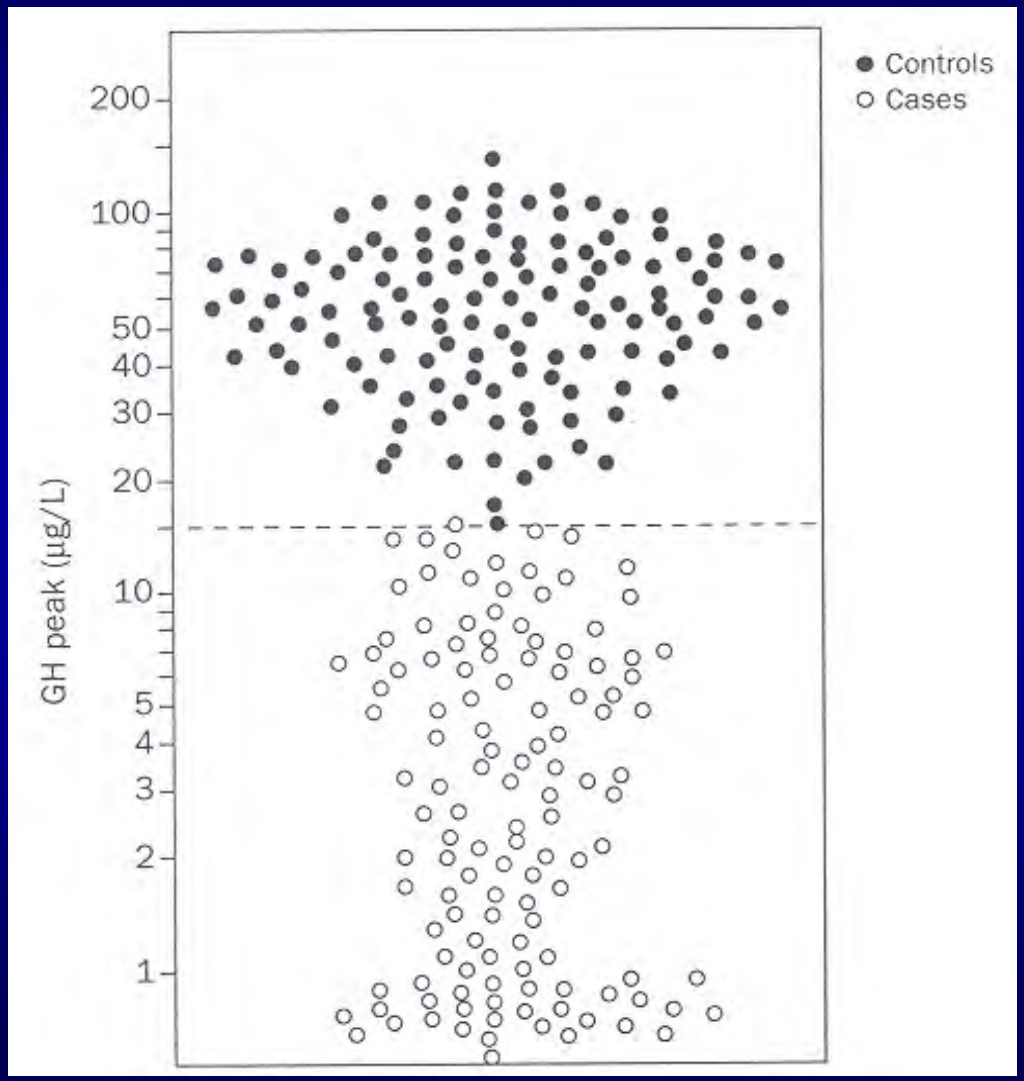
GHRH+ARG

normal GH response: 25.8 %

partial GHD: 9 %

severe GHD: 65.2 %

GHRH and GHRP-6 for diagnostic testing in GH-Deficient adults



Individual GHRH plus GHRP-6-mediated GH peaks in controls and cases.

GH secretion was a continuum between excessive secretion and abnormally low secretion, although a transition concentration between normality and abnormality may be seen around the 15 µg/L concentration.

Logarithmic representation

Popovic V, et al. *Lancet* 2000;356:1137-42.

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Mark E. Molitch, David R. Clemmons, Saul Malozowski, George R. Merriam, Stephen M. Shalet, and Mary Lee Vance, for The Endocrine Society's Clinical Guidelines Subcommittee

Additionally, the insulin tolerance test (ITT), which has been considered the "gold standard" may carry increased risk in patients with seizure disorders or cardiovascular disease and require constant monitoring even in healthy adults, although it is quite safe in experienced hands.

Ghigo and colleagues showed that the combined administration of arginine, which presumably reduces hypothalamic somatostatin secretion, and GHRH is safe and provides a strong stimulus to GH secretion that is less affected by aging or obesity and thus could be used as an alternative to the ITT as a test of pituitary GHD.

JCE&M 91: 1621, 2006

Provocative tests for the diagnosis of adult GHD

- Among provocative tests,
ITT remains the test of reference but
it is recognized that other tests are as reliable as ITT.

- Glucagon as classical test
and, particularly,
new maximal tests such as GHRH in combination with arginine or GHS (i.e. GHRP-6)
have well defined cut-off limits, are reproducible, able to distinguish between normal and GHD subjects and are at least as reliable as ITT.

- It must be noticed that cut-off values have to be appropriate to the potency of each test
(and are function of BMI).

0013-7227/02/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 87(5):2067–2079

Sensitivity and Specificity of Six Tests for the Diagnosis of Adult GH Deficiency

BEVERLY M. K. BILLER, MARY H. SAMUELS, ANTHONY ZAGAR, DAVID M. COOK, BAHA M. ARAFAH, VIVIEN BONERT, STAVROS STAVROU, DAVID L. KLEINBERG, JOHN J. CHIPMAN, AND MARK L. HARTMAN

Massachusetts General Hospital (B.M.K.B.), Boston, Massachusetts 02114; Oregon Health Sciences University (M.H.S., D.M.C.), Portland, Oregon 97201; Lilly Research Laboratories (A.Z., J.J.C., M.L.H.), Eli Lilly & Co., Indianapolis, Indiana

Using peak serum GH cut-points of 5.1 µg/liter for the ITT and 4.1 µg/liter for the ARG plus GHRH test, high sensitivity (96 and 95 %, respectively) and specificity (92 and 91 %, respectively) for GH deficiency were achieved.

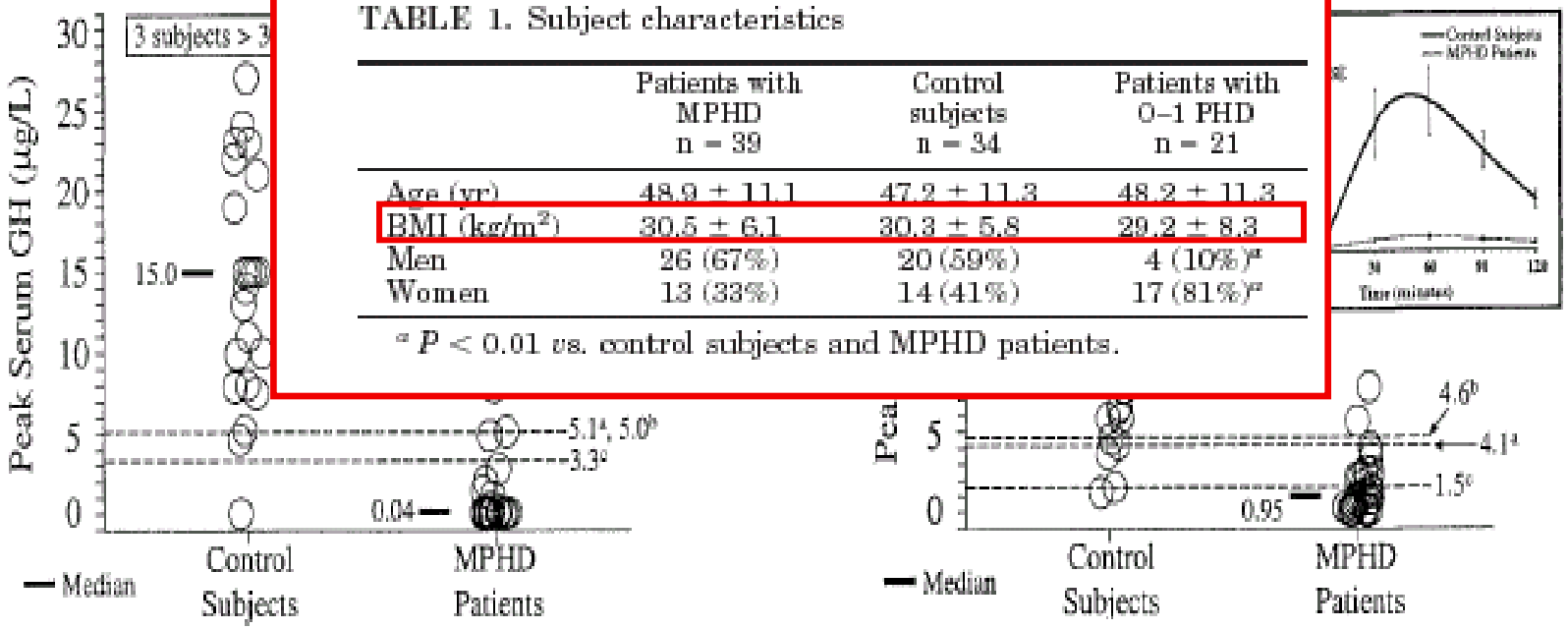
visits: ITT, arginine (ARG), levodopa (L-DOPA), ARG plus L-DOPA, and ARG plus GHRH. Serum IGF-I concentrations were also measured on two occasions. For purposes of analysis, patients with multiple pituitary hormone deficiencies were assumed to be GH deficient. Three diagnostic cut-points were calculated for each test to provide optimal separation of multiple pituitary hormone deficient and control subjects according to three criteria: 1) to minimize misclassification of control subjects and deficient patients (balance between high IGF-I levels provided less diagnostic discrimination than all five GH stimulation tests, a value below 77.2 µg/liter was 95% specific for GH deficiency. In conclusion, the diagnosis of adult GH deficiency can be made without performing an ITT, provided that test-specific cut-points are used. The ARG plus GHRH test represents an excellent alternative to the ITT for the diagnosis of GH deficiency in adults. (*J Clin Endocrinol Metab* 87: 2067–2079, 2002)

Sensitivity and specificity of six tests for the diagnosis of adult GH Deficiency

TABLE 1. Subject characteristics

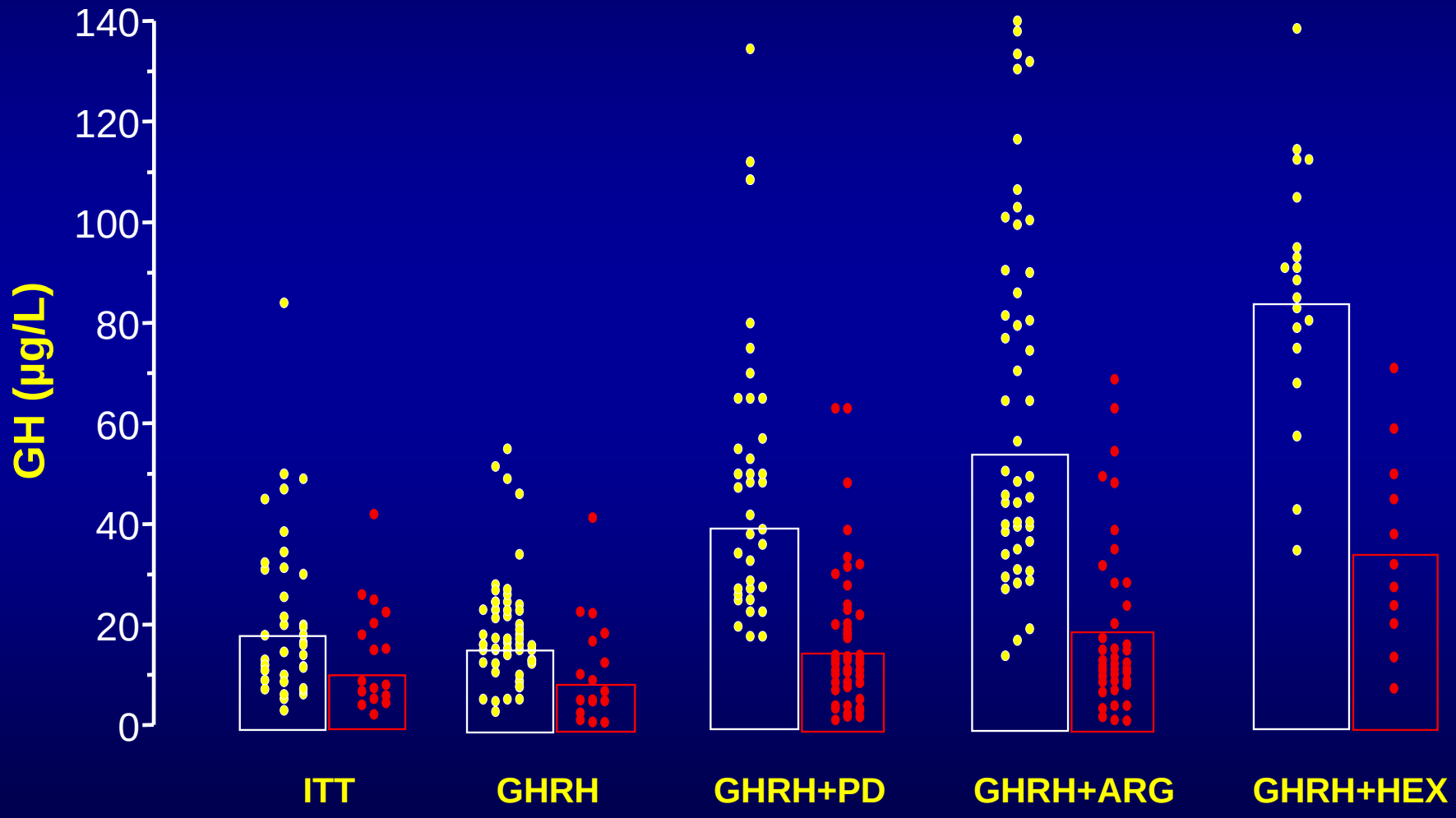
	Patients with MPHD n = 39	Control subjects n = 34	Patients with 0–1 PHD n = 21
Age (yr)	48.9 ± 11.1	47.2 ± 11.3	48.2 ± 11.3
BMI (kg/m^2)	30.5 ± 6.1	30.3 ± 5.8	29.2 ± 8.3
Men	26 (67%)	20 (59%)	4 (10%)[a]
Women	13 (33%)	14 (41%)	17 (81%)[a]

[a] $P < 0.01$ *vs.* control subjects and MPHD patients.



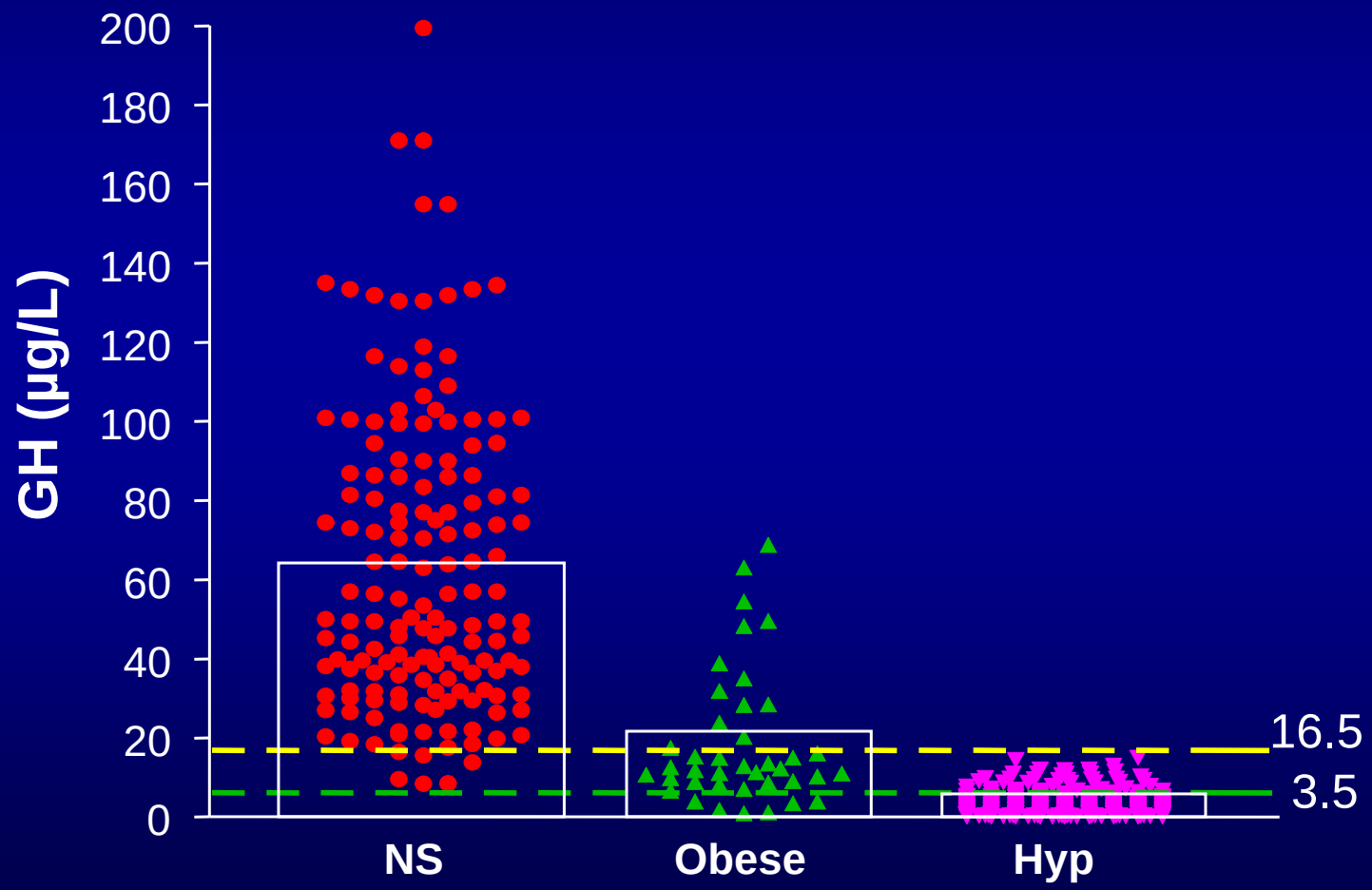
Biller BMK, et al. *JCEM* 2002;87:2067-79.

Mean and individual peak GH responses to provocative tests in normal lean and obese subjects



Mean and individual peak GH response to GHRH + arginine in normal subjects (NS), obese and hypopituitaric (Hyp) patients with GHD

(yellow dashed line represents the 3rd centile limits in normal lean subjects, green dashed line represents the 3rd centile limits in normal + obese subjects)



Body Mass Index Determines Evoked Growth Hormone (GH) Responsiveness in Normal Healthy Male Subjects: Diagnostic Caveat for Adult GH Deficiency

VIVIEN S. BONERT, JANET D. ELASHOFF, PHILIP BARNETT, AND SHLOMO MELMED

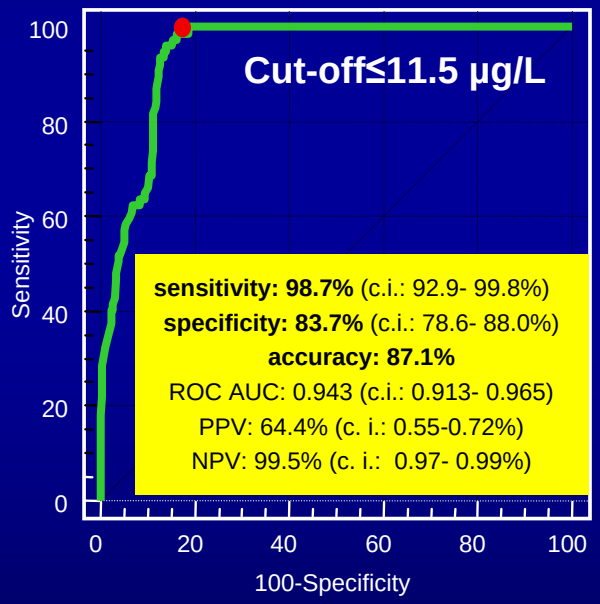
This study indicates that
provocative testing for diagnosis of GH deficiency
in patients with any degree of BMI elevation above normal
will not accurately distinguish normal from deficient responses.

BMI should be measured,
and GH results appropriately interpreted
for all adult subjects undergoing GH testing for adult GHD

evoked GH response (Pearson r = −0.59; $P < 0.01$), and the percentage of subjects exhibiting an abnormal evoked GH response, *i.e.* less than 9 ng/ml, increased from 5% for those and thus unnecessarily requiring GH replacement. (*J Clin Endocrinol Metab* 89: 3397–3401, 2004)

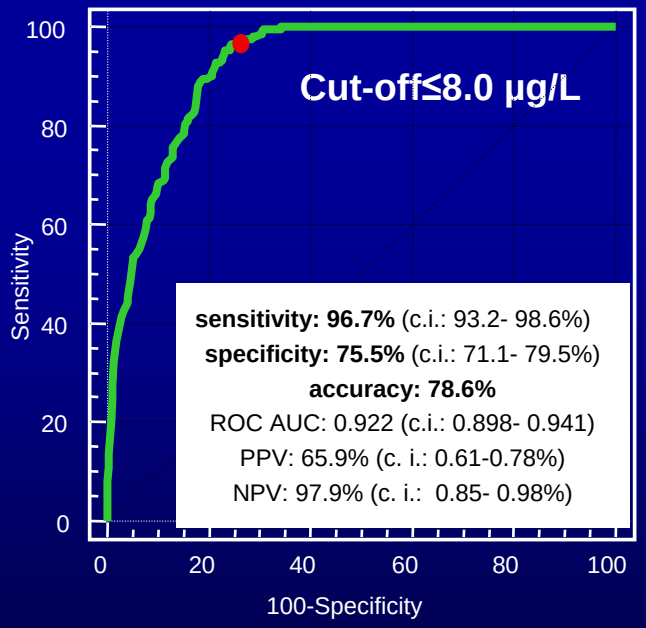
Bonert V, et al. *JCEM* 2004;89:3397-3401.

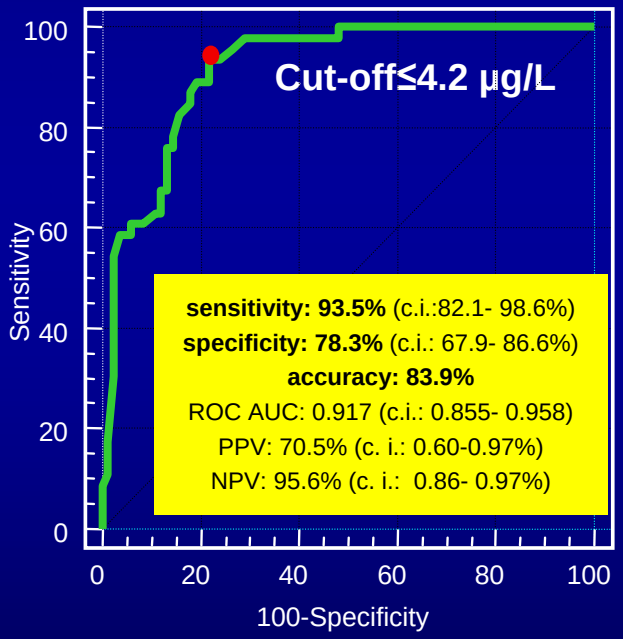
The cut-off limits of the GH response to GHRH+arginine test related to body mass index



LEAN

OVERWEIGHT





OBESE

Corneli G, et al. *EJE* 2005;153:257-64.

Diagnosis of adult GHD in overweight and in obese patients

- Cut-off values of the GH response to provocative tests have to be appropriate to the potency of each test and, particularly, are function of BMI.

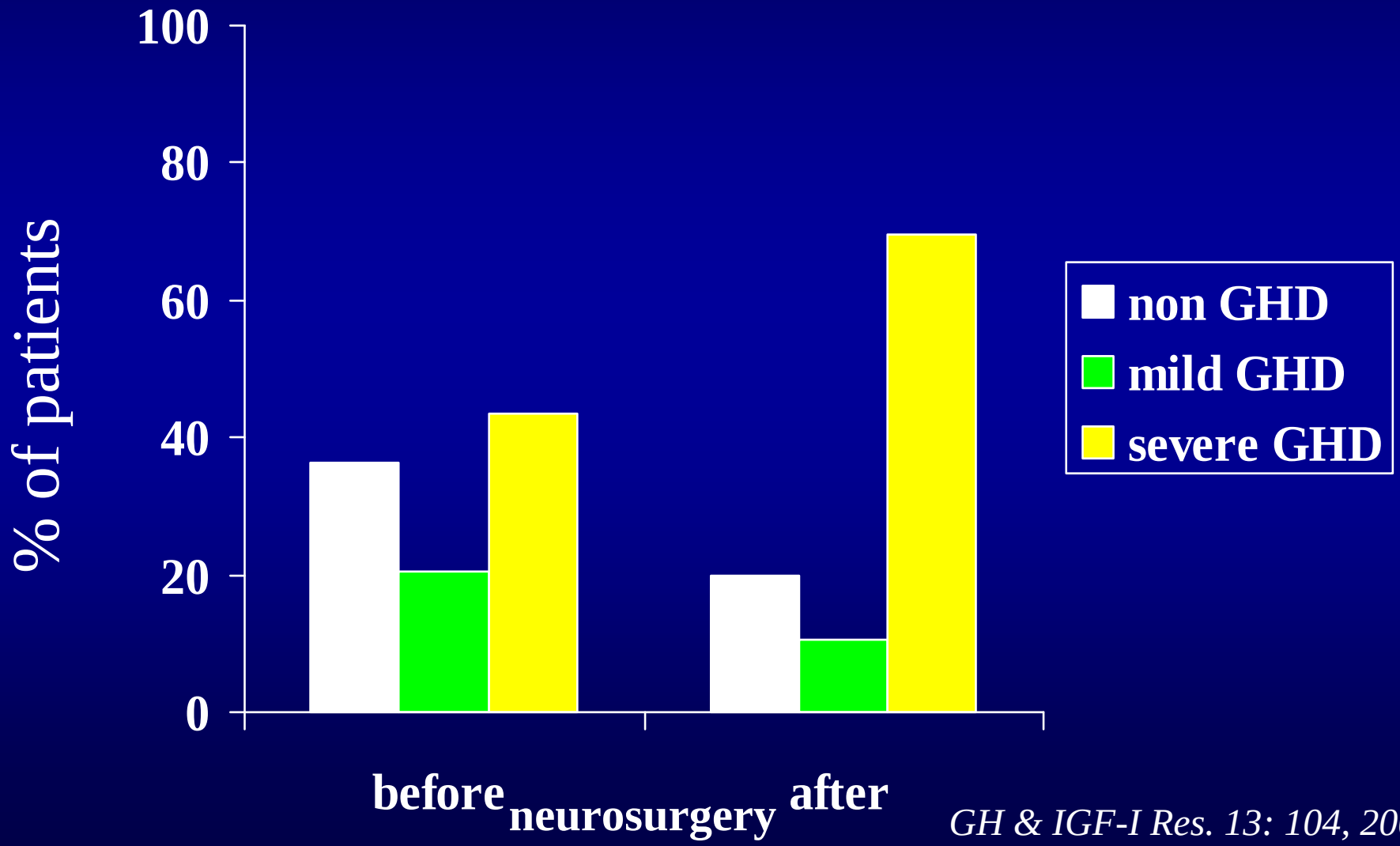
- Obesity is a condition connoted by GH insufficiency that sometimes is as marked as that in hypopituitaric patients with severe GHD.

- GH insufficiency in obesity is generally associated to normal levels of total IGF-I and increased levels of free IGF-I.

- Thus, low IGF-I levels in obese patients strongly suggest GHD. This would have major relevance in patients with primary empty sella.

OCCURRENCE OF GH DEFICIENCY (GHD) IN ADULT PATIENTS WHO UNDERWENT NEUROSURGERY IN THE HYPOTHALAMUS-PITUITARY AREA FOR NON-FUNCTIONING TUMOR MASSES

G. Corneli, R. Baldelli, C. Di Somma**, S. Rovere, D. Gaia, M. Pellegrino, V. Gasco, C. Durante***, S. Grottoli, A. Colao**, G. Tamburrano***, G. Lombardi**, E. Ghigo, G. Aimaretti*



GH & IGF-I Res. 13: 104, 2003

Consensus Guidelines for the Diagnosis and Treatment of Adults with GHD: Summary Statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency

when we consider these appropriate clinical contexts we can say we are focusing on conditions that are

at obvious more than at high risk for hypopituitarism !!!

- Those with evidence of hypothalamic or pituitary disease or cranial irradiation (likelyhood of deficiency increases with number of pituitary hormone deficits)
- Patients with childhood-onset GHD (all patients should be retested as adults before continuing treatment with GHD)

JCEM 1998;83: 379-81.

Thank you very much
for your kind attention

Management of Endocrine Sequelae in Patients Sustaining a Traumatic Brain Injury or Subarachnoid Hemorrhage

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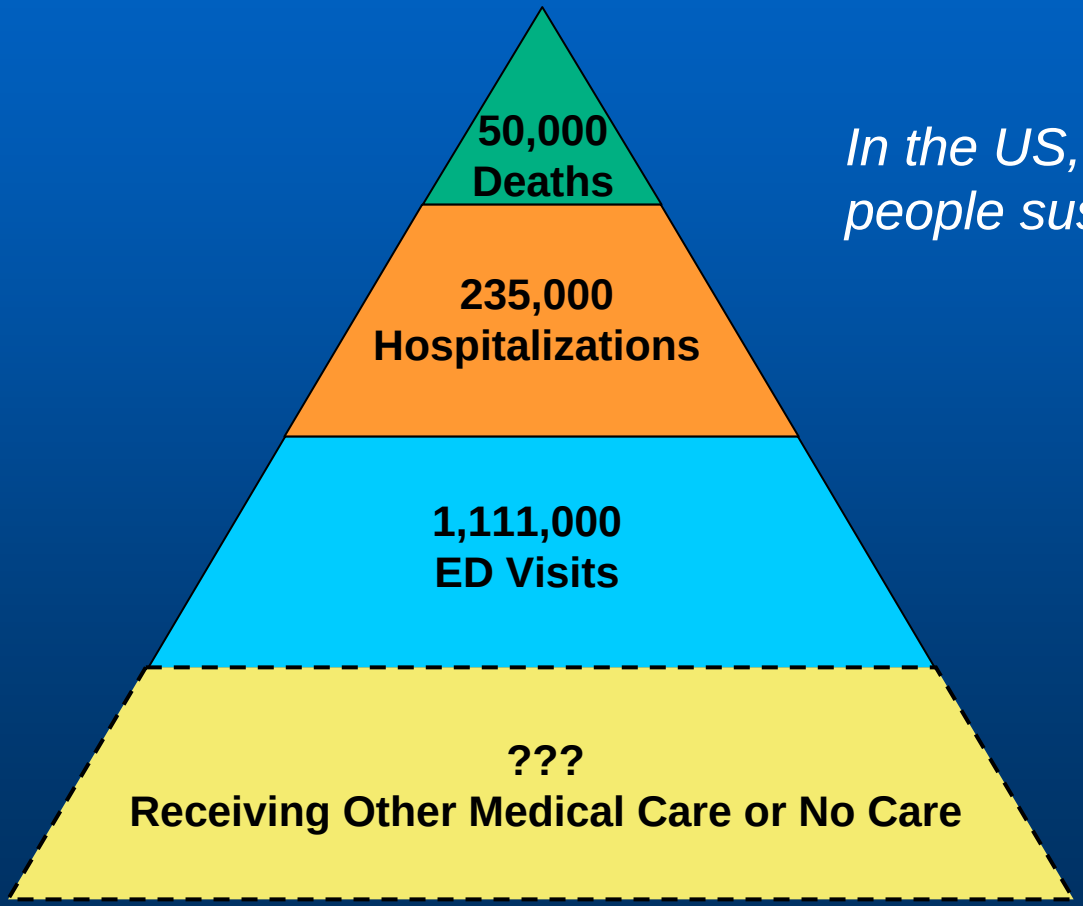
Sponsored by an unrestricted educational grant from Pfizer, Inc.

Epidemiology of Traumatic Brain Injury

Emergency Department Visits, Hospitalizations, and Deaths due to Traumatic Brain Injury in the US (all ages)



In the US, at least 1.4 million people sustain a TBI each year

Langlois JA, et al. *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths*. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2004.

TBI: Worldwide Incidence and Mortality Rates (all ages)

Continent	Place of Study	Annual Admission Rate (cases/100,000)	Annual Mortality Rate (cases/100,000)	Case Fatality Rate (%)
Asia	Taiwan[R]	>200*	31-37**	17.3
Africa	Johannesburg[P]	316	81	25.6
Australia	So. Australia[R]	322	7	7.2
Europe	England and Wales[R]	270	10	3.7
	Scotland	313	10	3.2
	France[P]	281	22	7.8
	Spain[P]	91	20	21.9
	Northern Norway[R]	169	NR	NR
	Italy	314	--	--
	Romagna[P]	297	7.7	2.6
	Trentino[R]	332	2.1†	0.6†

R = Retrospective, P = Prospective, NR = Not Recorded.

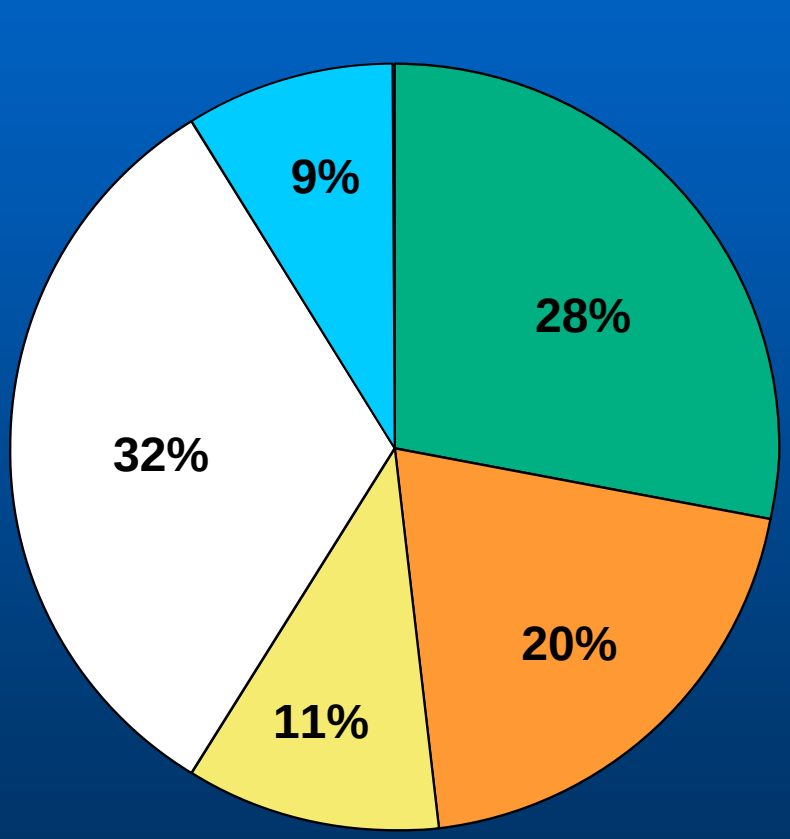
* Incidence higher than in North America due to type of traffic (mainly motorcycles) and lack of safety measures.

** Refers to road traffic accidents (National Health Statistics of Taiwan).

† Relative value due to lack of neurosurgery unit in this area.

Servadei F, et al. *Neuroepidemiology*. 2002;21:297-304.

External Causes of US TBI-related ED Visits, Hospitalizations, and Deaths 1995 to 2001 (all ages)



Falls

MVA / Traffic Accident*

Assault

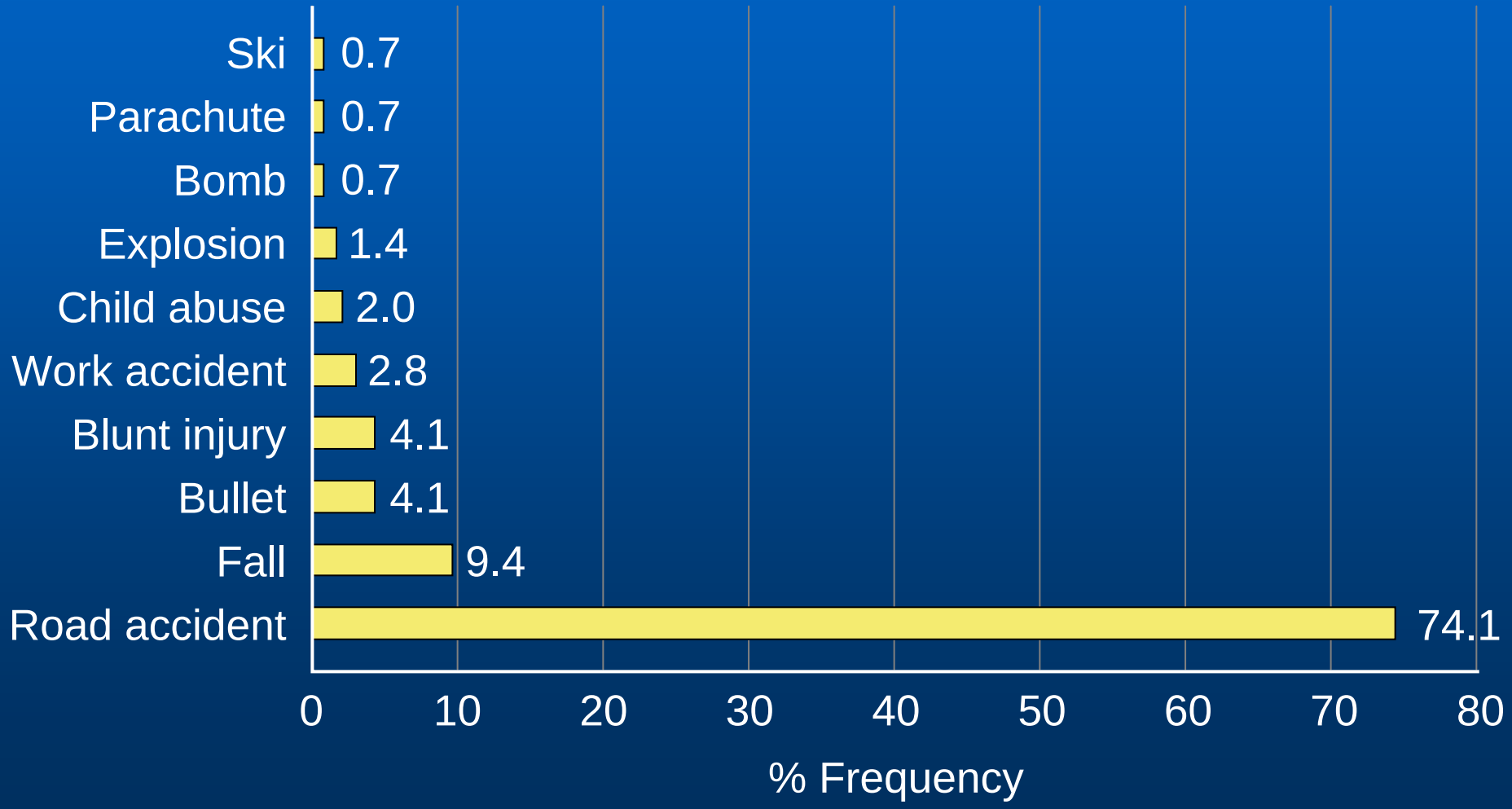
Unknown

Other

* Motor vehicle/traffic accidents include the following external causes of injury: occupant, motorcyclist, pedal cyclist, pedestrian, other and unspecified persons involved in a motor vehicle-traffic accident.

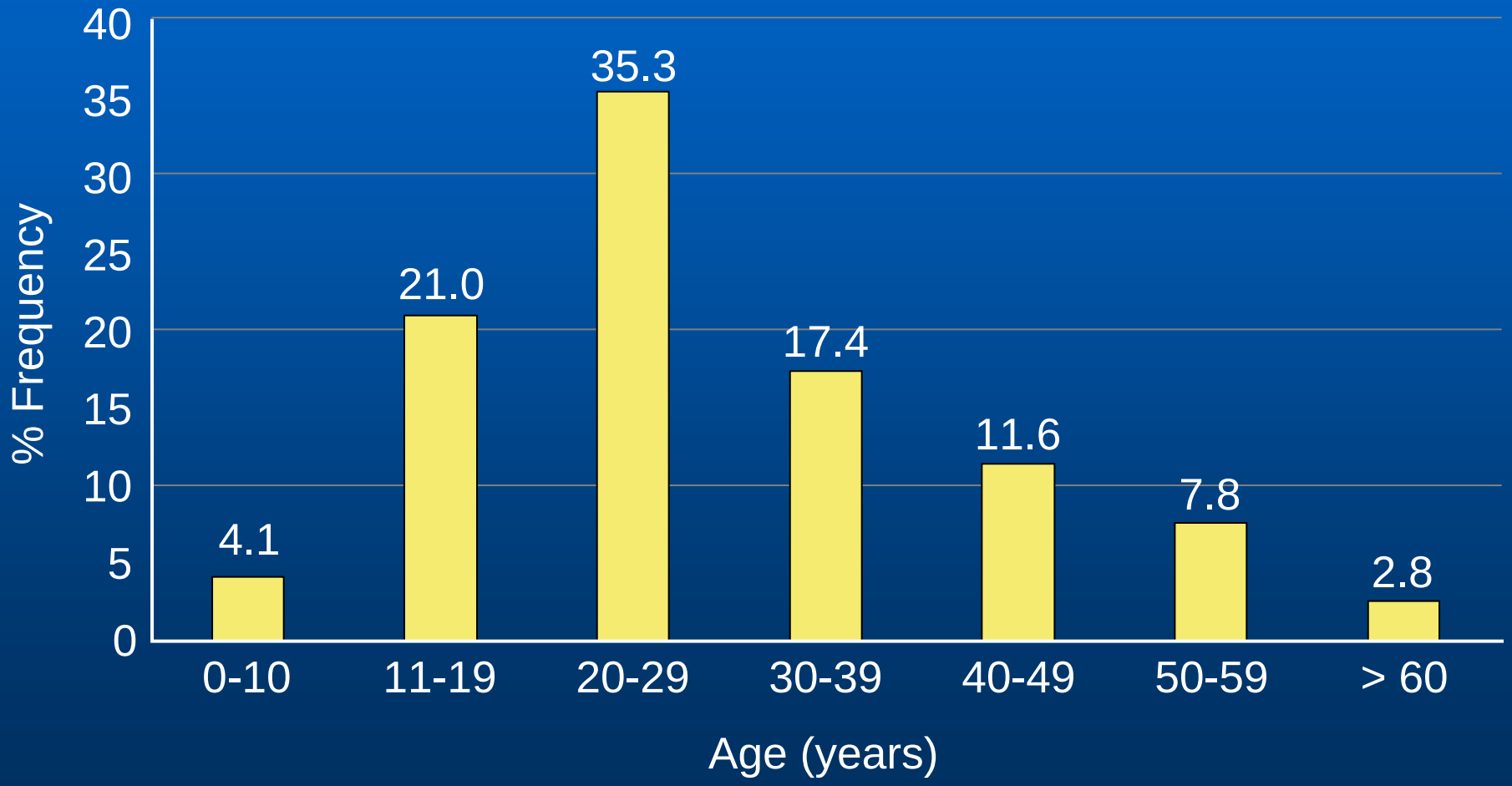
Langlois JA, et al. *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths*. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2004.

Frequency of Accidents Resulting in TBI in Adults from 1970 to 1998 (n=147)



Benvenga S, et al. *J Clin Endocrinol Metab*. 2000;85:1353-1361.

Prevalence of Age at the Time of TBI (n=218)



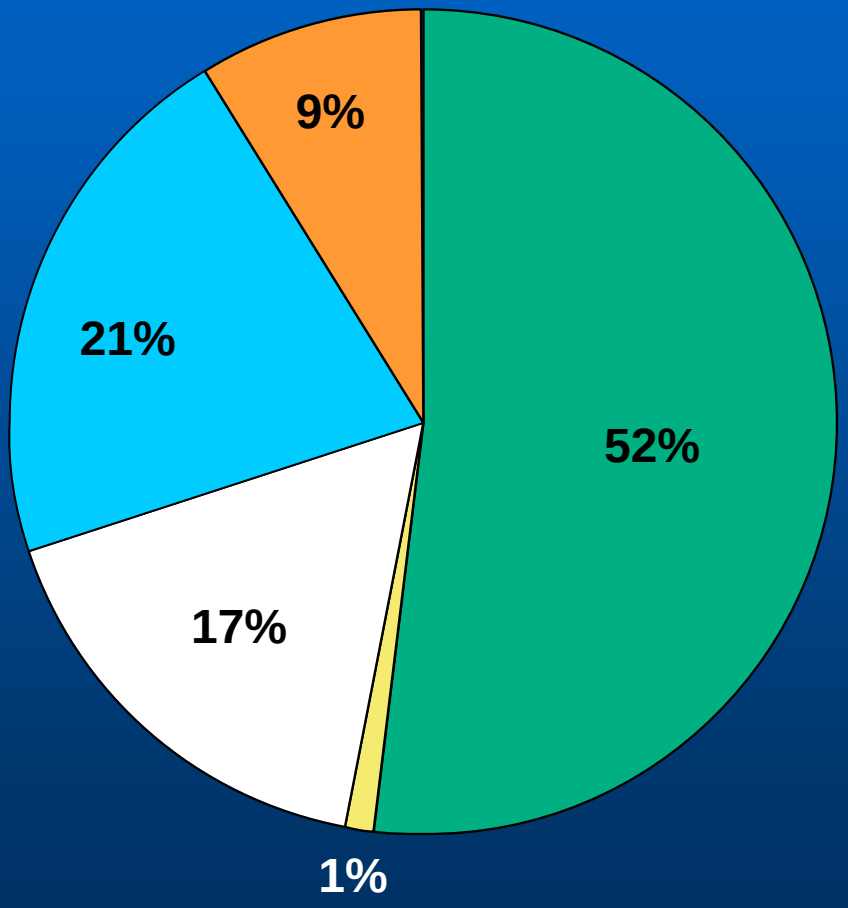
Benvenga S, et al. *J Clin Endocrinol Metab*. 2000;85:1353-1361.

TBI in Adults

- Approximately 75% of TBIs that occur each year are concussions or other forms of mild TBI
- Blasts are a leading cause of TBI for active duty military personnel in war zones
- Annually, 80,000 to 90,000 people experience the onset of long-term or lifelong disability associated with a TBI
- Today, about 5.3 million people in the US live with a disability caused by a TBI

Langlois JA, et al. *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths*. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2004.
Traumatic Brain Injury – Fact Sheet. Available at: http://www.cdc.gov/Migrated_Content/Fact_Sheet/Freeform_Fact_Sheet_(General)/Traumatic_Brain_Injury_updated_May_2004.pdf. Accessed 06 July 2005.
Okie S. *N Engl J Med*. 2005;352:2043-2047.

External Causes of US TBI-related ED Visits, Hospitalizations, and Deaths in Older Adults (≥65 years old)



Falls

MVA / Traffic Accident*

Assault

Unknown

Other

* Motor vehicle/traffic accidents include the following external causes of injury: occupant, motorcyclist, pedal cyclist, pedestrian, other and unspecified persons involved in a motor vehicle-traffic accident.

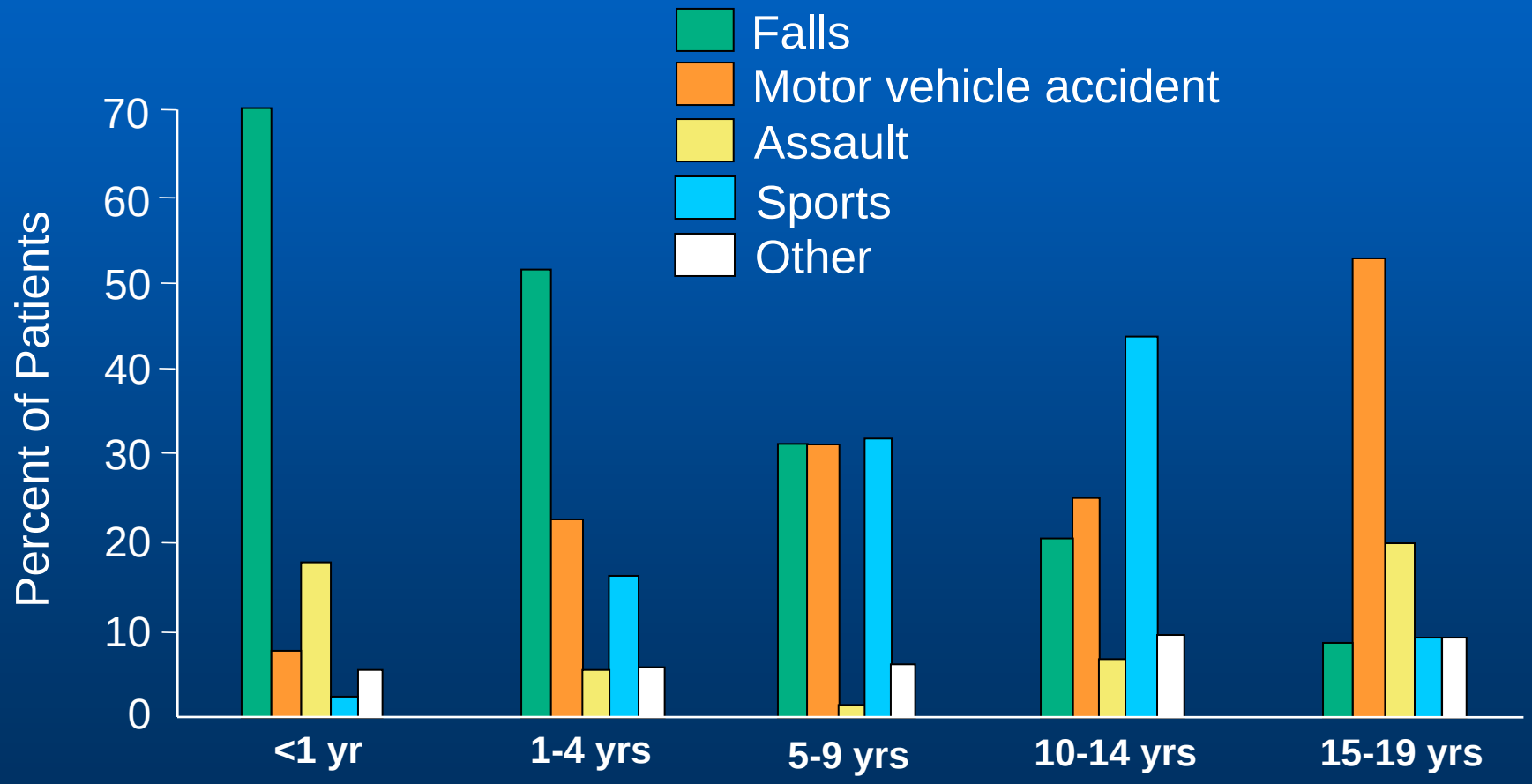
Langlois JA, et al. *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths*. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2004.

TBI in Children

- TBI is the leading cause of death and disability among children and young adults in the US
- Among children ages <1 to 14 years, TBI results in an annual estimated
  - 2,685 deaths
  - 37,000 hospitalizations, and
  - 435,000 emergency department visits
- An estimated 300,000 sports-related brain injuries of mild-to-moderate severity occur in the US each year

Langlois JA, et al. *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths*. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2004.
Popovic V, et al. *GH IGF-I Res*. 2005;15:177-184.
Traumatic Brain Injury – Fact Sheet. Available at: http://www.cdc.gov/Migrated_Content/Fact_Sheet/Freeform_Fact_Sheet_(General)/Traumatic_Brain_Injury_updated_May_2004.pdf. Accessed 06 July 2005.

External Causes of TBI in Children (≤19 years old)



Noppins R, Brambrink AM. *Exp Toxicol Pathol*. 2004;56:113-125.

Epidemiology of Aneurysmal Subarachnoid Hemorrhage (SAH)

- Annual incidence
  - US: 6-25 per 100,000
  - Internationally: varying incidences reported (2-49 per 100,000)
- Age peak in the sixth decade (ages 50 to 59 yrs)
- Ruptured intracranial aneurysms account for 85% of all spontaneous subarachnoid hemorrhages
  - In the US, >27,000 ruptured intracranial aneurysms occur annually
  - Risk factors: familial predisposition, smoking, hypertension, and heavy drinking

Kreitschmann-Andermahr I, et al. *J Clin Endocrinol Metab*. 2004;89:4986-4992.
Kazzi AA, Ellis K. *Subarachnoid Hemorrhage*. Available at: http://www.emedicine.com/EMERG/topic559.htm. Accessed 16 Jun 2005.

Deaths from SAH

- Mortality due to SAH
  - Approximately 10% to 15% of patients die before reaching the hospital
  - Mortality rates are as high as 40% during the first week after SAH
  - Half of patients die within the first six months
- Morbidity/mortality rates increase with age and poorer overall health
- Advances in the management of SAH have resulted in a greater than 25% reduction in mortality rate; however, more than one-third of patients are left with major neurological deficits

Kazzi AA, Ellis K. *Subarachnoid Hemorrhage*. Available at: http://www.emedicine.com/EMERG/topic559.htm. Accessed 16 Jun 2005.

Glasgow Coma Scale (GCS)

Grade	Loss Of Consciousness	Score Range	Posttraumatic Amnesia (PTA) Duration
MILD	None	13 to 15	5 min – 1 hr
MODERATE	Unconscious	9 to 12	< 24 hours
SEVERE	Coma	8 to 6	≥ 24 hours
VERY SEVERE	Coma	5	> 4 weeks
EXTREMELY SEVERE	Coma	Below 5	> 4 weeks

Available at: http://www.bt.cdc.gov/masstrauma/gscale.asp. Accessed 06 July 2005.

Physical Sequelae of TBI

- Fractures
- Paralysis
- Hemiparesis
- Pain
- Fatigue
- Sleep disturbances
- Faintness
- Loss of libido
- Impotence
- Disorders of movement (gaiting, ataxia, spasticity, tremors)
- Damage to pituitary gland/hypothalamus
- Headaches
- Visual disturbances
- Photosensitivity
- Seizures / epilepsy
- Dysphagia / aphagia
- Loss of smell / taste
- Speech impairment
- Brain swelling
- Hematoma
- Weight loss

Aimaretti G, et al. *GH IGF Res*. 2004;14:S114-S117.
Masel BE, et al. *GH IGF-I Res*. 2004;14:S108-S113.
Traumatic Brain Injury – Fact Sheet. Available at: http://www.cdc.gov/Migrated_Content/Fact_Sheet/Freeform_Fact_Sheet_(General)/Traumatic_Brain_Injury_updated_May_2004.pdf. Accessed 06 July 2005.

Cognitive Sequelae of TBI

- Problems with
  - Attention
  - Concentration
  - Perception
  - Orientation
  - Memory
  - Comprehension
  - Communication
  - Reasoning
  - Problem solving
  - Judgment
  - Initiation
  - Planning
  - Self-monitoring
  - Awareness
  - Visual spatial processing
  - Executive functioning

- Repeated mild brain injuries occurring over an extended period of time (e.g., months, years) can results in cumulative neurological and cognitive deficits
  - e.g., sports injuries during football, boxing, soccer

Masel BE, et al. *GH IGF-I Res*. 2004;14:S108-S113.
Kelestimur F, et al. *J Endocrinol Invest*. 2004;27:RC28-RC32.
Cicerone KD, et al. *Arch Phys Med Rehabil*. 2000;81;1596-1615.

Assessing Cognitive Function Following TBI

- Cognitive impairment is a significant cause of disability following TBI
- Common cognitive competency tests
  - Visual scales
  - Questionnaires
  - Computerized models

Cicerone KD, et al. *Arch Phys Med Rehabil*. 2000;81;1596-1615.

Psychosocial Sequelae of TBI

Decreased sense of well-being including:

- Deficits in general health
- Depression
- Anxiety
- Phobias
- Psychoses
- Suicidal ideation
- Paranoia
- Aggression
- Compromised independent living skills
- Interpersonal alienation
- Diminished coping skills
- Decreased vitality
- Stunted personal development
- Inappropriate sexual behavior
- Emotional disinhibition
- Substance abuse
- Violent tendencies

Masel BE, et al. *GH IGF-I Res*. 2004;14:S108-S113.
Popovic V, et al. *J Endocrinol Invest*. 2004;27:1048-1054.
Lieberman SA, et al. *J Clin Endocrinol Metab.* 2001;86:2752-2756.
Cicerone KD, et al. *Arch Phys Med Rehabil*. 2000;81;1596-1615.
Simpson G, et al. *J Head Trauma Rehabil.* 1999;14:567-580.

Endocrine Aspects of Traumatic Brain Injury

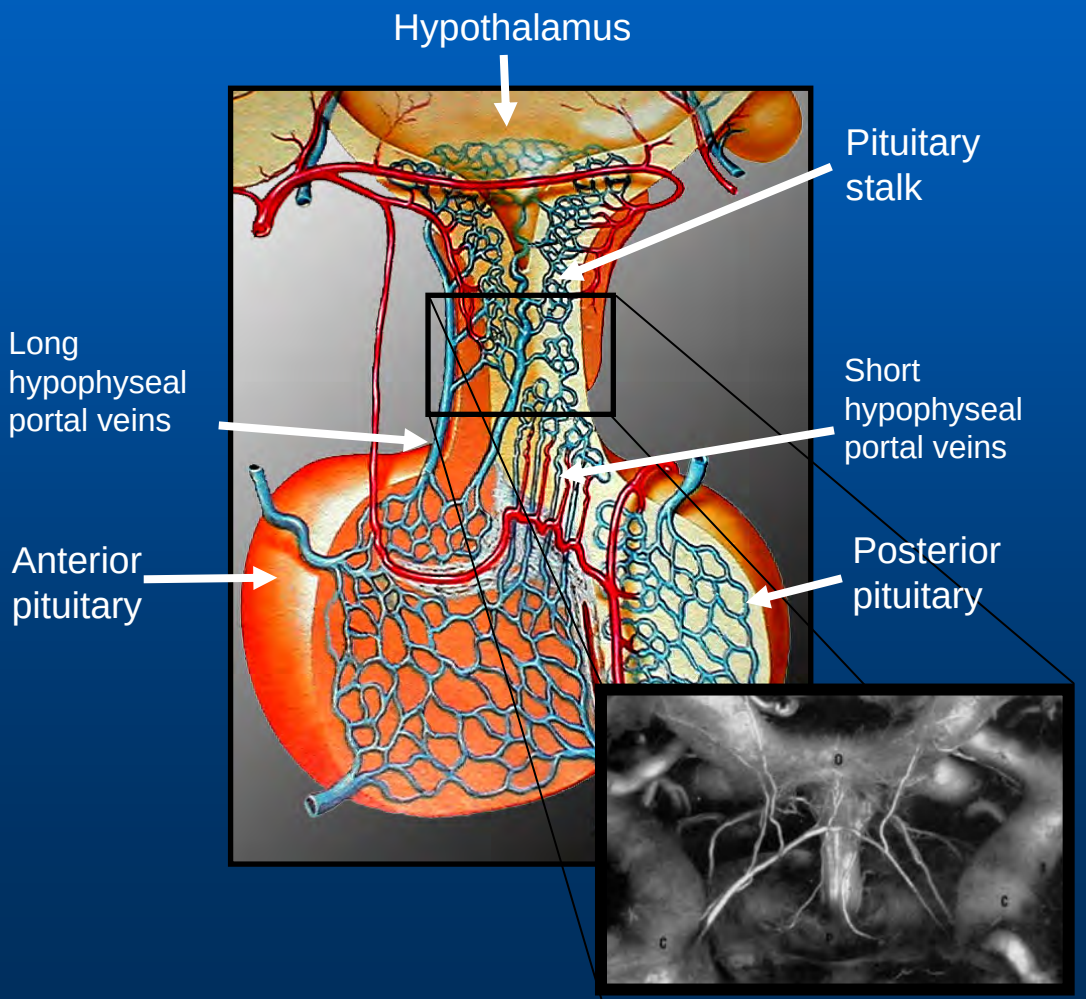
Historical Background of Hypopituitarism in TBI

- Simmonds (1914)
  - Described pathological hypophyseal cachexia
- Cyran (1918)
  - Reported first case of posttraumatic hypopituitarism
- Escamilla and Lisser (1942)
  - Published study, literature review of pathological hypopituitarism
- Edwards and Clark (1986)
  - Reviewed literature and reported on 53 patients
- Benvenga, et al. (2000)
  - Literature review revealed 367 cases of posttraumatic hypopituitarism

Masel BE, et al. *GH IGF-I Res*. 2004;14:S108-S113.

Pathophysiology of Hypothalamic-Pituitary Vulnerability

- Sites of injury
  - Hypothalamus
  - Stalk
  - Pituitary gland
- Types of injury
  - Direct trauma
  - Vascular insults
    - Brain swelling / ICP
    - Vasospasm
    - Hemorrhage
    - Hypotension / hypoxia
    - Pituitary swelling
    - Infarction
    - Ischemia



Kelly DF, et al. *J Neurosurg*. 2000;93:743-752.

Hierarchy of Vulnerability of the Pituitary During Trauma

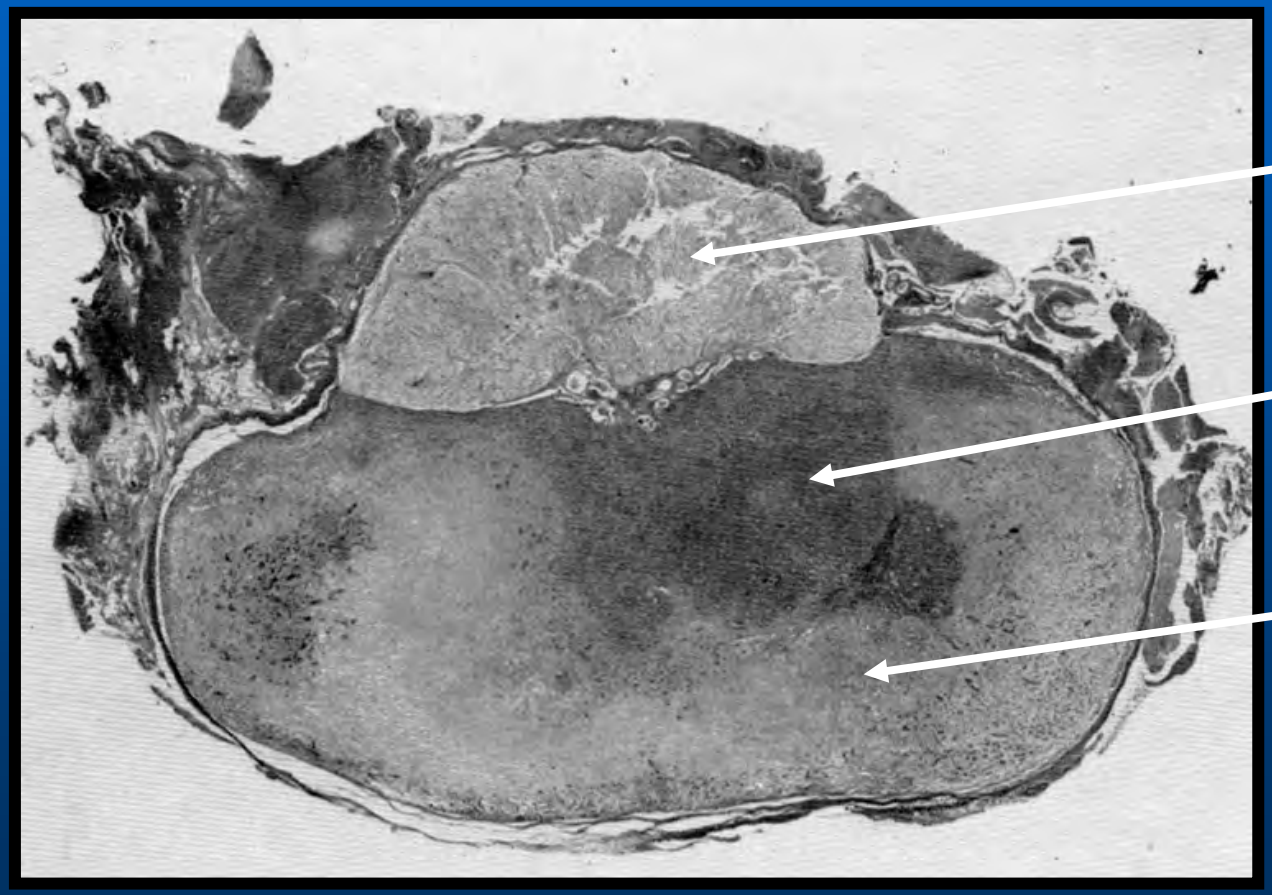
- Somatotrophs and gonadotrophs are the most vulnerable
  - Due to location in the wings of the pituitary gland and the fact that the vascular supply and oxygen they receive from the long hypophyseal pituitary portal vessels

- Corticotrophs and thyrotrophs are more resilient
  - Due to ventral location in the more protected, medial portion of the pituitary and the fact that they receive blood from the short hypophyseal portal vessels and the anterior pituitary artery branch

Edwards OM, Clark JD. *Medicine* . 1986;65:281-290.
Ghigo E, et al. *Brain Inj*. 2005;19:711-724.

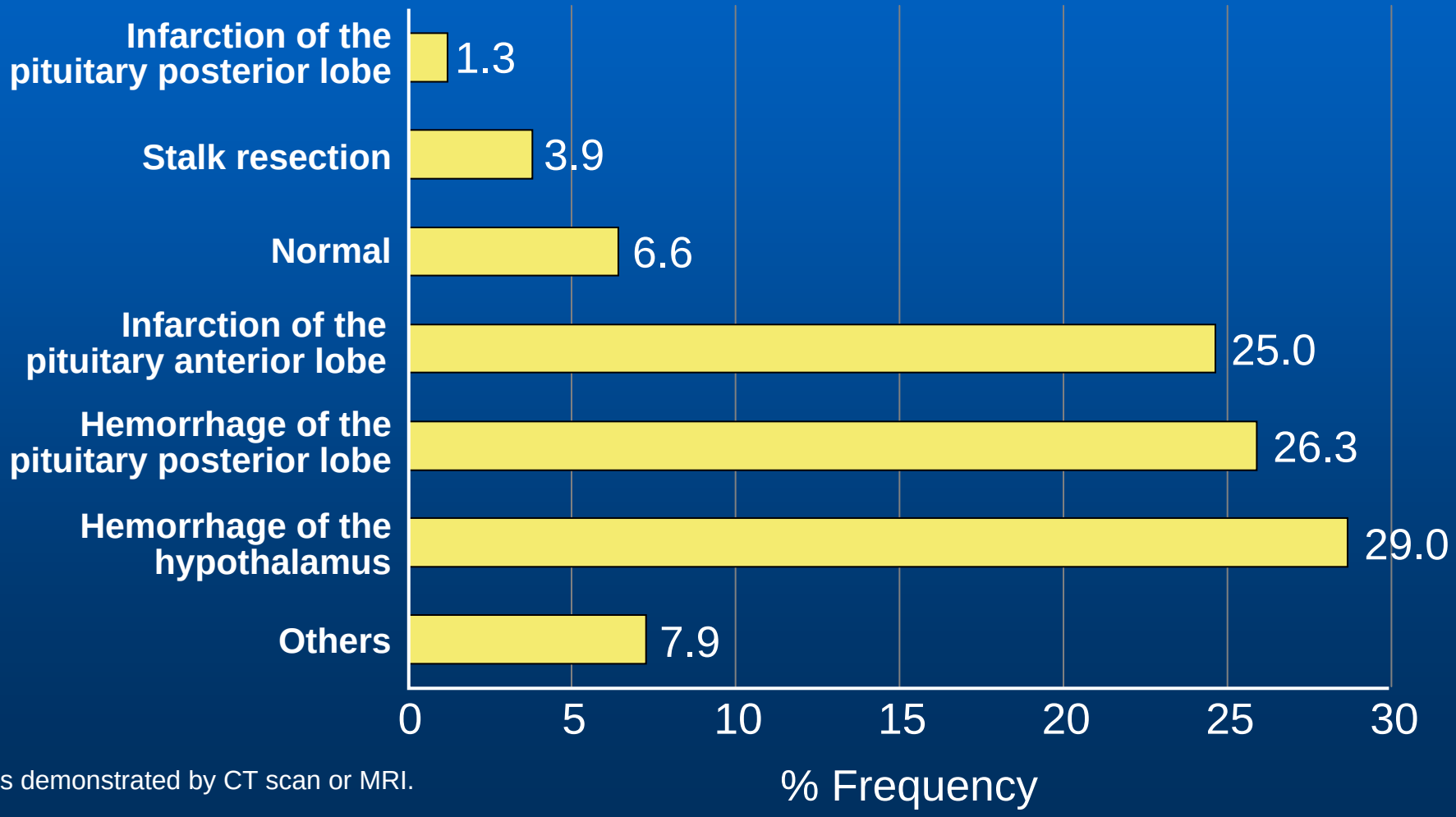
Traumatic Infarctions of the Anterior Lobe

Observed in 35% of patients living at least 12 hours



Daniel PM, et al. *Lancet*. 1959;2:927-931.
Kornblum RN, Fisher RS. *Arch Pathol*. 1969;88:242-248.

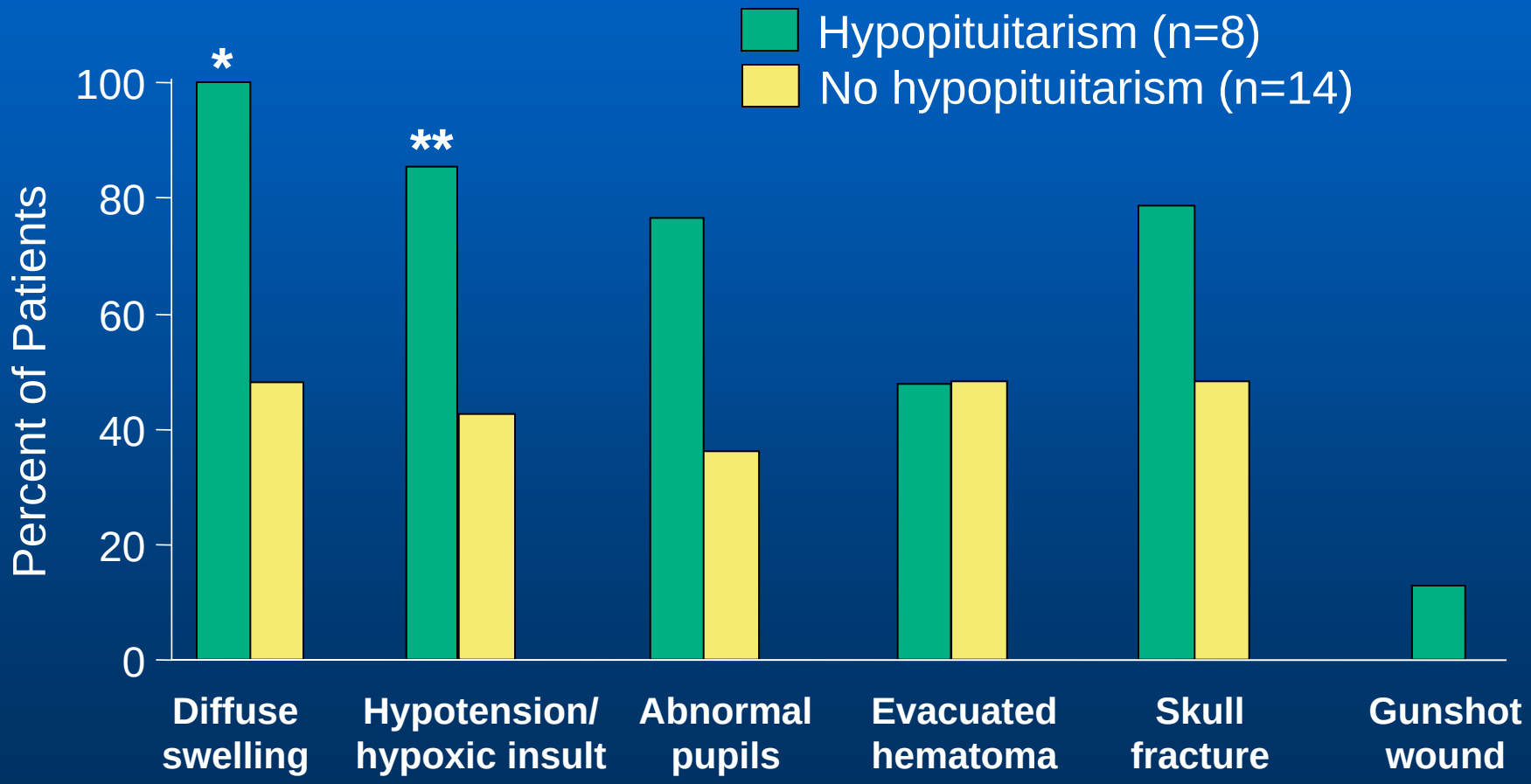
Anatomic Lesions* in Patients with Posttraumatic Hypopituitarism (n=76)



*As demonstrated by CT scan or MRI.

Benvenga S, et al. *J Clin Endocrinol Metab*. 2000;85:1353-1361.

Frequency of Potential Risk Factors in Patients with and without Posttraumatic Hypopituitarism



*P<0.05; **P=0.07

Kelly DF, et al. *J Neurosurg*. 2000;93:743-752.

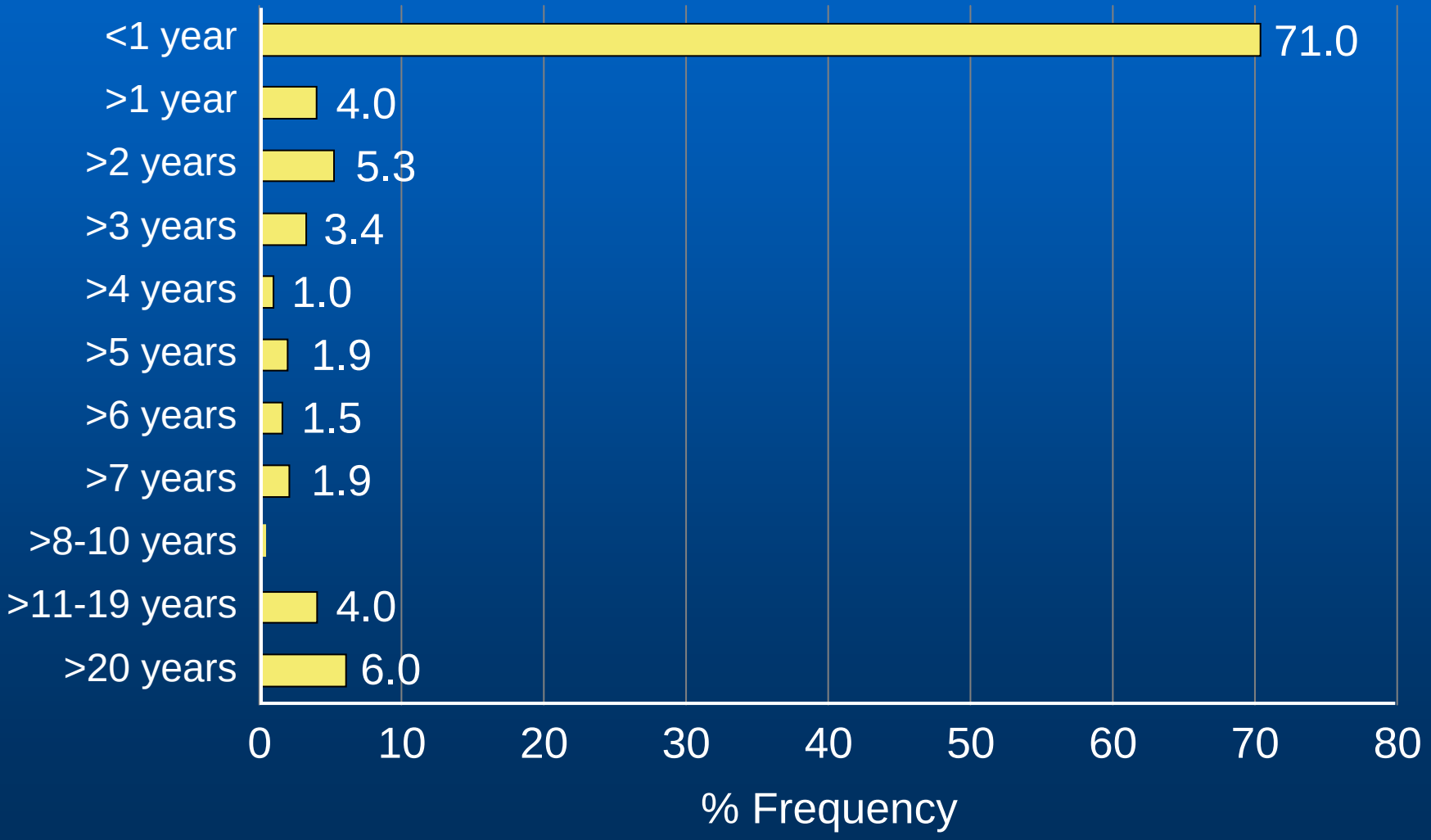
Difficult to Predict the Degree of Pituitary Dysfunction Following TBI/SAH

- Patients at highest risk appear to be those who have suffered moderate-to-severe head trauma; however…

- In patients with moderate-to-severe injuries, no correlation has been observed among the site of trauma, severity of cerebral injury, and the degree of impairment of pituitary dysfunction

Aimaretti G, et al. *Clin Endocrinol*. 2004;61:320-326.
Barreca T, et al. *J Clin Endocrinol Metab*. 1980;51:1279-1282.
Casanueva FF, et al. *J Endocrinol Invest*. 2004;27:793-795.
Kelly DF, et al. *J Neurosurg*. 2000;93:743-752.

Prevalence of Lag Time between Trauma and Diagnosis of Hypopituitarism (n=202)



Benvenga S, et al. *J Clin Endocrinol Metab*. 2000;85:1353-1361.

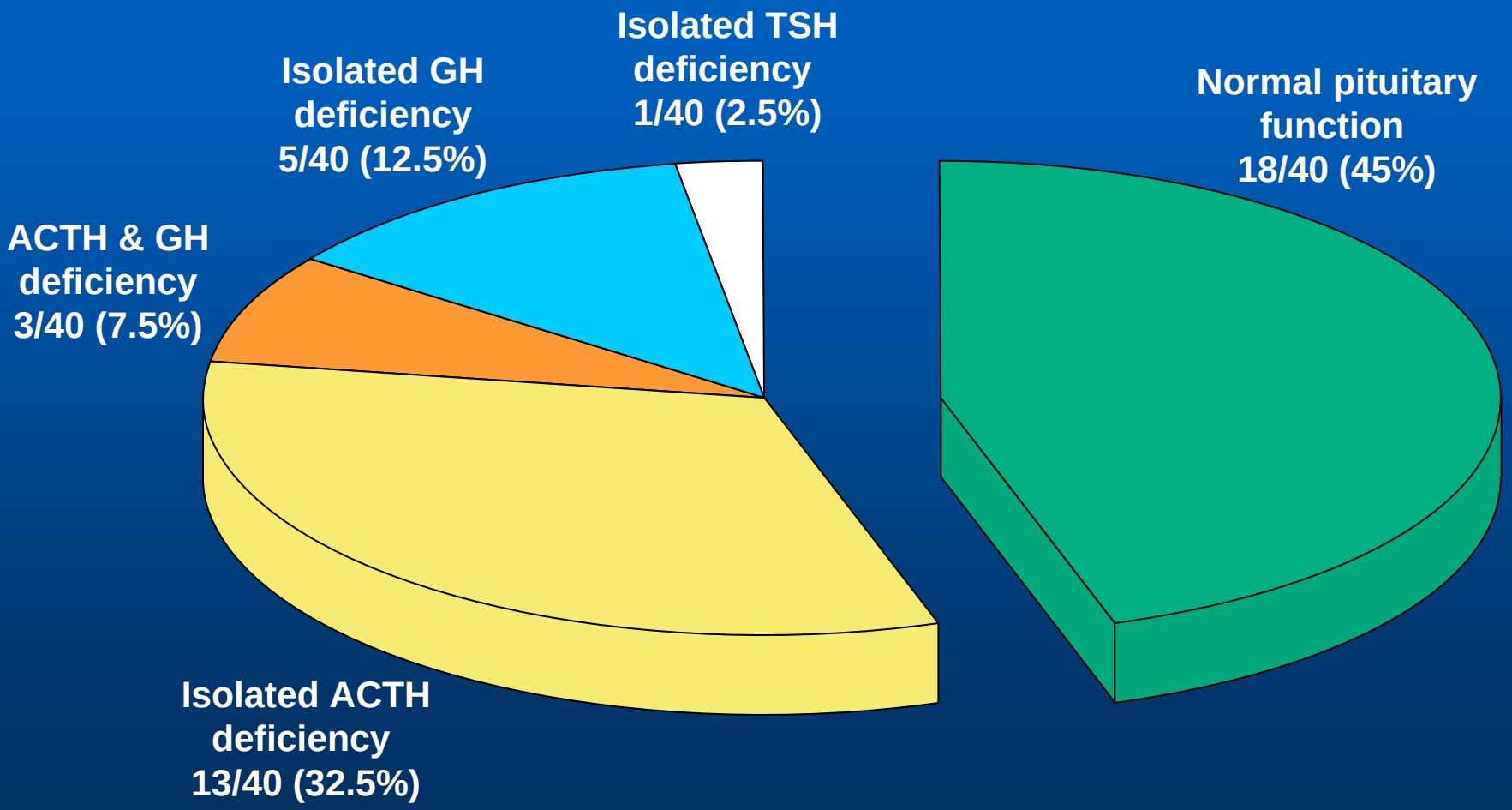
Prevalence of Pituitary Dysfunction in Patients with Previous TBI

Reference	No. of Cases	Age (yr)	Time since TBI	Prevalence of PD (%)	LH/FSH deficit (%)	GH deficit (%)	TSH deficit (%)	ACTH deficit (%)	Low PRL (%)	High PRL (%)	Perma-nent DI (%)
Kelly, et al.	22	20-52	3 months-23 years	36.4	22.7	18.2	4.5	4.5†	0	0	0
Lieberman, et al.	70	18-58	1 month-23 years	68.5	1	14.6	21.7	45.7§ 17.1†	0	10	0
Bondanelli, et al.	50	20-87	1-5 years	54	14	28*	10	0§	8	8	0
Aimaretti, et al.	100	37±2	3 months	35	17	37**	5	8§	NR	10	4
Agha, et al.	102	15-65	6-36 months	28.4	11.8	17.6***	1	22.5† 12.7‡	NR	11.8	NR
TOTAL	**344**			**42.7 (average)**							

PD: pituitary dysfunction; DI: diabetes insipidus; NR: not reported
GH deficit: * = severe GHD=8% and partial=20%; ** = severe GHD=21% and partial=16%; *** = severe GHD=7.8%
ACTH deficit: § = diagnosed by basal morning cortisol levels; †, ‡ = diagnosed after one or two standard cortisol stimulation tests, respectively

Bondanelli M, et al. *Eur J Endocrinol*. 2005;152:679-691.

Prevalence of Pituitary Dysfunction in Patients after SAH



Kreitschmann-Andermahr I, et al. *J Clin Endocrinol Metab*. 2004;89:4986-4992.

Case Report: SAH after Clipping of Ruptured Cerebral Aneurysm

Steps	Results
• 42-year-old male admitted to ER for unconsciousness (GCS=4)	• CT scan showed massive SAH • Specific angiography showed an aneurysm in the internal carotid
• Initial treatment	• Aneurysm successfully clipped through craniotomy; patient transferred to rehab unit with GCS=9
• Seven months after rupture, patient readmitted to ICU	• Septic shock with pulmonary infection associated with vomiting and diarrhea
• Standard therapy and inotropic support initiated	• No improvement; adrenal failure suspected
• Treatment started immediately with hydrocortisone	• Within hours, clinical condition improved
• Follow up	• Patient weaned from tracheotomy; endocrine tests confirmed cortisol insufficiency, but also hypothyroidism and hypogonadotropic hypogonadism secondary to hypopituitarism

Vernet M, et al. *Crit Care Med*. 2001;29:2220-2222.

Case Report : Hypopituitarism following TBI in 16-year-old Boy

Steps	Results
• 16-year-old boy hospitalized following road traffic accident • Stable through initial observation period; surgery followed 12 days post trauma • Discharged 11 days later • Almost 2 years post trauma, abnormalities noted during National Service pre-enlistment check-up • Hormonal investigations were compatible with anterior hypopituitarism	• Conscious; right malar depressed and tender; diplopia; pupils unequal but reactive to light; no visual field loss • During surgery, malar fracture noted in orbital floor; soft tissue had herniated through fracture; repaired • Restricted eye movements and diplopia persisted • Hypoandrogenism (regression of chest/axillary/pubic hair, micropenis), headaches, general weakness, giddiness in sunlight • Received L-thyroxine, cortisone acetate and IM testosterone propionate; penis length/testes volume improved, axillary/pubic hair and faint mustache appeared; thyroxine and cortisol levels normalized after 2 months

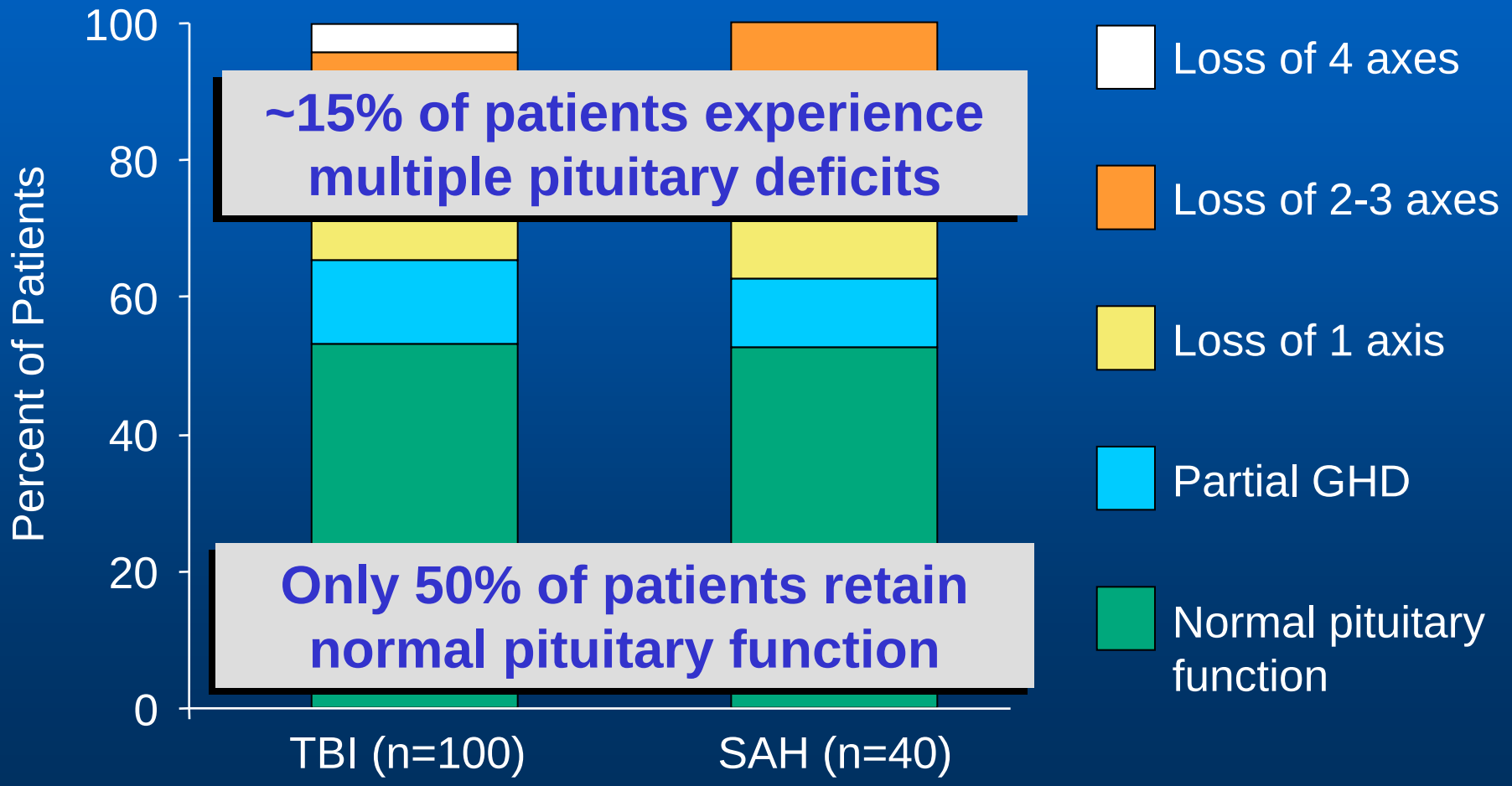
Lim HS, et al. *Ann Acad Med (Singapore)*. 1990;19:851-855.

Case Report: GHD in Four-year-old Boy Following Severe TBI

Steps	Results
• 4-year-old boy suffered severe head trauma	• Resulted in several right-sided parietotemporal fractures; 3rd degree coma for 3 days • Height was in 25th centile; preceding growth velocity was 6.6 cm/yr
• Discharged two months later	• Complained of unsteadiness of vestibular origin
• Admitted to endocrinology ward at age 6 years, 4 months	• Short stature; height less than 3rd centile, bone age delayed by 18 months
• Anterior pituitary testing	• Showed adequate TSH, cortisol and gonadotropin responses; basal thyroid and PRL levels WNL; GH response blunted
• GH therapy initiated	• Induced an acceleration of growth velocity to 8 cm in the first year of treatment

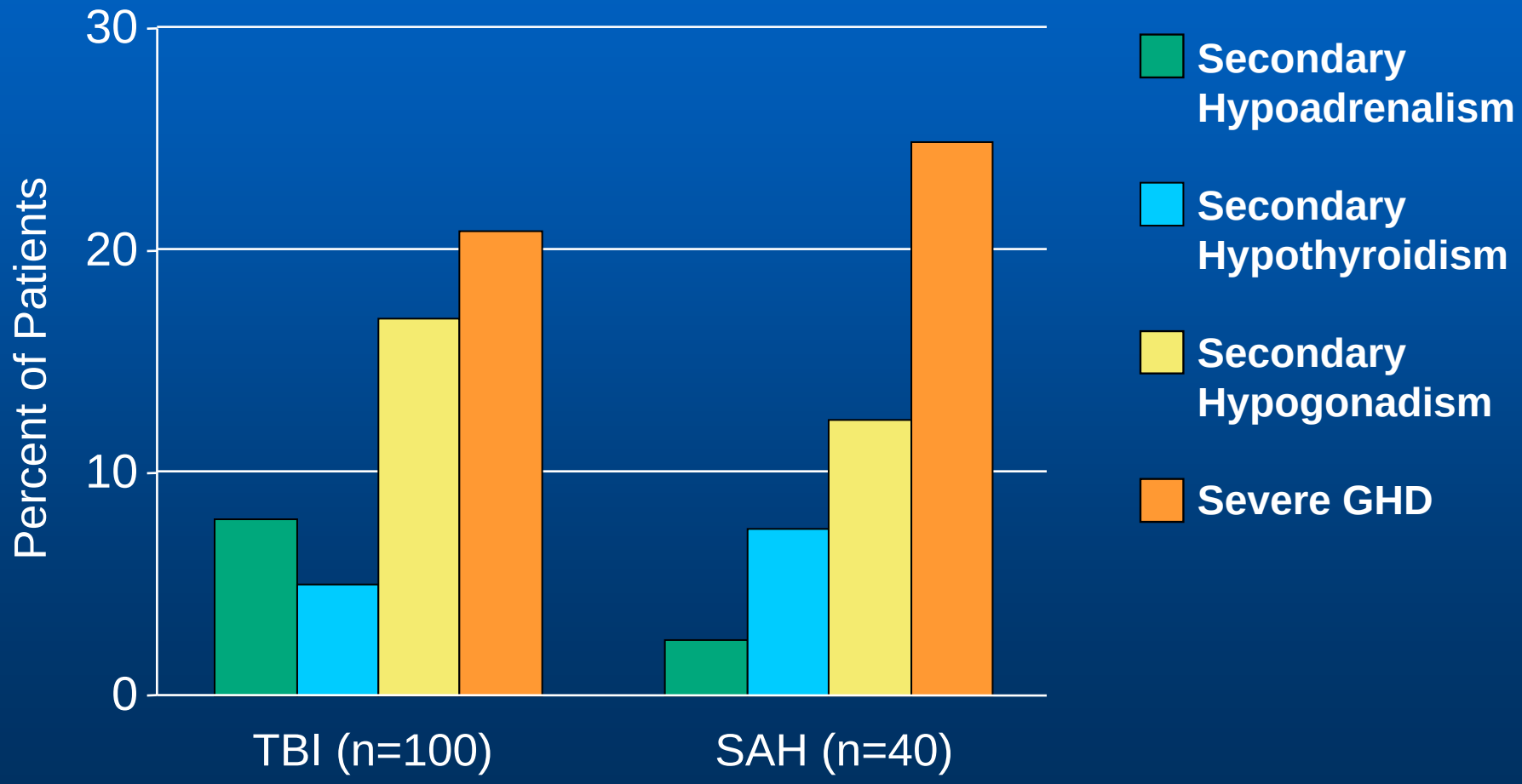
Lopez Guzman A, et al. *Acta Paediatrica*. 1992;81:698-699.

Pituitary Function Three Months after TBI or SAH



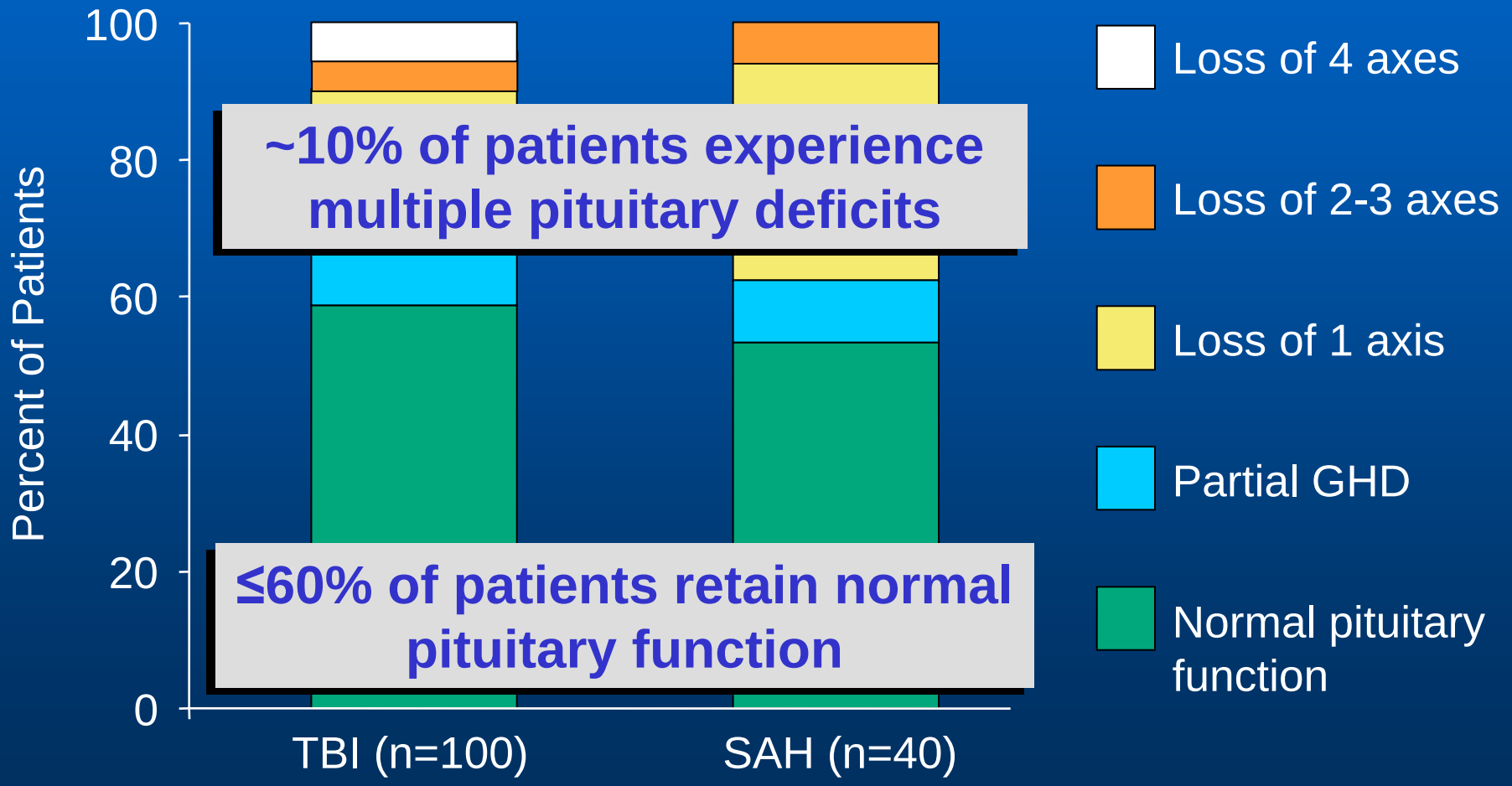
Aimaretti G, et al. *Clin Endocrinol*. 2004;61:320-326.

Percentage of Single Pituitary Deficits Three Months after TBI or SAH



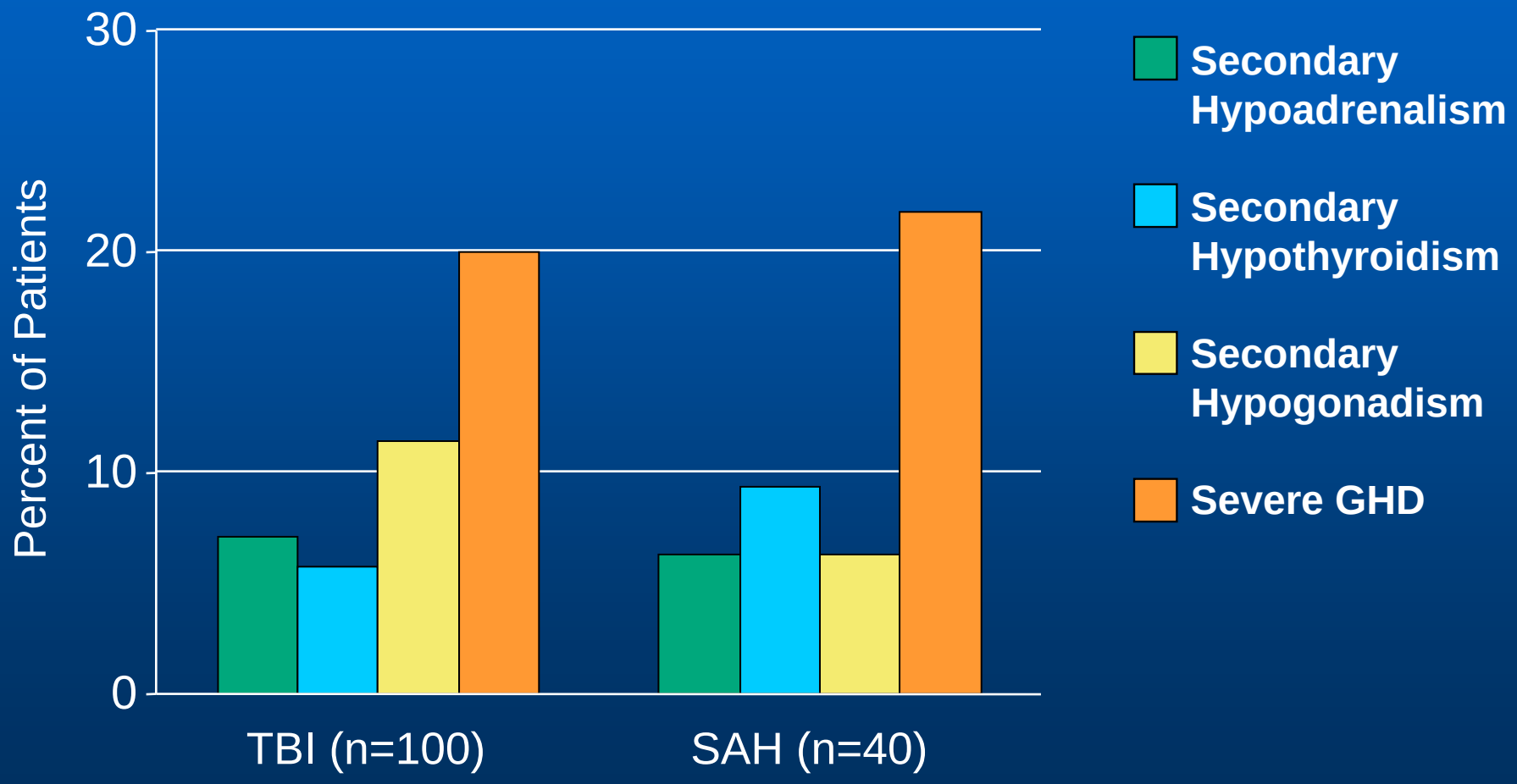
Aimaretti G, et al. *Clin Endocrinol*. 2004;61:320-326.

12-Month Follow-up of Hypopituitarism Induced by TBI or SAH



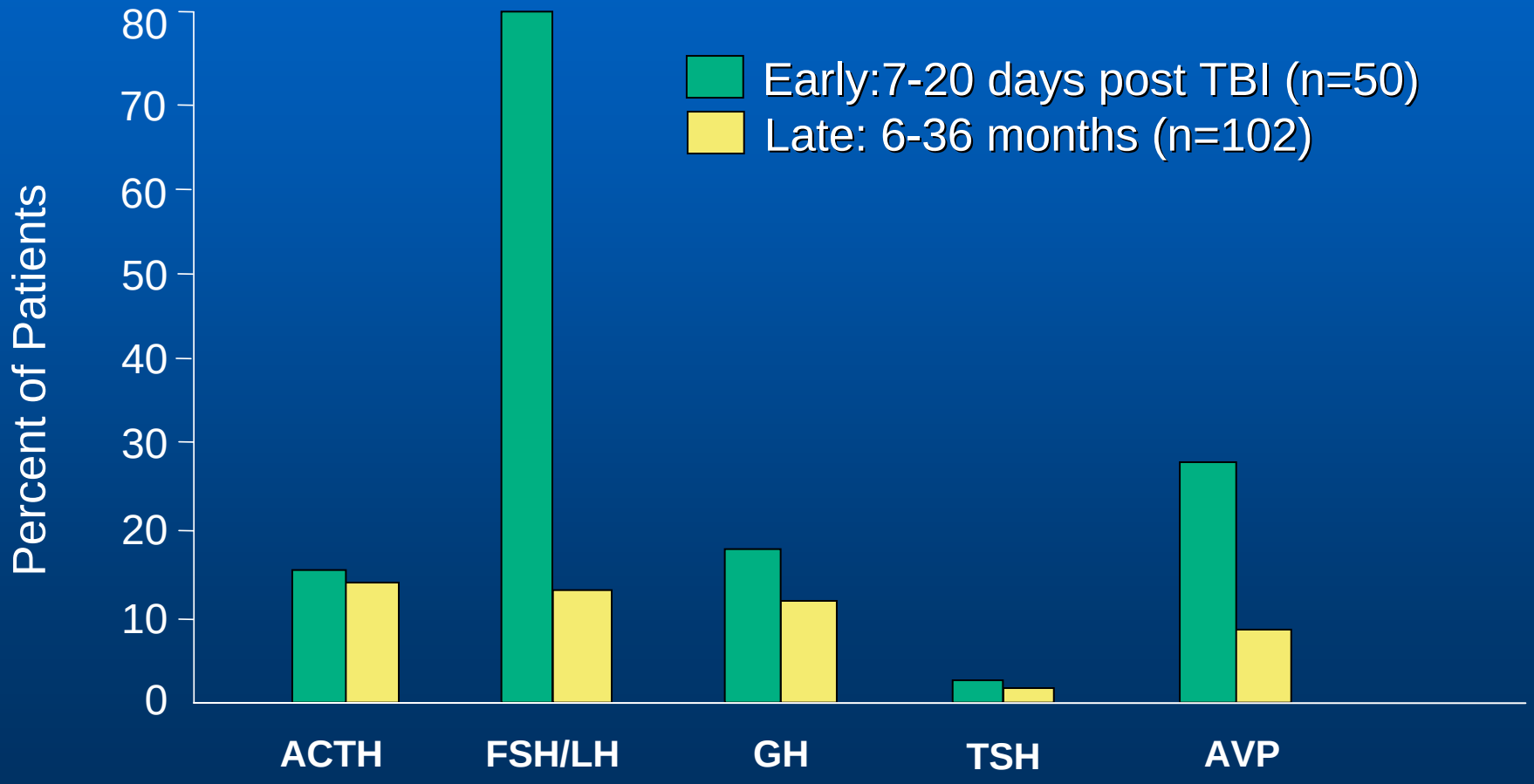
Aimaretti G, et al. Provisionally accepted, *J Clin Endocrinol Metab.* 2005.

Percentage of Single Pituitary Deficits 12 Months after TBI or SAH



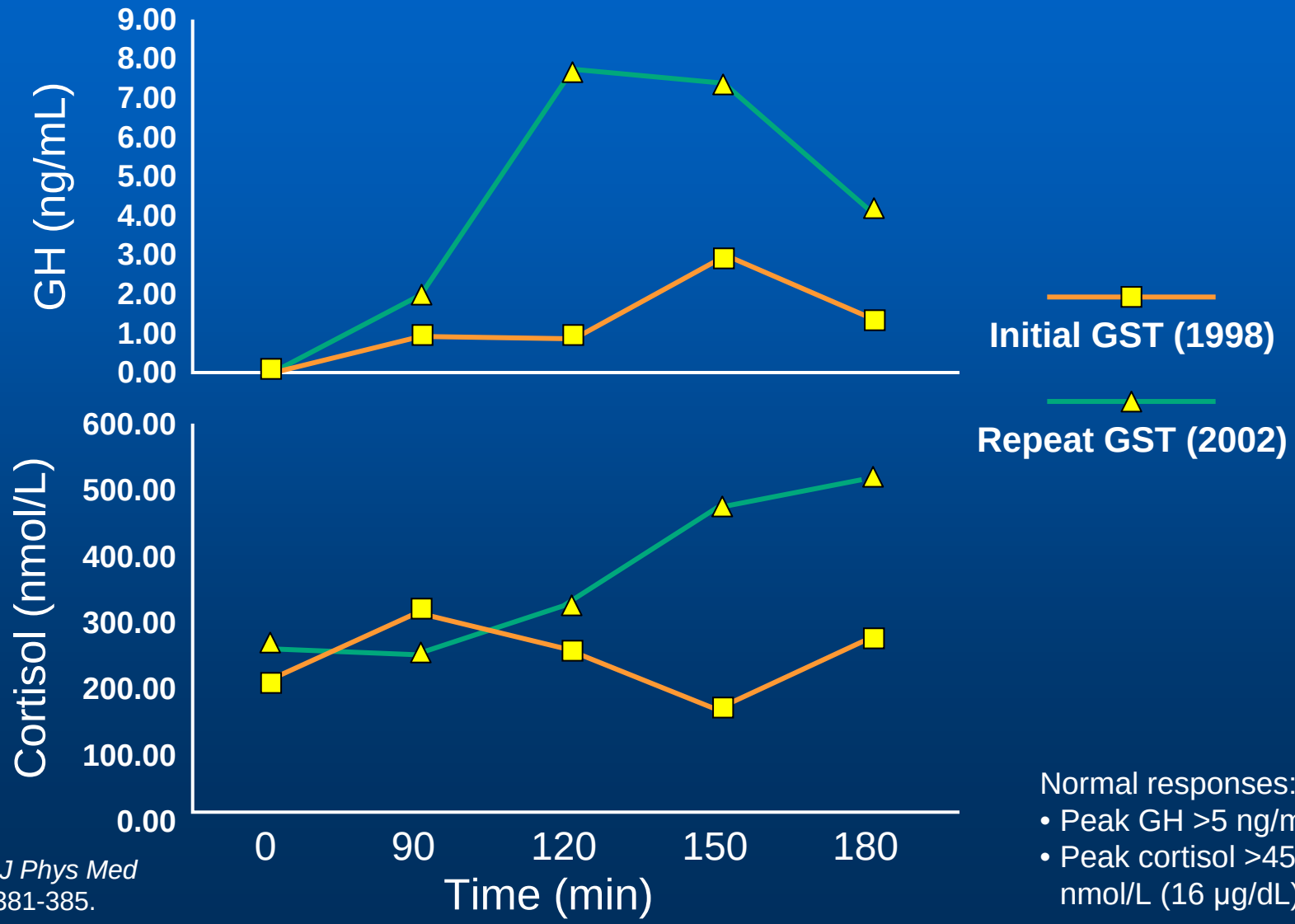
Aimaretti G, et al. Provisionally accepted, *J Clin Endocrinol Metab.* 2005.

Comparison of Pituitary Dysfunction during Early and Late Phases of TBI



Agha A, et al. *Clin Endocrinol*. 2004;60:584-591.
Agha A, et al. *J Clin Endocrinol Metab*. 2004;89:4929-4936.

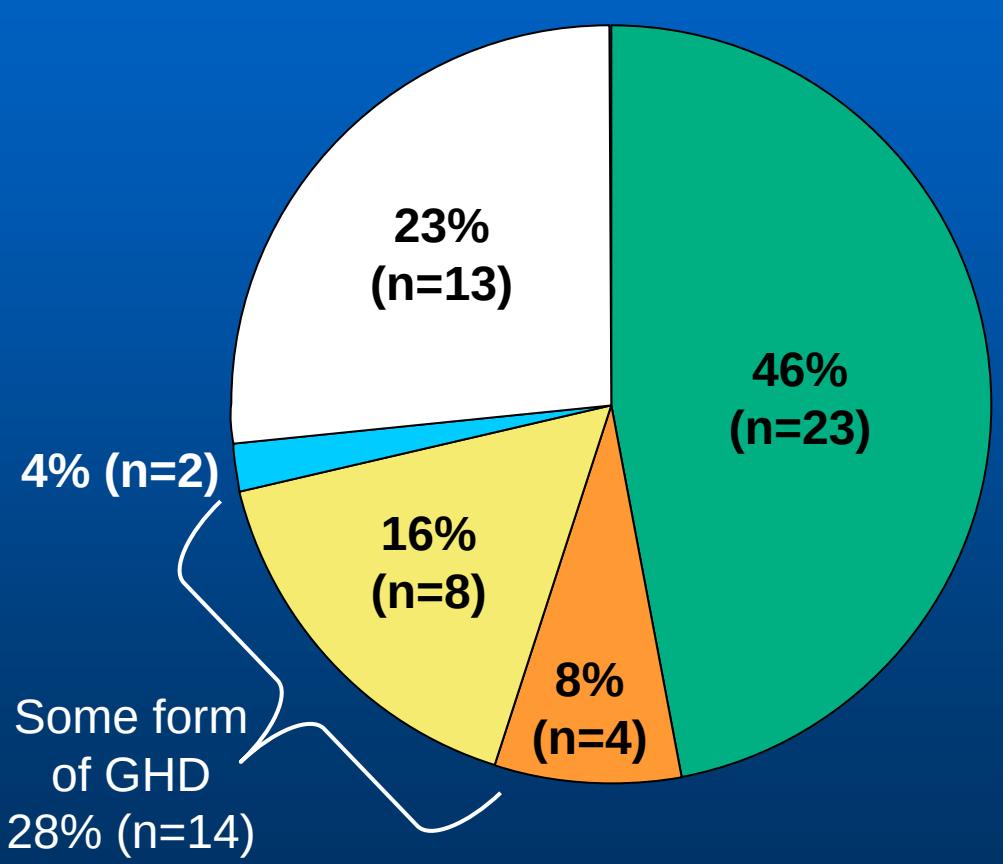
Dynamic GH and Cortisol Responses to Glucagon Stimulation Testing: a Case of Spontaneous Recovery Four Years Post-TBI



Normal responses:
- Peak GH >5 ng/mL
- Peak cortisol >450 nmol/L (16 µg/dL)

Agha A, et al. *Am J Phys Med Rehabil*. 2005;84:381-385.

Pituitary Function in 50 Adult Patients with TBI over 5 Years



- Normal pituitary function
- Severe GHD
- Partial GHD
- Partial GHD + other
- Other pituitary dysfunction

GHRH + ARG test

Partial GHD defined as:

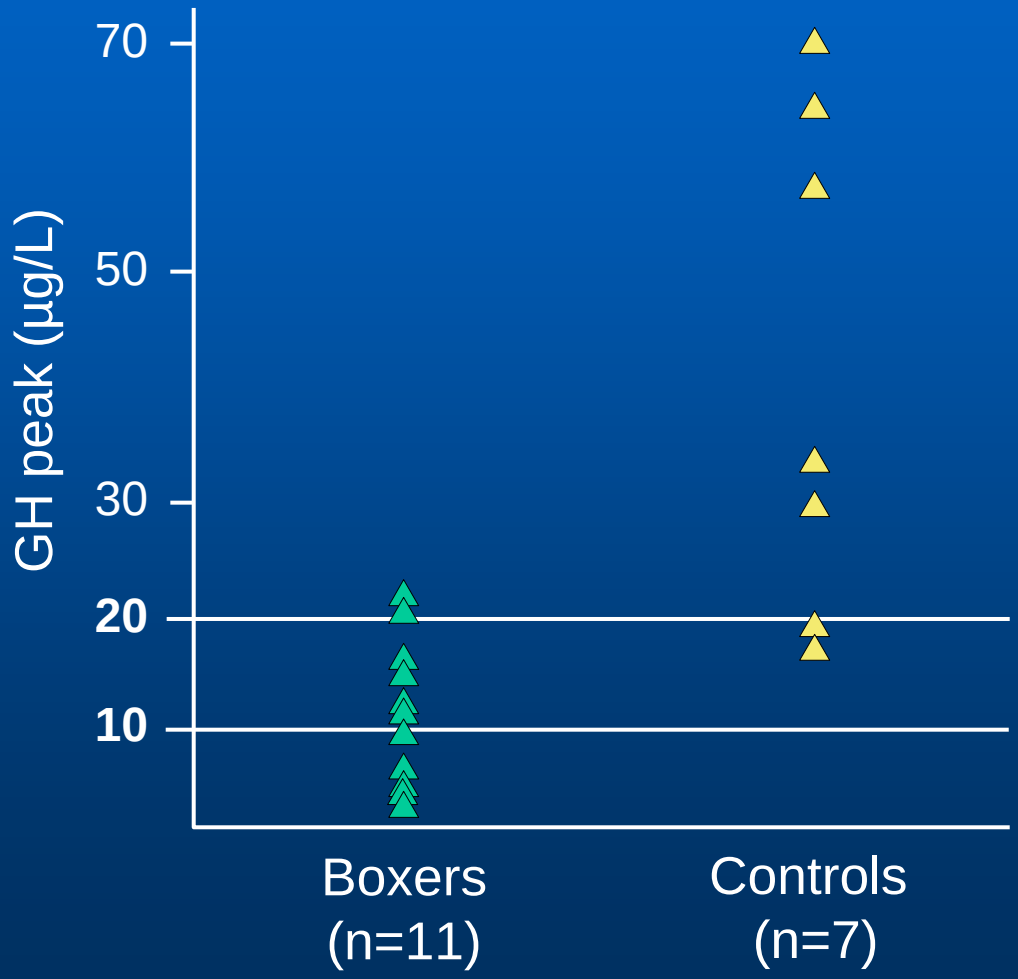
- GH peak 9 µg/L to 16.5 µg/L

Severe GHD defined as:

- GH peak <9 µg/L

Bondanelli M, et al. *J Neurotrauma*. 2004;21:685-696.

Chronic, Repetitive Head Trauma During Boxing Associated with Isolated GHD



- Individual GHRH+GHRP-6 stimulated GH peaks in controls and boxers
- Cut-off peak GH value for GHD was ≤10 µg/L
- Peak GH values ≥20 µg/L were considered normal

Kelestimur F, et al. *J Endocrinol Invest*. 2004;27:RC28-RC32.

Summary of Relevant Data on TBI-mediated Hypopituitarism

Age at trauma (decade most affected)	20–29 years (~35% of the cases)
Most frequent type of trauma	Falls/MVAs in ≥50% of all TBIs
Occurrence of coma/unconsciousness	93%
Most frequent type of anatomical lesions (CT/MRI)	
Hypothalamic hemorrhage	29%
Pituitary posterior lobe hemorrhage	26%
Most frequent pituitary deficits (12 mths post TBI)	
Growth hormone	20%
Gonadotropin	12%
Adrenocorticotropic hormone	7%
Thyroid stimulating hormone	5%

Benvenga S, et al. *J Clin Endocrinol Metab*. 2000;85:1353-1361.
Aimaretti G, et al. Provisionally accepted, *J Clin Endocrinol Metab.* 2005.
Langlois JA, et al. *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths*. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2004.

Summary of Relevant Data on SAH-mediated Hypopituitarism

Age peak (decade most affected)	50–59 years
Most frequent type of aneurysm	Intracranial (85% of SAHs)
Most frequent location of aneurysm*	
Anterior communicating artery	35%
Middle cerebral artery	18%
Internal carotid artery	13%
Posterior communicating artery	13%
Most frequent pituitary deficits (~2 yrs post SAH)	
ACTH	33%
Isolated severe GHD	13%
ACTH + severe GHD	8%
Isolated TSH	3%

*Diagnosis of SAH proven by CT scan/lumbar puncture; location of aneurysm made by four-vessel angiography.

Kreitschmann-Andermahr I, et al. *J Clin Endocrinol Metab*. 2004;89:4986-4992.

Screening and Recommended Therapeutic Options

Who Should Screen Patients?

- Trauma surgeons / neurosurgeons
- Intensive care unit specialists / neurologists
- Rehabilitation physicians
- Endocrinologists / internists
- Primary care physicians

Ghigo E, et al. *Brain Inj*. 2005;19:711-724.

When Should Patients be Screened?

All TBI Patients (regardless of severity)

First visit during hospitalization in Neurosurgery or ICU: Conduct hormonal testing if clinically indicated

3-month evaluation: Conduct baseline hormonal work-up

12-month evaluation: Conduct baseline hormonal work-up

Patients with Moderate or Severe TBI >12 months prior

First visit: Record a detailed patient and family history

Conduct baseline: hormonal work-up in a single session

Ghigo E, et al. *Brain Inj*. 2005;19:711-724.

Routine Basal Hormonal Screening Tests for Posttraumatic Hypopituitarism

Basal Hormone Test	Test Time
Serum cortisol (morning)	**0900 hours**
fT3*, free T_4, thyroid stimulating hormone (TSH)	**0900 hours**
IGF-I	**0900 hours**
Follicle stimulating hormone (FSH), Luteinzing hormone (LH), Testosterone (in men) or 17 βE2 (in women)	**0900 hours**
Prolactin (PRL)	**0900 hours**
Urinary free cortisol (UFC)	**24 hours**
Patients with polyuria: Diuresis, urine density, Na^{++} and plasma osmolality	

*May be omitted per physician discretion.

Ghigo E, et al. *Brain Inj*. 2005;19:711-724.

Summary of Typical GH Provocative Tests

Provocative agent & dosage	Assay times (min)	Response (peak GH)
Insulin tolerance test (ITT)* **0.05-0.15 IU/kg regular insulin IV at 0 min***	**0, +30, +45, +60, +75, +90**	**Normal: >5 µg/L** **Severe deficiency: <3 µg/L**
Glucagon stimulation test **1 mg IM at 0 min**	**0, +90, +120, +150, +180**	**Normal: >5 µg/L** **Severe deficiency: <3 µg/L**
GHRH + Arginine **GHRH: 1 µg/kg IV at 0 min** **Arginine†: 0.5 g/kg (max. dose 30 g)**	**0, +30, +45, +60**	**Normal: >16.5 µg/L** **Severe deficiency: <9 µg/L**
GHRH + GHRP-6 **GHRH: 1 µg/kg IV at 0 min** **GHRP-6: 90 µg in single dose IV at 0 min**	**0, +30, 45, +60, +90**	**Normal: >20 µg/L** **Severe deficiency: <10 µg/L**

*The ITT is contraindicated in patients with CNS pathologies.

†Arginine HCl (30 g in 100 mL) to be administered as infusion over 30 min from 0 to +30 min.

Ghigo E, et al. *Brain Inj*. 2005;19:711-724.

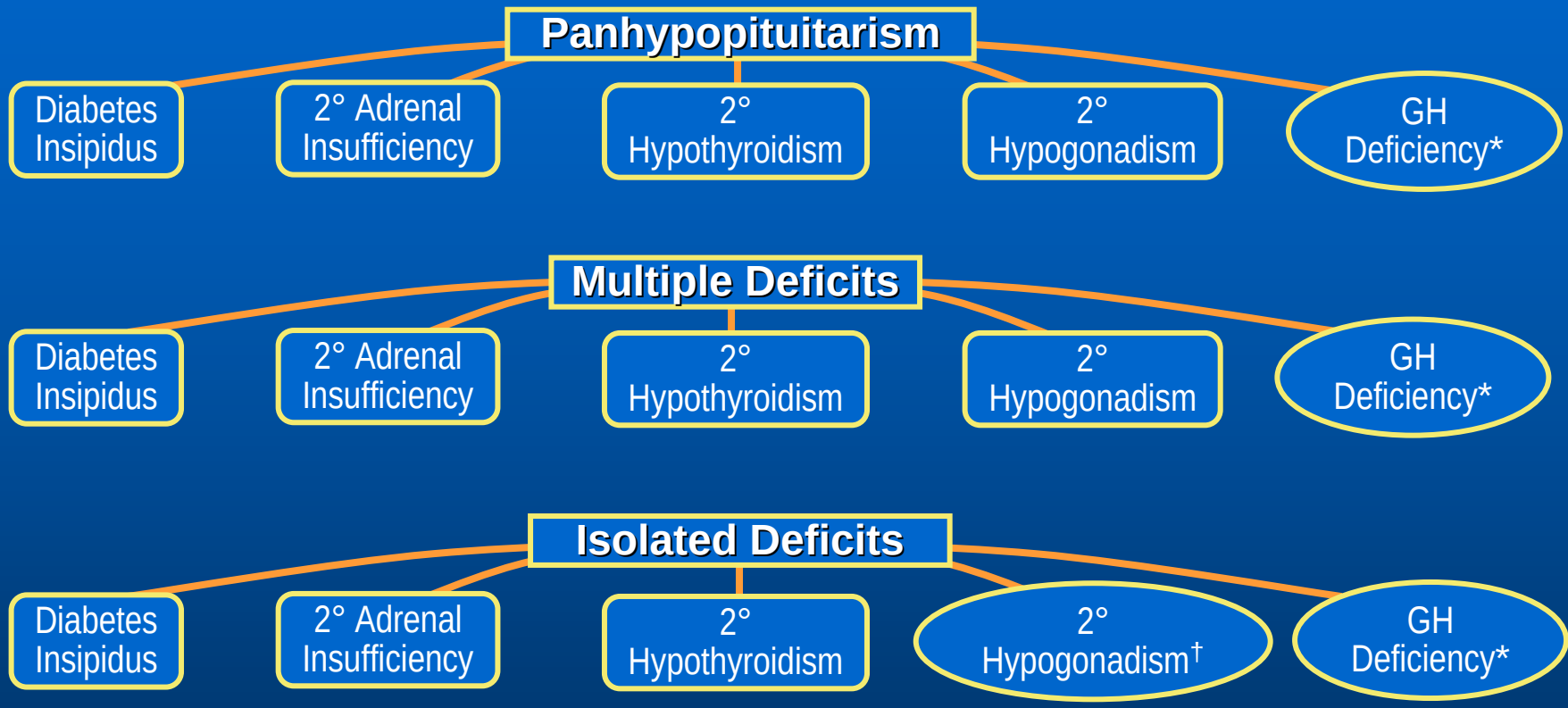
Summary of Typical Provocative Testing of ACTH / Cortisol Reserve

Provocative agent & dosage	Assay times (min)	Response
Insulin tolerance test (ITT)* 0.05-0.15 IU/kg regular insulin IV at 0 min	0, +30, +45, +60, +90, +120	Serum cortisol should rise to >500 nmol/L (>18 µg/dL)
Short Synacthen test (SST) 250 mg Synacthen IM	0, +30, +60	30-min cortisol should rise to at least 550 nmol/L (19.9 µg/dL)
Glucagon stimulation test 1 mg SC (1.5 mg if >90 kg)	-30, 0, +30, +90, +120, +150, +180, +210, +240	Plasma glucose should peak at 90 min; serum cortisol should rise to >500 nmol/(718.1 µg/dL)
Metyrapone test 30 mg/kg PO at 2400 hrs	Between 0800 and 0900 hrs	Normal: 11-desoxycortisol level >200 nmol/L (7µg/dL) Abnormal: 11-desoxycortisol level <200 nmol/L

*The ITT is contraindicated in patients with CNS pathologies.

Ghigo E, et al. *Brain Inj*. 2005;19:711-724.
Drake WM, Trainer PJ. In: Harris PE, et al., eds. *Endocrinology in Clinical Practice*. United Kingdom: Martin Dunitz Ltd, 2003;487-498.

Recommended Therapeutic Options for Patients Less Than One Year Post-injury Based on Type of Deficit



Note: These indications do not rule out any hormone replacement therapy (HRT) when definitely indicated.

*Replacement of other hormonal deficits can restore normal GH response to provocative testing; thus, GH deficiency needs to be confirmed after appropriate replacement of other hormone deficiencies.

†Isolated insufficiency of the gonadal axis could reflect functional stress-induced impairment and be transient. Patients should be retested before HRT is initiated.

Replace immediately

Replace as appropriate

Adapted from Ghigo E, et al. *Brain Inj*. 2005;19:711-724.

Which Patients Should Undergo Further Follow-up before Initiating HRT?

Patients with:

- Total hypopituitarism or multiple deficits including severe GH deficiency
- Isolated pituitary deficit of severe GH deficiency
- Isolated, secondary hypogonadism

Ghigo E, et al. *Brain Inj*. 2005;19:711-724.

Treatment and Management of Endocrine Sequelae

Symptoms of Hypopituitarism Often Mimic Sequelae of TBI or SAH

Hormone	Symptoms of Deficiency
• GH	• Abnormal body composition (decreased lean body mass, increased abdominal adiposity), dyslipidemia, reduced strength and exercise capacity, impaired psychological well-being, fatigue, osteoporosis
• TSH	• Fatigue, myopathy, weakness, decreased cognitive function, decreased libido, depression, irritability, menstrual irregularity
• ACTH / cortisol	• Hypotension, fatigue, weakness, weight loss, anorexia, inability to respond to stress, mood disorders, decreased memory
• FSH / LH	• Menstrual irregularity, decreased libido, impotence, infertility, decreased bone/muscle mass, fatigue, depression
• ADH	• Dehydration, polyuria

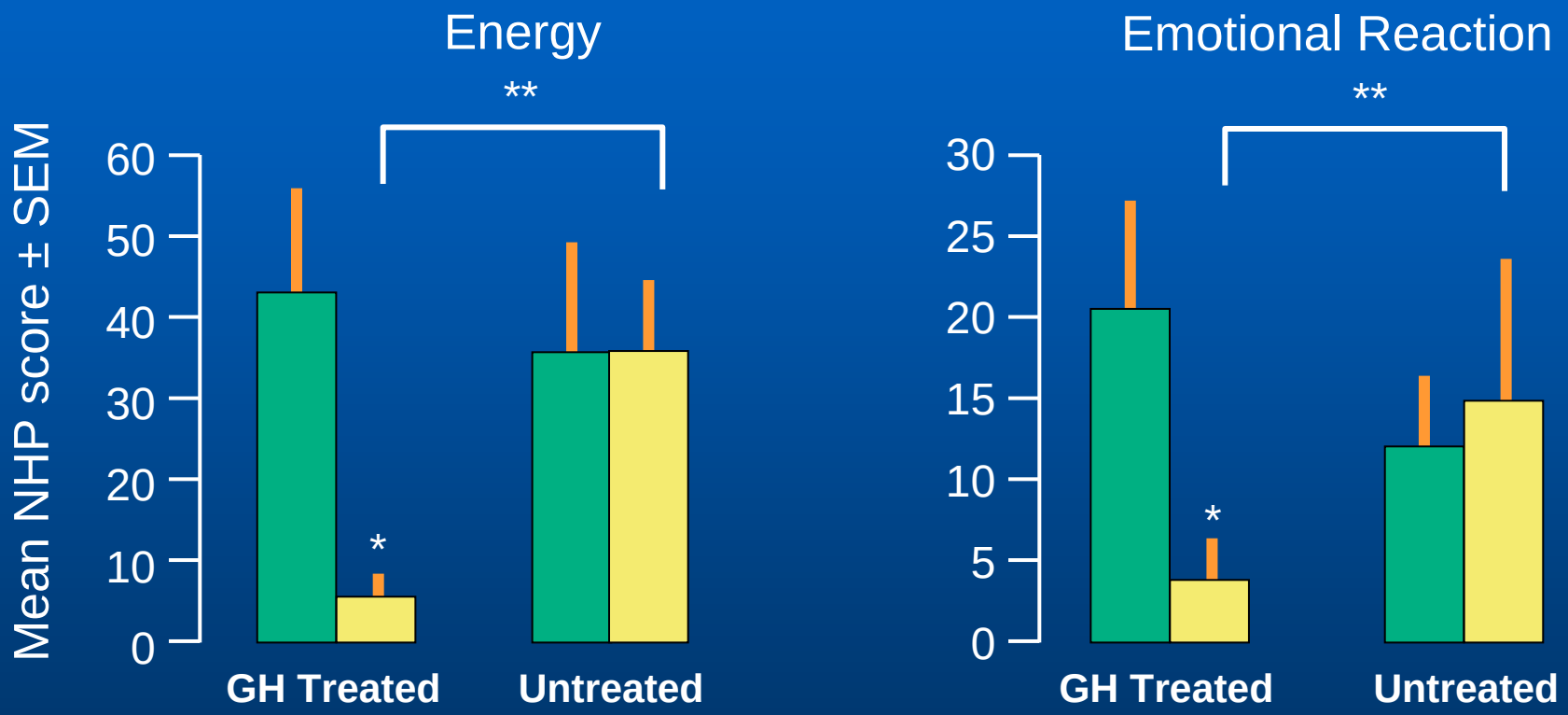
Elovic E. *J Head Trauma Rehabil*. 2003;18:541-543.
Ghigo E, et al. *Brain Inj*. 2005;19:711-724.

Similarities between Neurobehavioral and Quality of Life Complaints among TBI and GH-Deficient Patients

Deficit	Moderate to Severe TBI	Adult GHD
Neurobehavioral complaints		
Memory impairment	Yes	Yes
Concentration impairment	Yes	Yes
Decreased IQ	Yes	Yes
Impaired judgment / problem solving	Yes	No
Poor organizational skills	Yes	No
Poor exercise tolerance	No	Yes
Decreased muscle strength	No	Yes
Decreased quality of life		
Fatigue	Yes	Yes
Anxiety	Yes	Yes
Depression	Yes	Yes
Social isolation	Yes	Yes
Deterioration in sex life	Yes	Yes
Increased unemployment	Yes	Yes

Lieberman SA, et al. *J Clin Endocrinol Metab.* 2001;86:2752-2756.
Lieberman SA, Hoffman AR. *J Pediatr*. 1996;128:S58-S60.
Carroll PV, et al. *J Clin Endocrinol Metab.* 1998;83:382-395.

10-Year Effect of GH Treatment on Quality of Life



*, *P*<0.02 vs baseline; **, *P*<0.02 between groups
NHP=Nottingham Health Profile
Note: higher scores reflect poorer quality of life

Gibney J, et al. *J Clin Endcrinol Metab.* 1999;84:2596-2602.

Neuropsychological and Psychiatric Variables that Correlate with Peak GH Response*

	Linear regression analyses		Multiple linear regression analyses	
Dependent Variable	Predictor	*P*	Predictor	*P*
Immediate free recall	Sex	0.011	Sex	0.028
	GH peak	0.017	Peak GH	0.044
Delayed free recall	Sex	0.032		
	GCS	0.032	GCS	0.032
	GH peak	0.040		
Somatization	Age	0.006	Age	0.006
	Peak GH	0.040		
Paranoid ideation	Time from trauma	0.039		
	Peak GH	0.030	Peak GH	0.030

*GHRH + GHRP-6 provocation test utilized.

Popovic V, et al. *J Endocrinol Invest*. 2004;27:1048-1054.

GH Replacement Therapy in Adults with TBI-mediated GH Deficiency

- Patients from KIMS
  - 51 patients with GH deficiency resulting from TBI
  - 688 patients with GH deficiency resulting from a non-functioning pituitary adenoma (NFPA)

- Patients with TBI-related GH deficiency
  - Were younger at study entry, at pituitary disease onset, and at GH deficiency diagnosis; however, treatment was notably delayed
  - Were significantly shorter (167.2 cm ± 1.7 cm) and had lower GH reserves than those with NFPA

Casanueva FF, et al. *Arch Phys Med Rehabil*. 2005;86:463-468.

Adults with TBI-mediated GH Deficiency Benefit from GH Replacement Therapy

- Cohorts included patients that were GH-naive before entering KIMS
  - A total of 15 patients with TBI and 125 patients with NFPA were studied
  - Patients of matched cohorts were analyzed before and after one year of rhGH therapy
- TBI group
  - After one year of treatment, significant improvement seen in IGF-I SD scores
  - Required higher maintenance dose of GH
- NFPA group
  - After one year of treatment, improvements included reduced body fat mass, reduced total and LDL cholesterol, increased lean body mass, increased blood glucose, and favorable QoL-AGHDA scores

Casanueva FF, et al. *Arch Phys Med Rehabil*. 2005;86:463-468.

Outcomes Following rhGH Treatment in GH-Deficient Patients

- Improved lipid profile
  - Decreases total cholesterol, LDL-C, and apolipoprotein (ApoB) levels; increases HDL-C
- Increased bone mineral density/bone metabolism
  - Stimulates bone formation leading to net gain in bone mass after 12-24 months of treatment
- Improved body composition
  - Increases lean body mass and total body/extracellular water; reduces fat mass, especially in the abdominal region
- Enhanced exercise performance
  - Significantly improves exercise capacity and maximum oxygen uptake after 6 months of therapy
- Enriched cardiovascular health
  - Increases left ventricular mass, stroke volume, and cardiac output; reduces peripheral vascular resistance after 6 months of treatment
- Enriched sense of well-being and quality of life
  - Reduced sense of social isolation and improved emotional stability

Carroll PV, et al. *J Clin Endocrinol Metab*. 1998;83:382-395.

Hormone Replacement Therapy in Adults with TBI-mediated Deficiencies

Syndrome	Treatment	Monitoring Therapy
Hypothyroidism	Levothyroxine	Easily monitored; effective therapy may alleviate fatigue and improve cognitive function including initiation, lethargy, decreases in memory and dementia in the elderly
Secondary Hypoadrenalism	Hydrocortisone	Monitoring of dosing is subjective with no objective criteria; clinicians use weight, BP, and how patient feels to monitor effectiveness; therapy may alleviate fatigue, weakness, inability to respond to stress
Hypogonadism	GnRH Bromocriptine Testosterone Estrogen	Issues of fertility need to be differentiated from issues that simply require testosterone, such as decreased energy/muscle mass/libido, fatigue, depressed affect; administration of GnRH is normal treatment for FSH/LH deficiency and facilitates spermatogenesis
Growth Hormone Deficiency	rhGH	IGF-I and stimulation challenge used to assess GH levels; GHD is associated with increased mortality; effective therapy may return mortality risk to normal

Elovic E. *J Head Trauma Rehabil*. 2003;18:541-543.
Elovic E. *J Head Trauma Rehabil*. 2004;19:184-187.

Assessing the Efficacy of Hormonal Replacement

- Any assessment of the efficacy of HRT should be done in collaboration with an endocrinologist and according to the classical guidelines for hypopituitary deficiencies
- Suggested possible measures:
  - Fatigue: Fatigue Severity Scale (MFI 20) using a Visual Analog Scale
  - Emotion: Neurologic Changes of Personality Inventory (NECHAPI) and Visual Analog Mood Scale
  - Cognition: Digit Vigilance Task; CogState™
  - QoL: Assessment of GH Deficiency in Adults (AGHDA)

Ghigo E, et al. *Brain Inj*. 2005;19:711-724.

Conclusions

- Posttraumatic hypopituitarism occurs frequently, and is under-diagnosed and under-treated
- Hormonal deficits may significantly contribute to the chronic disability of TBI and its physical, cognitive, health, and social sequelae
- Subjects at highest risk of hypopituitarism appear to be those with moderate-to-severe head trauma
- Timely diagnosis of children and adolescents with posttraumatic hypopituitarism is critical since the burden of disease on their development may be extensive
- In addition to conventional pituitary hormone replacement, the potential of GH treatment to enhance patient recovery can be anticipated based on results seen in adult patients with GH deficiency due to other etiologies

Casanueva FF, et al. *J Endocrinol Invest*. 2004;27:793-795.
Popovic V, et al. *GH IGF-I Res*. 2005;15:177-184.

VERONA 26-28 OTTOBRE 2006

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GHD in Adults. An Update at 15-yrs from the Beginning

GHD in Brain Injury

Massimo Marchetti

Medicina Interna – Ospedale " San Bassiano" Bassano del Grappa

GHD in Brain Injury

There are conditions at obvious risk (primary Hyphotalamic-Pituitary diseases, radioterapy, neurosurgery) to develop hypopituitarism but for the fragility of the infundibular-hypothalamic structures would be other pathological conditions of the CNS that can develop hypopituitarism , such as:

Traumatic Brain Injury (TBI)

Subarachnoid Haemorrhage (SAH)

Primary Brain Tumours (pBT)

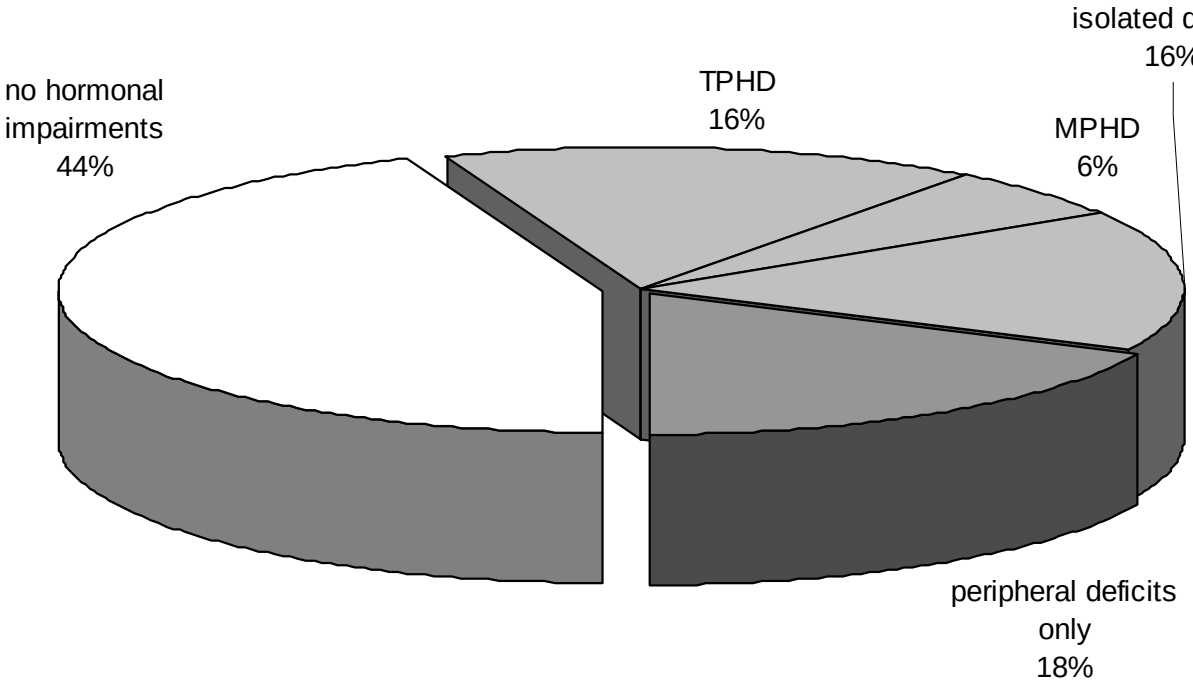
Table 1 Aetiology of GHD in 1034 hypopituitary adult patients

Cause	%
Pituitary tumour	53.9
Craniopharyngioma	12.3
Idiopathic	10.2
CNS tumour	4.4
Empty sella syndrome	4.2
Sheehan's syndrome	3.1
Head trauma	2.4
Hypophysitis	1.6
Surgery other than for pituitary treatment	1.5
Granulomatous diseases	1.3
Irradiation other than for pituitary treatment	1.1
CNS malformation	1.0
Perinatal trauma or infection	0.5
Other	2.5

Abs et al. 1999

Endocrine dysfunction in patients operated on for non-pituitary intracranial tumors

H J Schneider, S Rovere, G Corneli1, C G Croce, V Gasco1, R Rudà, S Grottoli, G K Stalla, R Soffietti, E Ghigo and G Aimaretti



TPHD: Total pituitary hormone deficit; MPHD: multiple pituitary hormone deficit.

The most common pituitary deficits were, in decreasing order: LH/FSH 29.4%, GH 27.9%,

Hypopituitarism frequently occurs after NS for intracranial tumors. Also, exposure of these patients to CT and/or RT is frequently associated with peripheral endocrinopathies. Thus, endocrine evaluation and follow-up of patients treated for intracranial tumors should be performed on a regular basis.

Epidemiology of Traumatic Brain Injury and Aneurysmal Subarachnoid Hemorrhage

TBI: Worldwide Incidence and Mortality Rates (all ages)

Continent	Place of Study	Annual Admission Rate (cases/100,000)	Annual Mortality Rate (cases/100,000)	Case Fatality Rate (%)
Asia	Taiwan[R]	>200*	31-37**	17.3
Africa	Johannesburg[P]	316	81	25.6
Australia	So. Australia[R]	322	7	7.2
Europe	England and Wales[R]	270	10	3.7
	Scotland	313	10	3.2
	France[P]	281	22	7.8
	Spain[P]	91	20	21.9
	Northern Norway[R]	169	NR	NR
	Italy	314	--	--
	Romagna[P]	297	7.7	2.6
	Trentino[R]	332	2.1†	0.6†

R = Retrospective, P = Prospective, NR = Not Recorded.

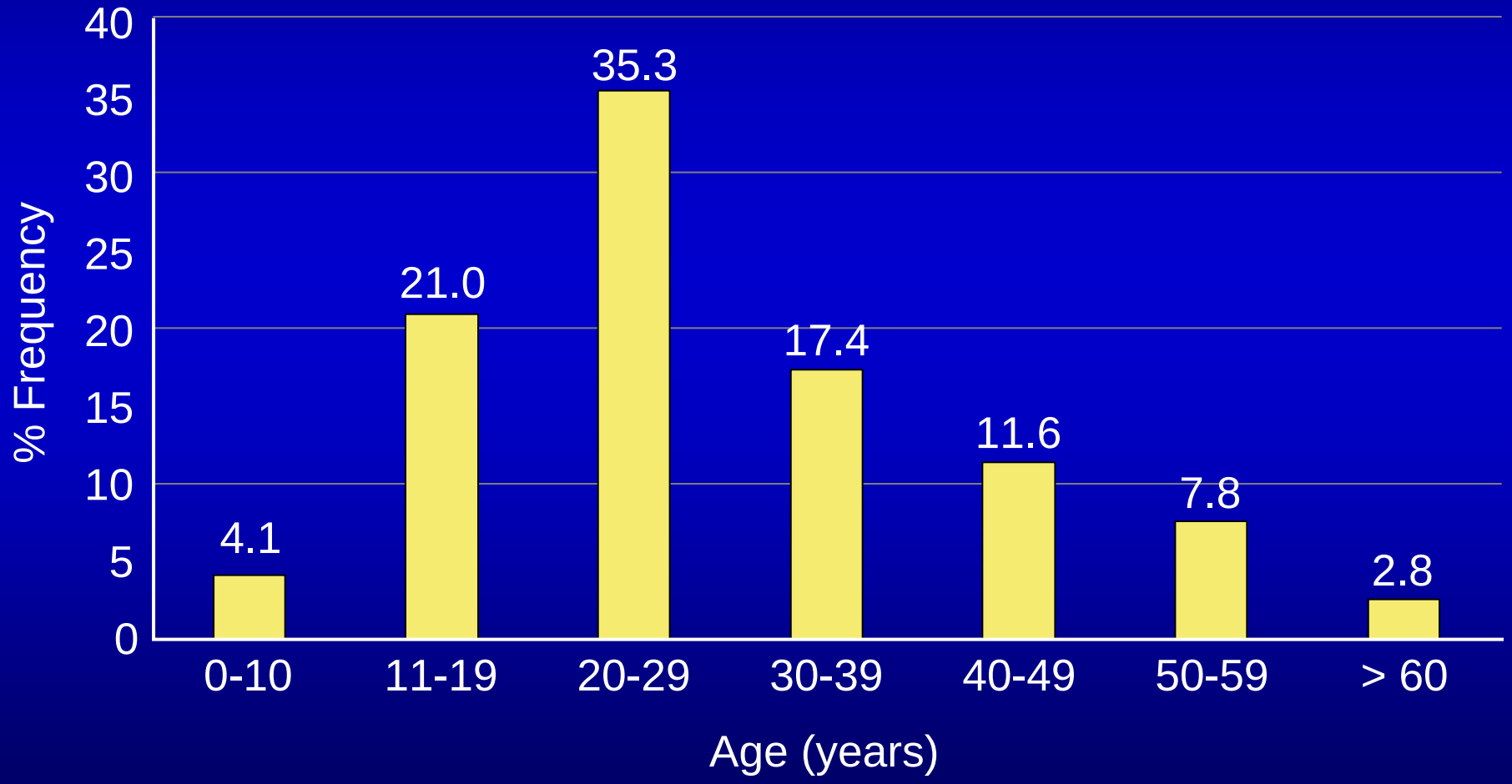
* Incidence higher than in North America due to type of traffic (mainly motorcycles) and lack of safety measures.

** Refers to road traffic accidents (National Health Statistics of Taiwan).

† Relative value due to lack of neurosurgery unit in this area.

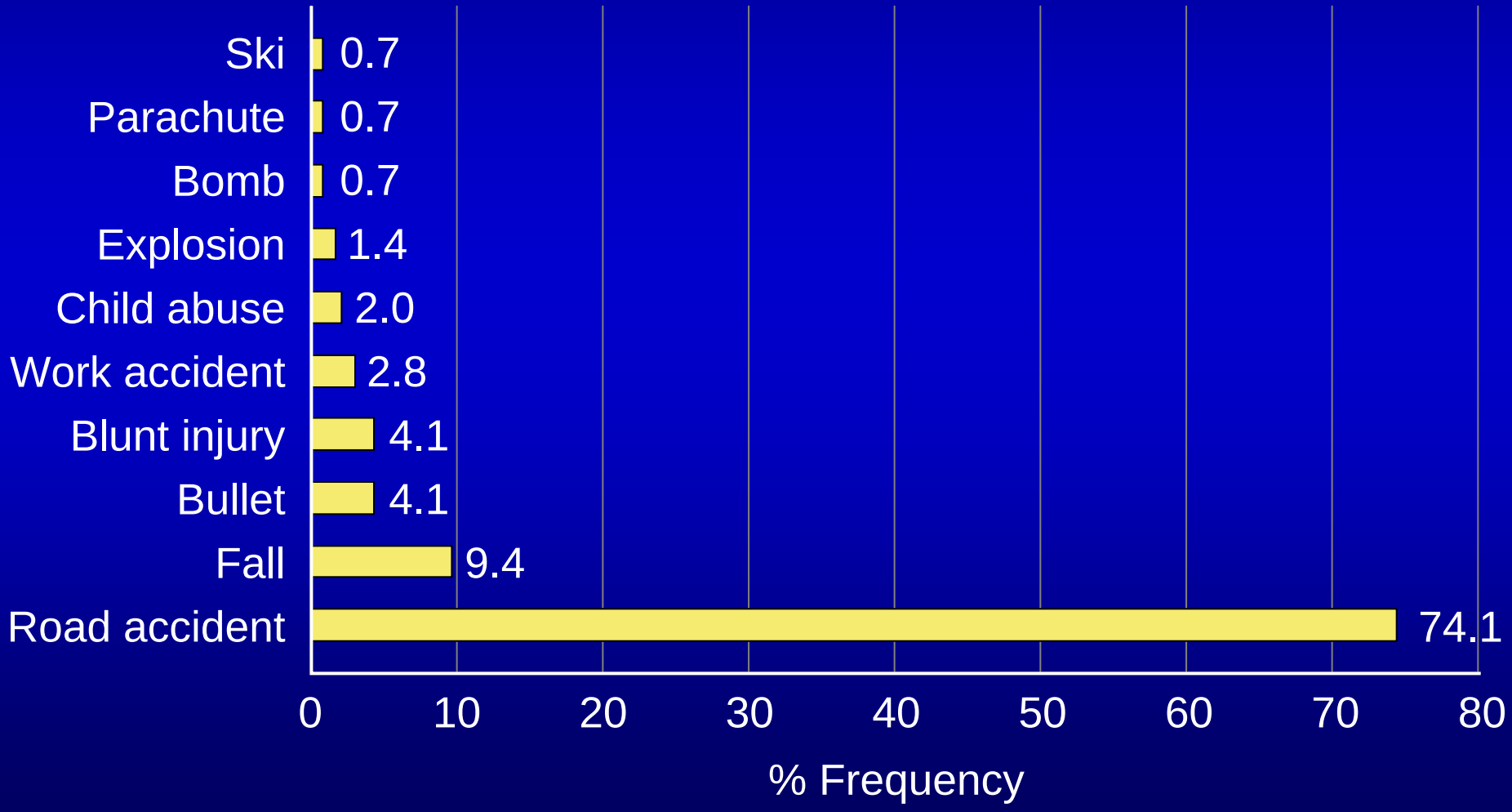
Servadei F, et al. *Neuroepidemiology*. 2002;21:297-304.

Prevalence of Age at the Time of TBI (n=218)



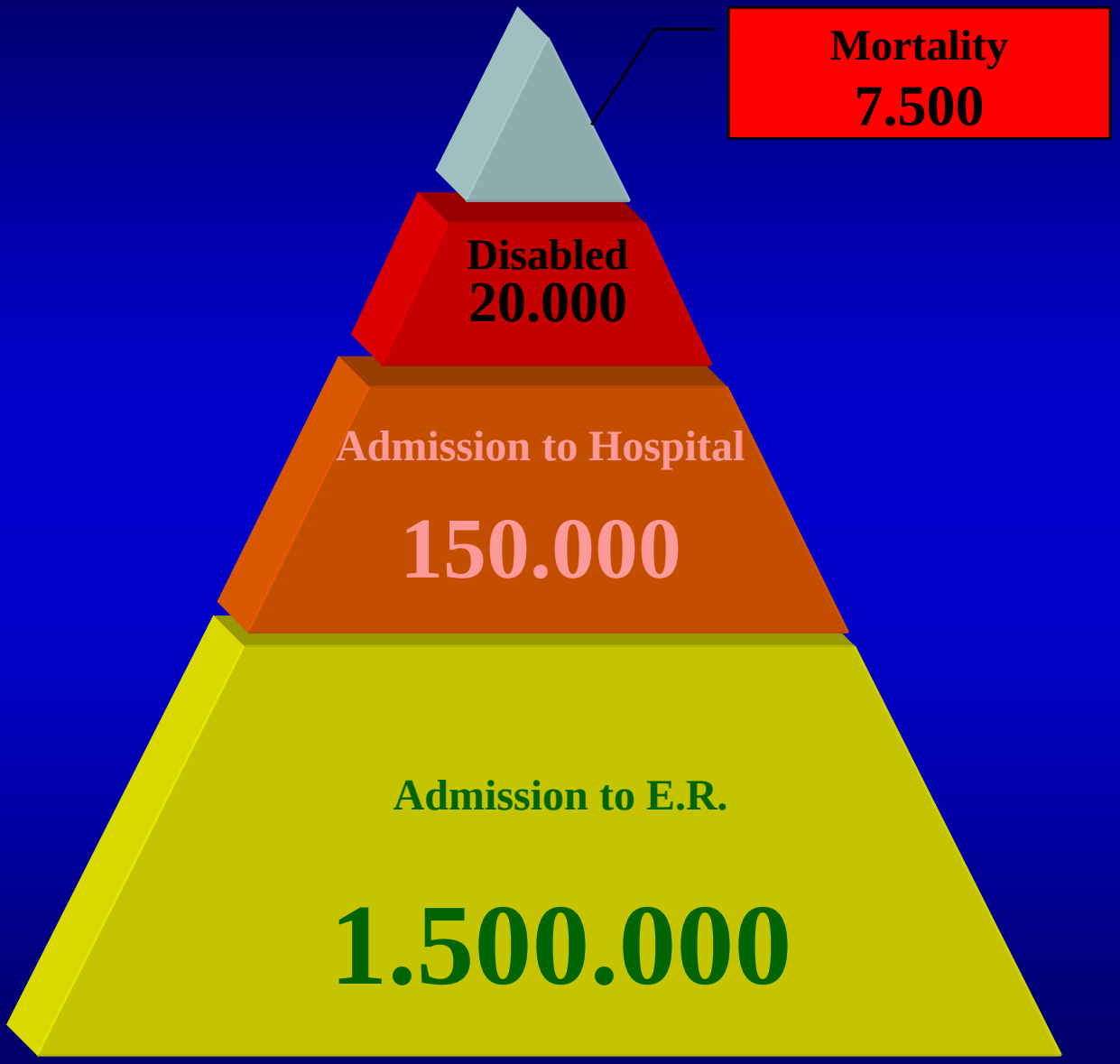
Benvenga S, et al. *J Clin Endocrinol Metab*. 2000;85:1353-1361.

Frequency of Accidents Resulting in TBI in Adults from 1970 to 1998 (n=147)



Benvenga S, et al. *J Clin Endocrinol Metab*. 2000;85:1353-1361.

Road accidents : Italy 2003



First cause of death
(Europe, 1999)

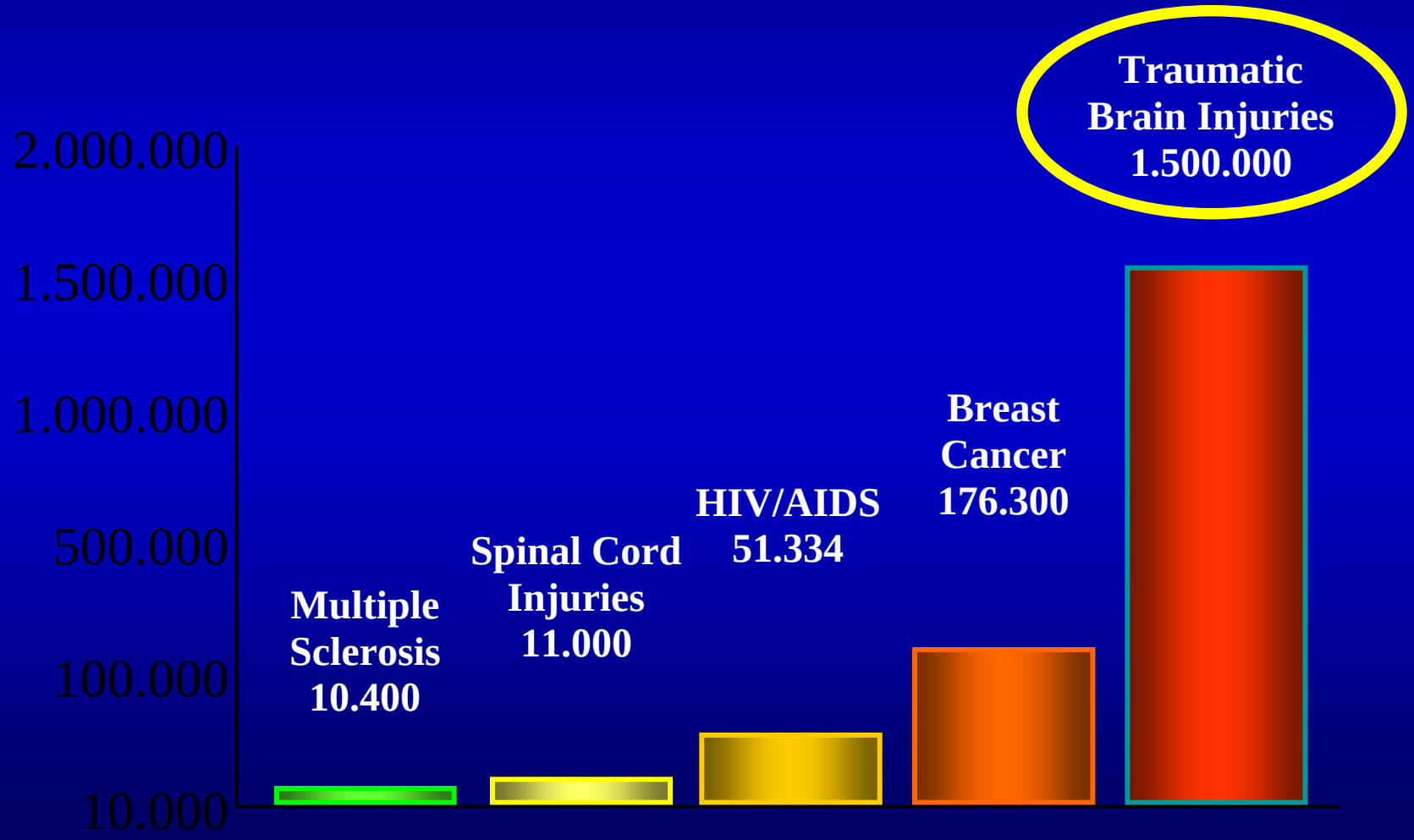
- 0-4 years : Perinatal Diseases
- 5-44 years : Road Traffic Accidents (> 65% brain injuries)
- >45 years : Cardiac Ischemia

"Clinical research in trauma and more specifically in head injury has received in Europe less founding than any other kind of human misery…"

Roberts I., BMJ, 2000

Comparison of Annual Incidence

(Data compiled and arranged by the Brain Injury Association of America based on data from the Centers for Disease Control and Prevention, American Cancer Society, and National Multiple Sclerosis Society)



Epidemiology of Aneurysmal Subarachnoid Hemorrhage (SAH)

- Annual incidence
  - US: 6-25 per 100,000
  - Internationally: varying incidences reported (2-49 per 100,000)
- Age peak in the sixth decade (ages 50 to 59 yrs)
- Ruptured intracranial aneurysms account for 85% of all spontaneous subarachnoid hemorrhages
  - In the US, >27,000 ruptured intracranial aneurysms occur annually
  - Risk factors: familial predisposition, smoking, hypertension, and heavy drinking

Kreitschmann-Andermahr I, et al. *J Clin Endocrinol Metab*. 2004;89:4986-4992.
Kazzi AA, Ellis K. *Subarachnoid Hemorrhage*. Available at: http://www.emedicine.com/EMERG/topic559.htm. Accessed 16 Jun 2005.

Deaths from SAH

- Mortality due to SAH
  - Approximately 10% to 15% of patients die before reaching the hospital
  - Mortality rates are as high as 40% during the first week after SAH
  - Half of patients die within the first six months
- Morbidity/mortality rates increase with age and poorer overall health
- Advances in the management of SAH have resulted in a greater than 25% reduction in mortality rate; however, more than one-third of patients are left with major neurological deficits

Kazzi AA, Ellis K. *Subarachnoid Hemorrhage*. Available at: http://www.emedicine.com/EMERG/topic559.htm. Accessed 16 Jun 2005.

Glasgow Coma Scale (GCS)

Grade	Loss Of Consciousness	Score Range	Posttraumatic Amnesia (PTA) Duration
MILD	None	13 to 15	5 min – 1 hr
MODERATE	Unconscious	9 to 12	< 24 hours
SEVERE	Coma	8 to 6	≥ 24 hours
VERY SEVERE	Coma	5	> 4 weeks
EXTREMELY SEVERE	Coma	Below 5	> 4 weeks

Evaluation of Severity of TBI

Glasgow Coma Scale (GCS)

GCS defines severity of TBI within 48 hours of injury

Eye opening

Spontaneous = 4
To speech = 3
To painful stimulation = 2
No response = 1

Verbal response

Oriented to person, place, and date = 5
Converses but is disoriented = 4
Says inappropriate words = 3
Says incomprehensible sounds = 2
No response = 1

Motor response

Follows commands = 6
Makes localizing movements to pain = 5
Makes withdrawal movements to pain = 4
Flexor (decorticate) posturing to pain = 3
Extensor (decerebrate) posturing to pain = 2
No response = 1

Physical Sequelae of TBI

- Fractures
- Paralysis
- Hemiparesis
- Pain
- Fatigue
- Sleep disturbances
- Faintness
- Loss of libido
- Impotence
- Disorders of movement (gaiting, ataxia, spasticity, tremors)
- Damage to pituitary gland/hypothalamus
- Headaches
- Visual disturbances
- Photosensitivity
- Seizures / epilepsy
- Dysphagia / aphagia
- Loss of smell / taste
- Speech impairment
- Brain swelling
- Hematoma
- Weight loss

Cognitive Sequelae of TBI

- Problems with
  - Attention
  - Concentration
  - Perception
  - Orientation
  - Memory
  - Comprehension
  - Communication
  - Reasoning
  - Problem solving
  - Judgment
  - Initiation
  - Planning
  - Self-monitoring
  - Awareness
  - Visual spatial processing
  - Executive functioning

- Repeated mild brain injuries occurring over an extended period of time (e.g., months, years) can results in cumulative neurological and cognitive deficits
  - e.g., sports injuries during football, boxing, soccer

Psychosocial Sequelae of TBI

Decreased sense of well-being including:

- Deficits in general health
- Depression
- Anxiety
- Phobias
- Psychoses
- Suicidal ideation
- Paranoia
- Aggression
- Compromised independent living skills
- Interpersonal alienation
- Diminished coping skills
- Decreased vitality
- Stunted personal development
- Inappropriate sexual behavior
- Emotional disinhibition
- Substance abuse
- Violent tendencies

Masel BE, et al. *GH IGF-I Res*. 2004;14:S108-S113. Popovic V, et al. *J Endocrinol Invest*. 2004;27:1048-1054. Lieberman SA, et al. *J Clin Endocrinol Metab.* 2001;86:2752-2756. Cicerone KD, et al. *Arch Phys Med Rehabil*. 2000;81;1596-1615. Simpson G, et al. *J Head Trauma Rehabil.* 1999;14:567-580.

Endocrine Aspects of Traumatic Brain Injury and Aneurysmal Subarachnoid Hemorrhage

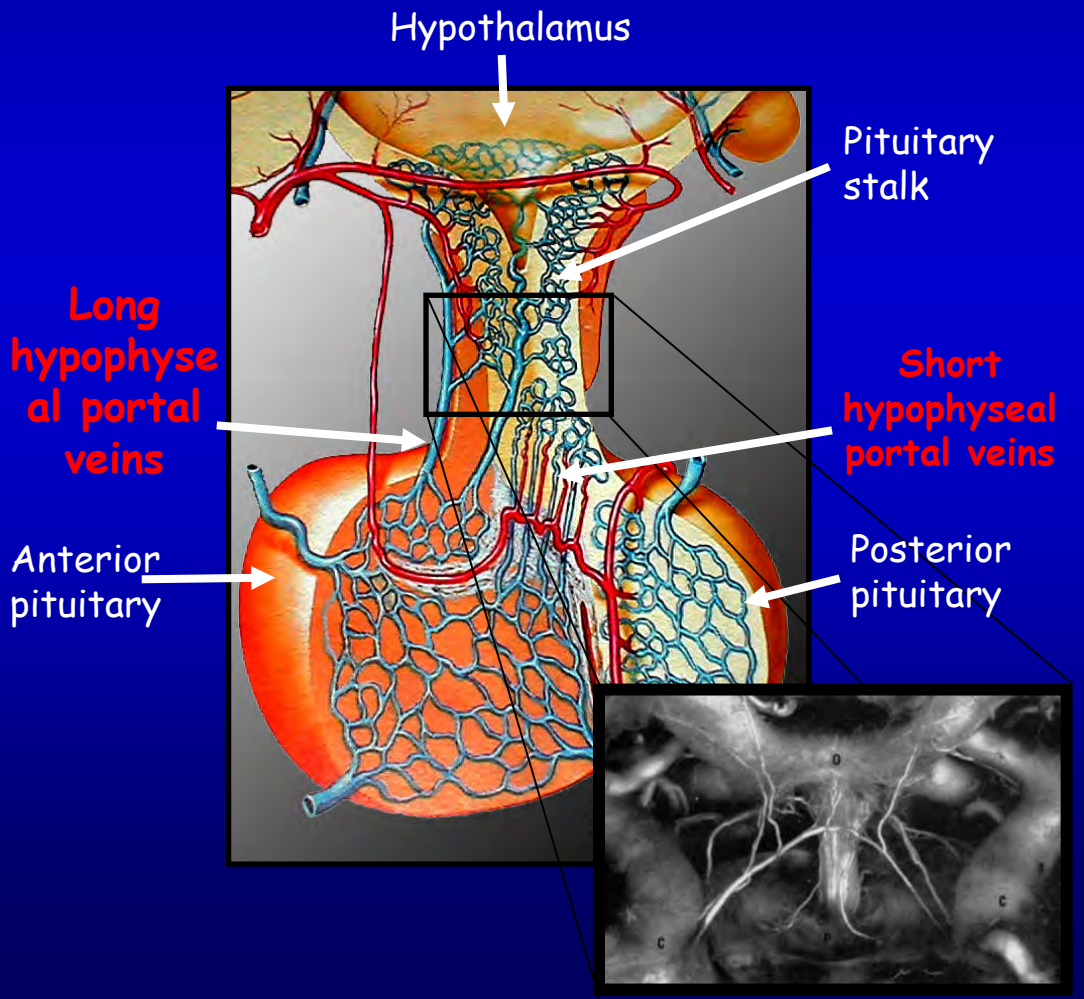
Historical Background of Hypopituitarism in TBI

- Simmonds (1914)
  - Described pathological hypophyseal cachexia
- Cyran (1918)
  - Reported first case of posttraumatic hypopituitarism
- Escamilla and Lisser (1942)
  - Published study, literature review of pathological hypopituitarism
- Edwards and Clark (1986)
  - Reviewed literature and reported on 53 patients
- Benvenga, et al. (2000)
  - Literature review revealed 367 cases of posttraumatic hypopituitarism

Masel BE, et al. *GH IGF-I Res*. 2004;14:S108-S113.

Pathophysiology of Hypothalamic-Pituitary Vulnerability

- Sites of injury
  - Hypothalamus
  - Stalk
  - Pituitary gland
- Types of injury
  - Direct trauma
  - Vascular insults
    - Brain swelling / ICP
    - Vasospasm
    - Hemorrhage
    - Hypotension / hypoxia
    - Pituitary swelling
    - Infarction
    - Ischemia



Kelly DF, et al. *J Neurosurg*. 2000;93:743-752.

Pituitary Damage by Trauma Associated with Fatal Head Injury

Ceballos (1966) and Kornblum (1969); n = 202

• Normal	26%
• Capsular hemorrhage	59%
• Posterior lobe hemorrhage	31%
• Anterior lobe necrosis	22%
• Stalk necrosis	3%
• Stalk laceration	0.5%

Hypothalamic Damage by Trauma in Fatal Head Injury

Crompton (1971); n = 106

42%

micro-hemorrhages in 31 and/or ischemic lesions in 26

Hierarchy of Vulnerability of the Pituitary During Trauma

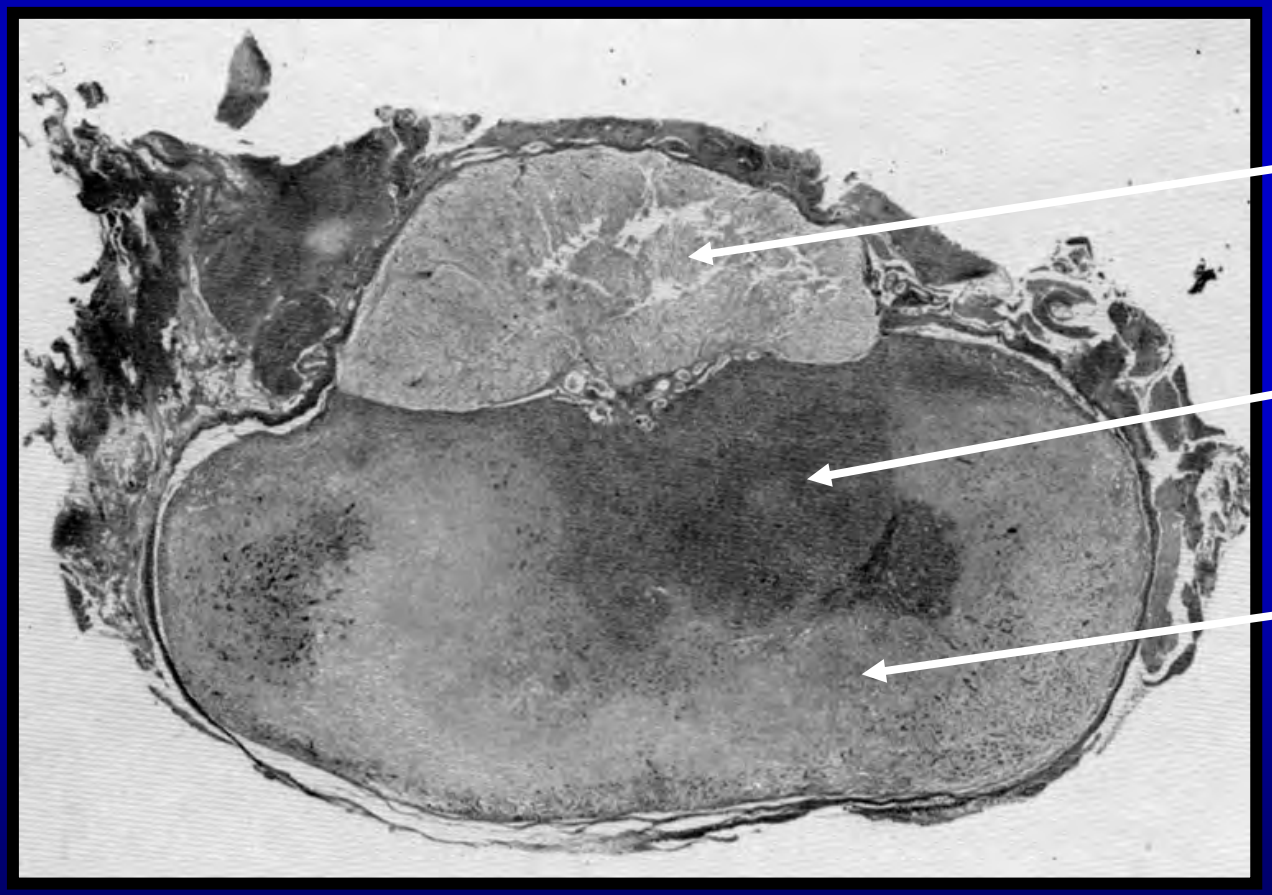
- **GH** and **gonadotrophs** are the most vulnerable
  - Due to location in the wings of the pituitary gland and the fact that the vascular supply and oxygen they receive from the long hypophyseal pituitary portal vessels

- Corticotrophs and thyrotrophs are more resilient
  - Due to ventral location in the more protected, medial portion of the pituitary and the fact that they receive blood from the short hypophyseal portal vessels and the anterior pituitary artery branch

Edwards OM, Clark JD. *Medicine* . 1986;65:281-290.
Ghigo E, et al. *Brain Inj*. 2005;19:711-724.

Traumatic Infarctions of the Anterior Lobe

Observed in 35% of patients living at least 12 hours



Daniel PM, et al. *Lancet*. 1959;2:927-931.
Kornblum RN, Fisher RS. *Arch Pathol*. 1969;88:242-248.

Difficult to Predict the Degree of Pituitary Dysfunction Following TBI/SAH

- Patients at highest risk appear to be those who have suffered moderate-to-severe head trauma; however…
- In patients with moderate-to-severe injuries, no correlation has been observed among the site of trauma, severity of cerebral injury, and the degree of impairment of pituitary dysfunction

Aimaretti G, et al. *Clin Endocrinol*. 2004;61:320-326. Barreca T, et al. *J Clin Endocrinol Metab*. 1980;51:1279-1282. Casanueva FF, et al. *J Endocrinol Invest*. 2004;27:793-795. Kelly DF, et al. *J Neurosurg*. 2000;93:743-752.

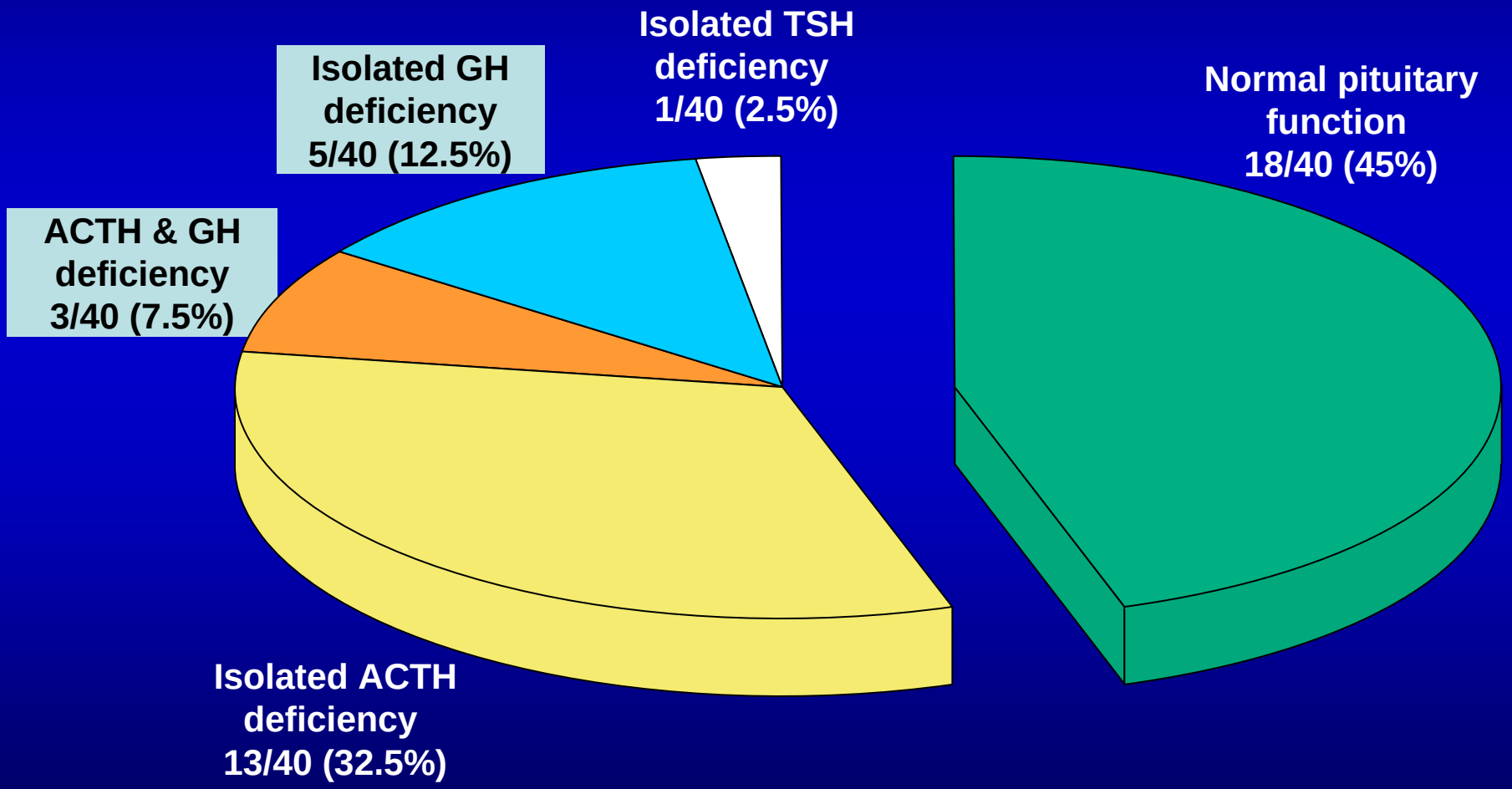
Prevalence of Pituitary Dysfunction in Patients with Previous TBI

Reference	No. of Cases	Age (yr)	Time since TBI	Prevalence of PD (%)	LH/FSH deficit (%)	GH deficit (%)	TSH deficit (%)	ACTH deficit (%)	Low PRL (%)	High PRL (%)	Perma-nent DI (%)
Kelly, et al.	22	20-52	3 months -23 years	36.4	22.7	18.2	4.5	4.5†	0	0	0
Lieberman, et al.	70	18-58	1 month-23 years	68.5	1	14.6	21.7	45.7§ 17.1†	0	10	0
Bondanelli, et al.	50	20-87	1-5 years	54	14	28*	10	0§	8	8	0
Aimaretti, et al.	100	37±2	3 months	35	17	37**	5	8§	NR	10	4
Agha, et al.	102	15-65	6-36 months	28.4	11.8	17.6***	1	22.5† 12.7‡	NR	11.8	NR
TOTAL	**344**			**42.7 (average)**							

PD: pituitary dysfunction; DI: diabetes insipidus; NR: not reported
GH deficit: * = severe GHD=8% and partial=20%; ** = severe GHD=21% and partial=16%; *** = severe GHD=7.8%
ACTH deficit: § = diagnosed by basal morning cortisol levels; †, ‡ = diagnosed after one or two standard cortisol stimulation tests, respectively

Bondanelli M, et al. *Eur J Endocrinol*. 2005;152:679-691.

Prevalence of Pituitary Dysfunction in Patients after SAH



Kreitschmann-Andermahr I, et al. *J Clin Endocrinol Metab*. 2004;89:4986-4992.

Neuroendocrine dysfunction in the acute phase of traumatic brain injury

Agha A, Rogers B, Mylotte D, Taleb F, Tormey W, Phillips J, Thompson CJ
Clin Endo 60:584, 2004

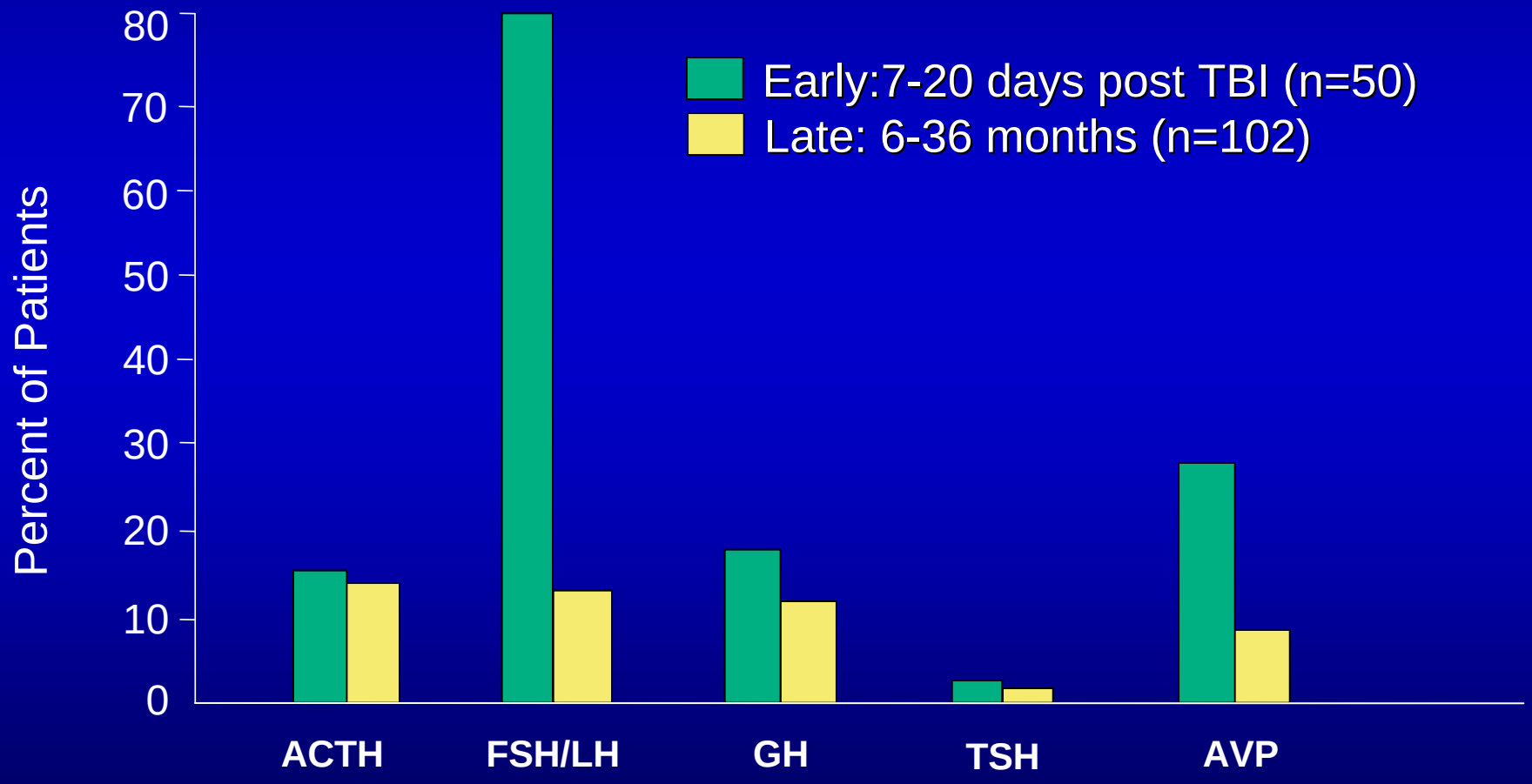
AIM: To evaluate the prevalence of pituitary dysfunction in the early phase following TBI (median 12 days from TBI).

SUBJECTS: 50 consecutive patients admitted to the neurosurgical unit with severe or moderate TBI [initial Glasgow Coma Scale (GCS) score 3–13], and 31 matched healthy control volunteers were studied.

RESULTS: Control data indicated that peak serum GH of > 5 ng/ml and cortisol > 450 nmol/l following glucagon stimulation should be taken as normal. Nine TBI patients (18%) had GH response < 5 ng/ml (12 mU/l). Compared to controls, basal cortisol values were significantly lower in patients with subnormal cortisol responses to glucagon and significantly higher in patients with normal cortisol responses ($P < 0.05$). Forty patients (80%) had gonadotrophin deficiency, with low sex steroid concentrations, which was unrelated to the presence of hyperprolactinaemia.

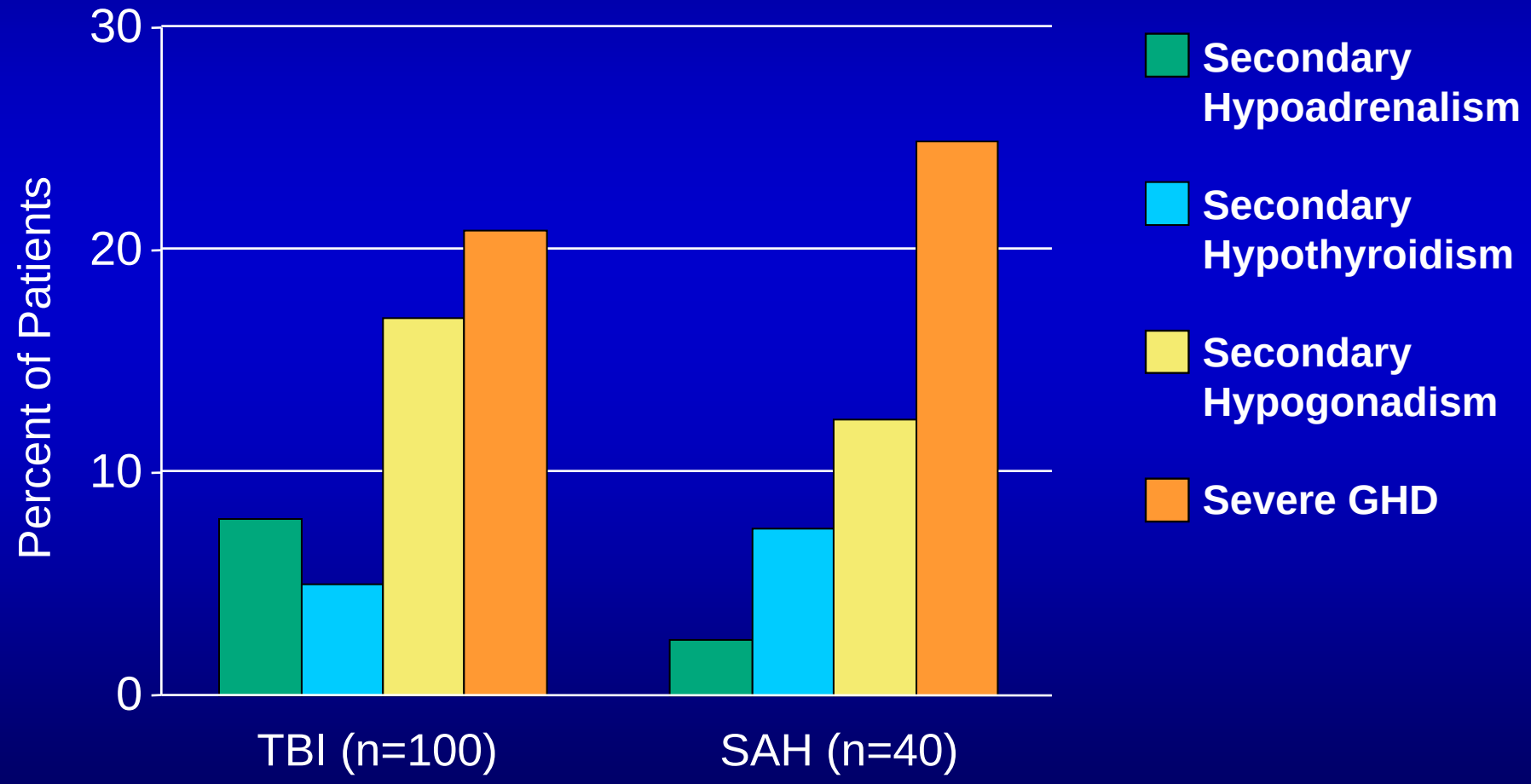
CONCLUSION: Post-traumatic neuroendocrine abnormalities occur early and with high frequency and may have implications for recovery and rehabilitation of TBI patients.

Comparison of Pituitary Dysfunction during Early and Late Phases of TBI



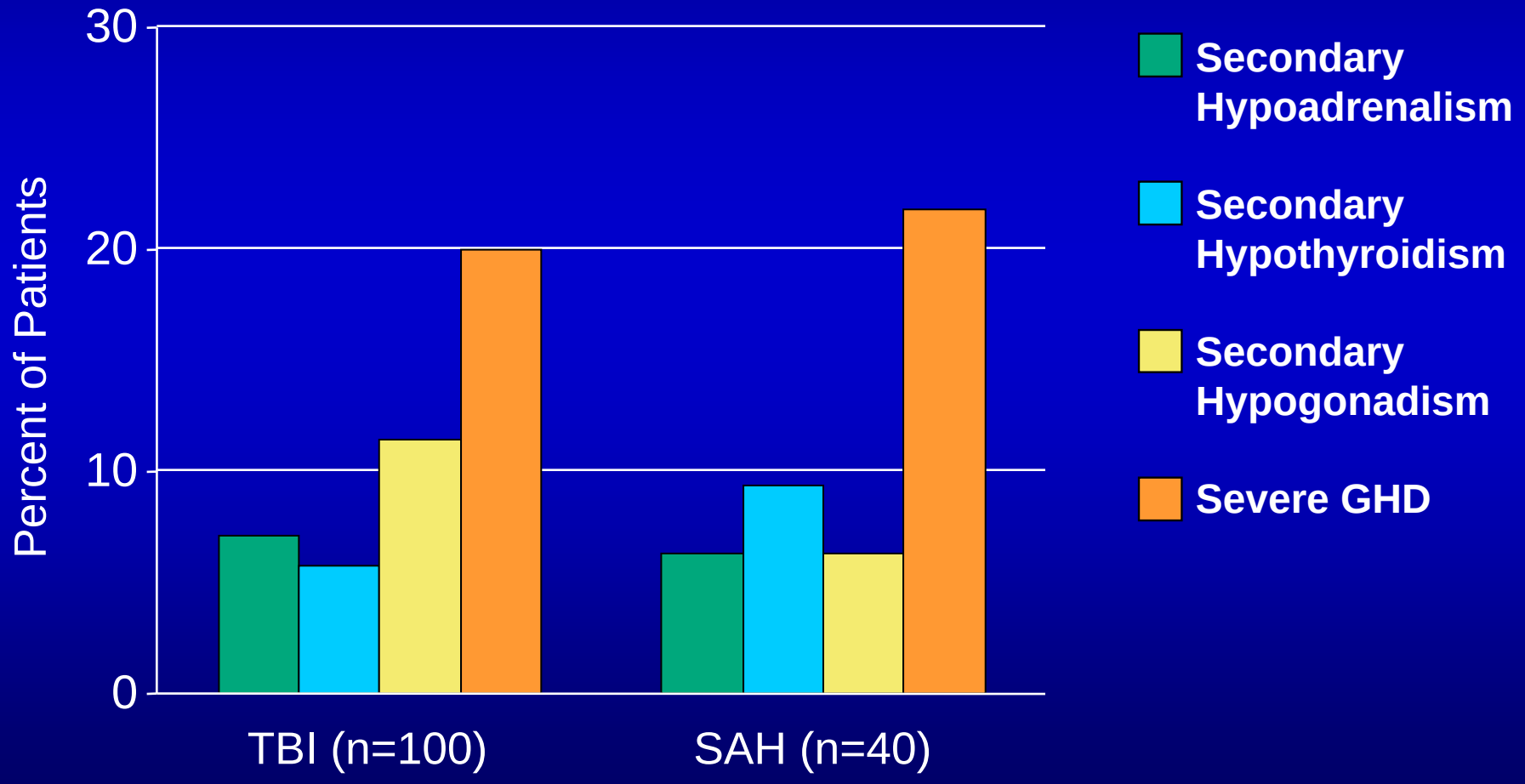
Agha A, et al. *Clin Endocrinol*. 2004;60:584-591.
Agha A, et al. *J Clin Endocrinol Metab*. 2004;89:4929-4936.

Percentage of Single Pituitary Deficits 3 Months after TBI or SAH



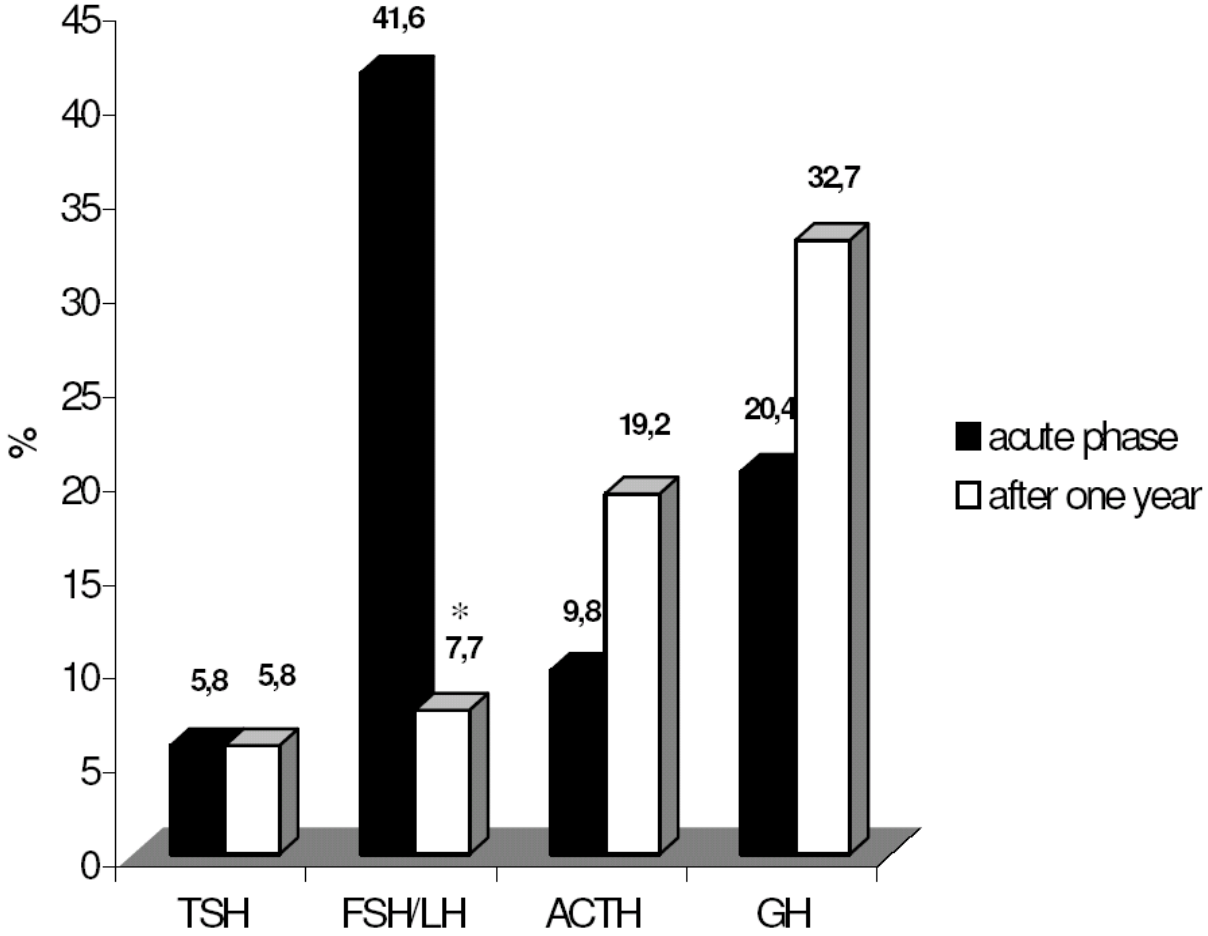
Aimaretti G, et al. *Clin Endocrinol*. 2004;61:320-326.

Percentage of Single Pituitary Deficits 12 Months after TBI or SAH



Aimaretti G, et al, *J Clin Endocrinol Metab.* 2006.

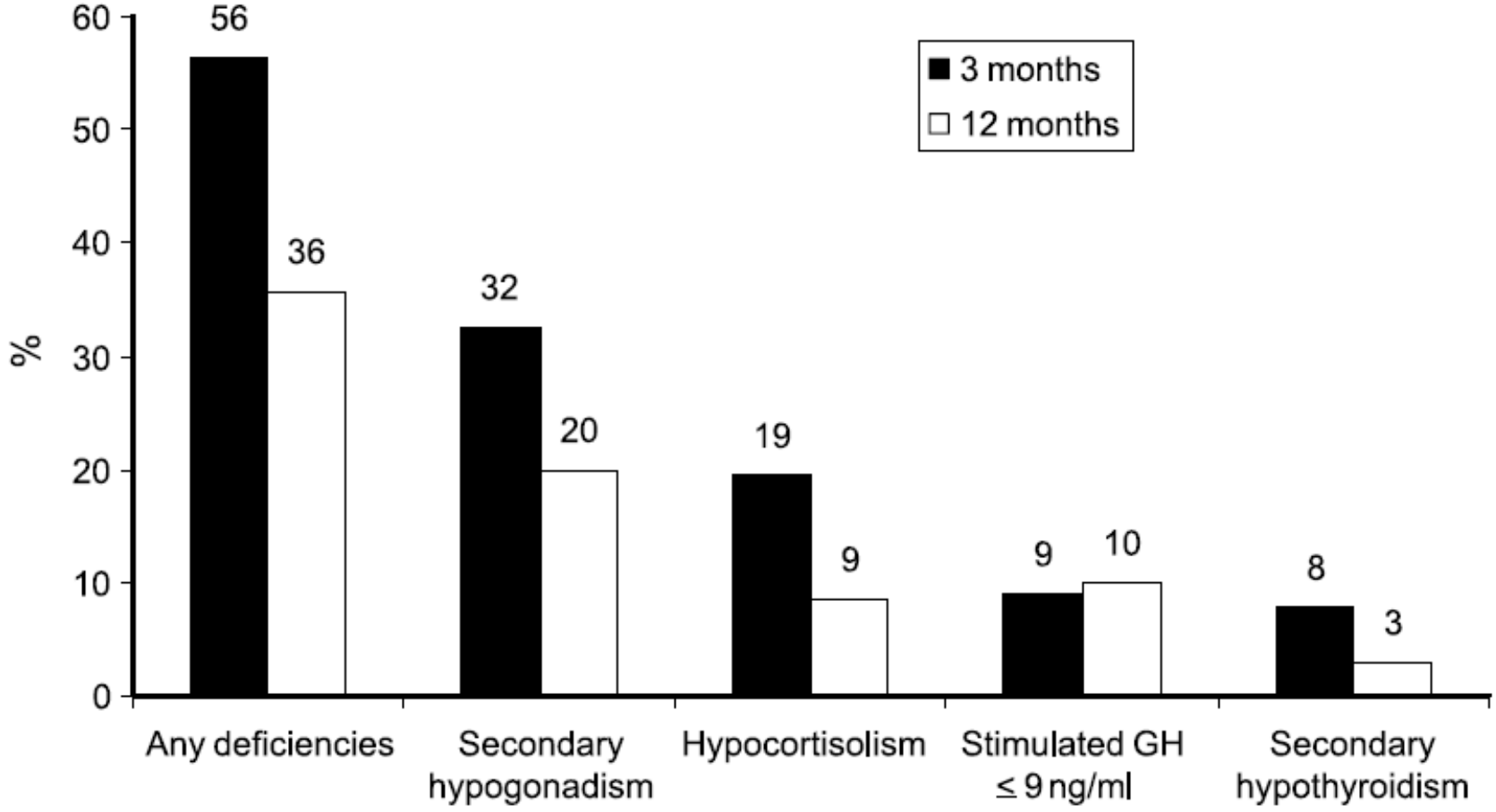
Percentage of patients with Hypopituitarism in the early acute phase (within 24 h) and 12 months after TBI



(* P < 0.05 versus after acute phase)

Tanriverdi et al. 2006

Percentage of patients with Hypopituitarism 3 and 12 months after TBI



Schneider et al. 2006

Prospective Studies

Studies	**Agha (2004)**	**Aimaretti (2005)**	**Tanriverdi (2006)**	**Schneider (2006)**
N° of cases	TBI=102	TBI =70 SAH=32	TBI=52	TBI=78
Timing	6-36 months	3 months 12 months	Acute phase 12 months	3 months 12 months
Test	ITT or GHRH+ Arginine	GHRH+ Arginine	GHRH+ GHRP6	GHRH+ Arginine
Conclusion	GHD: 17.6% (severe 7.8%)	GHD severe (12 m): 21%	GHD severe (12 m): 32.7%	GHD severe (12 m): 10%

Occurrence of Pituitary Dysfunction following Traumatic Brain Injury

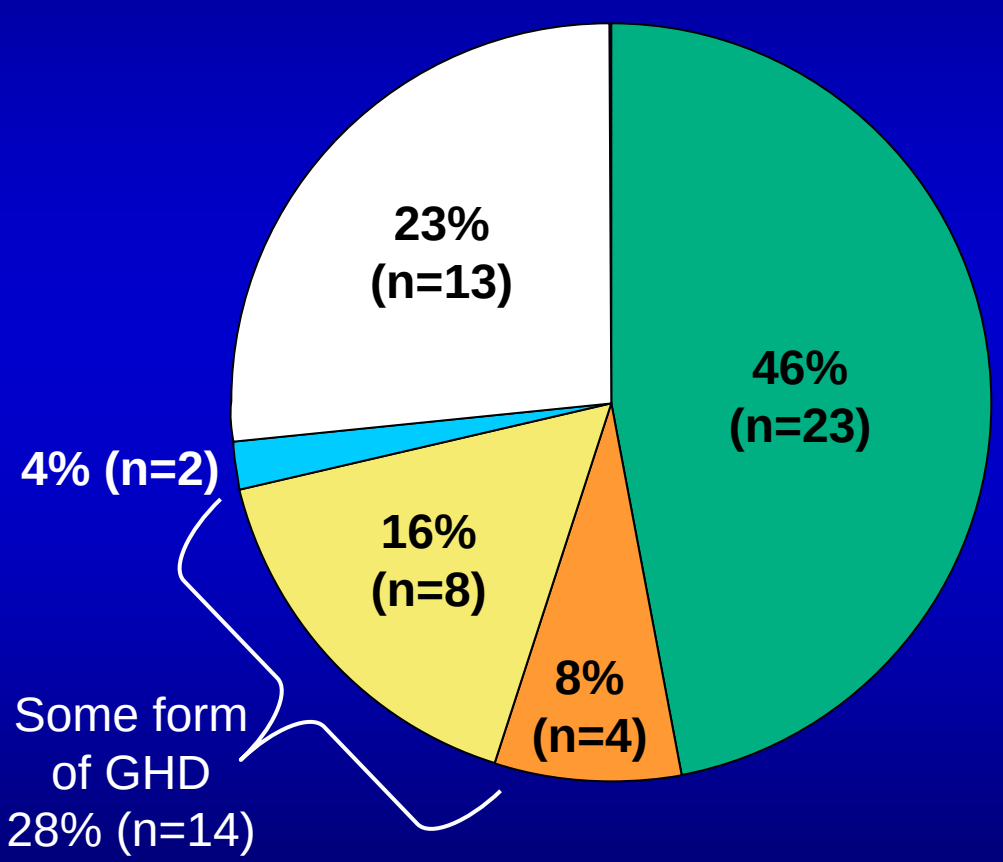
MARTA BONDANELLI, et al JOURNAL OF NEUROTRAUMA 21: 685-696, 2004

Traumatic brain injury (TBI) may be associated with impairment of pituitary hormone secretion, which may contribute to long-term physical, cognitive, and psychological disability. We studied

…altogether pituitary dysfunction was observed in 27 (54%) patients. Six patients (12%) showed a combination of multiple abnormalities.

and severe GHD in 4 (8%) cases. Patients with GHD were older ($p < 0.05$) than patients with normal GH secretion. Magnetic resonance imaging demonstrated pituitary abnormalities in 2 patients; altogether pituitary dysfunction was observed in 27 (54%) patients. Six patients (12%) showed a combination of multiple abnormalities. Occurrence of pituitary dysfunction was 37.5%, 57.1%, and 59.3% in the patients with mild, moderate, and severe TBI, respectively. GCS scores were significantly (p 0.02) lower in patients with pituitary dysfunction compared to those with normal pituitary function (8.3±0.5 vs. 10.2±0.6). No relationship was detected between pituitary dysfunction and years since TBI, type of injury, and outcome from TBI. In conclusion, subjects with a history of TBI frequently develop pituitary dysfunction, especially GHD. Therefore, evaluation of pituitary hormone secretion, including GH, should be included in the long-term follow-up of all TBI patients so that adequate hormone replacement therapy may be administered.

Pituitary Function in 50 Adult Patients with TBI over 5 Years



- Normal pituitary function
- Severe GHD
- Partial GHD
- Partial GHD + other
- Other pituitary dysfunction

GHRH + ARG test

Partial GHD defined as:

- GH peak 9 µg/L to 16.5 µg/L

Severe GHD defined as:

- GH peak <9 µg/L

Bondanelli M, et al. *J Neurotrauma*. 2004;21:685-696.

Boxing as a sport activity associated with isolated GH deficiency

F. Kelestimur[1], F. Tanriverdi[1], H. Atmaca[2], K.Unluhizarci[1], A. Selcuklu[3], and FF. Casanueva[4]

Contact sports: boxing, soccer, football, ice hockey, and martial arts cause acute or chronic TBI (CTBI)

20% retired professional boxer developed chronic traumatic encephalopathy (CTE)

Table 1 - *Baseline characteristics of boxers.*

Subjects	Age (yr)	BMI (kg/m^2)	Duration (yr)	Number of bouts*	Current status	Level
1	35	26	15	825	Retired in 1996	Gold medal (Turkey, Balkan)
2	36	25	14	840	Retired in 1998	Gold medal (Turkey, Balkan) Bronze medal (Europe)
3	35	29	12	720	Retired in 1996	Gold medal (Turkey, Balkan) Bronze medal (World Championship)
4	18	21	9	450	Still boxing	Gold medal (Turkey)
5	20	23	6	300	Still boxing	Bronze medal (Kayseri region; Junior category)
6	55	25	12	700	Retired in 1974	Gold medal (Turkey)
7	46	31	10	250	Retired in 1984	Gold medal (Turkey, Balkan)
8	41	27	15	550	Retired in 1990	Gold medal (Turkey), Silver medal (Europe)
9	32	33	14	850	Still boxing	Gold medal, Silver medal (Turkey)
10	53	28	10	800	Retired in 1978	Silver medal, Bronze medal (Turkey)
11	47	28	11	550	Retired in 1983	Gold medal (Turkey, Balkan)

Conclusion: amateur boxers had GHD in 45% (GHRH+GHRP-6 test)

No correlation between peak GH levels and boxing duration

Neurobehavioral and quality of life changes associated with growth hormone insufficiency after complicated mild, moderate, or severe traumatic brain injury.

- This prospective study tested the hypothesis that TBI patients with GHD or GH insufficiency (GHI) would exhibit greater NB/QOL impairment than patients without GHD/GHI
- 44 patients had pituitary function (GHRH-ARG) and NB/QOL testing performed 6-9 months postinjury.
- GHD and GHI were defined as peak GH<6 or <or=12 ng/mL
- one (2%) was GHD, seven (16%) were GHI at 6-9 months post-injury.
- At 6-9 months, patients with GHD/GHI had higher rates of depression , and reduced QOL in the domains of limitations due to physical health , energy and fatigue , emotional well-being , pain , and general health .
- Chronic GHI develops in approximately 18% of patients with TBI, and is associated with depression and diminished QOL.

Kelly DF, McArthur DL, Levin H, Swimmer S, Dusick JR, Cohan P, Wang C, Swerdloff R. J Neurotrauma. 2006 Jun;23(6):928-42

Summary of Relevant Data on TBI-mediated Hypopituitarism

Age at trauma (decade most affected)	20–29 years (~35% of the cases)
Most frequent type of trauma	Falls/MVAs in ≥50% of all TBIs
Occurrence of coma/unconsciousness	93%
Most frequent type of anatomical lesions (CT/MRI)	
Hypothalamic hemorrhage	29%
Pituitary posterior lobe hemorrhage	26%
Most frequent pituitary deficits (12 mths post TBI)	
Growth hormone	20%
Gonadotropin	12%
Adrenocorticotropic hormone	7%
Thyroid stimulating hormone	5%

Benvenga S, et al. *J Clin Endocrinol Metab*. 2000;85:1353-1361.Aimaretti G, et al., *J Clin Endocrinol Metab*. 2006.
Langlois JA, et al. *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths*. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2004.

Summary of Relevant Data on SAH-mediated Hypopituitarism

Age peak (decade most affected)	50–59 years
Most frequent type of aneurysm	Intracranial (85% of SAHs)
Most frequent location of aneurysm*	
Anterior communicating artery	35%
Middle cerebral artery	18%
Internal carotid artery	13%
Posterior communicating artery	13%
Most frequent pituitary deficits (~2 yrs post SAH)	
ACTH	33%
Isolated severe GHD	13%
ACTH + severe GHD	8%
Isolated TSH	3%

*Diagnosis of SAH proven by CT scan/lumbar puncture; location of aneurysm made by four-vessel angiography.

Kreitschmann-Andermahr I, et al. *J Clin Endocrinol Metab*. 2004;89:4986-4992.

Screening and Recommended Therapeutic Options

In Brain Injuries patients:

- Who should screen patients?
- Who should be tested ?
- When should we test ?
- How should we test ?
- Who and how to treat ?

Who Should Screen Patients?

- Trauma surgeons / neurosurgeons
- Intensive care unit specialists / neurologists
- Rehabilitation physicians
- Endocrinologists / internists
- Primary care physicians

Ghigo E, et al. *Brain Inj*. 2005;19:711-724.

Who should be tested ?

All patients ?

All patients who had moderate to severe TBI ?

All patients who show endocrine symptoms and/or signs after brain injuries ?

Which are symptoms and signs representing the appropriate clinical context to suspect hypopituitarism in BJ?

Who should be tested ?

Patients who had:

Acute Diabetes Insipidus or SIADH or electrolyte alterations

+

Neurosurgical invervention → in the first phase after TBI

1) **The subjects at risk are those who have suffered a moderate to severe head trauma.** Although even mild intensity trauma may precede hypopituitarism, **for operational purposes the subjects who should be tested and followed up are those with an initial Glasgow Coma Scale score of 13 or lower,** those with intracranial hemorrhagic lesions, and those with signs or symptoms of hypopituitarism.

2) Patients in chronic vegetative state are not targeted at this stage.

3) **Particular attention** should be paid to this problem in **children and adolescents**, as the burden of the disease on their development may be extensive.

When Should Patients be tested?

All TBI Patients (regardless of severity)

First visit during hospitalization in Neurosurgery or ICU: Conduct hormonal testing if clinically indicated

3-month evaluation: Conduct baseline hormonal work-up

12-month evaluation: Conduct baseline hormonal work-up

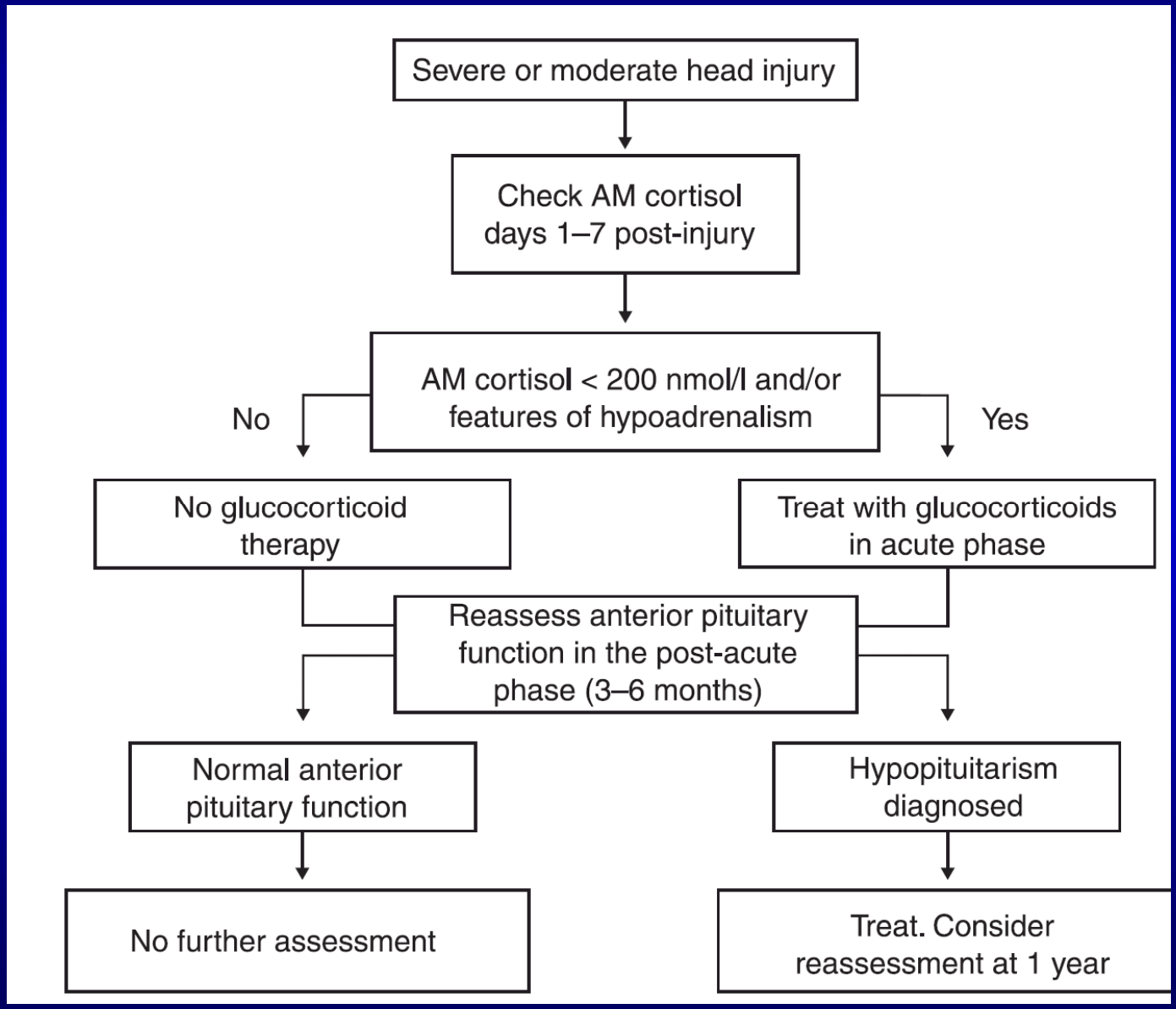
Patients with Moderate or Severe TBI >12 months prior

First visit: Record a detailed patient and family history

Conduct baseline: hormonal work-up in a single session

Ghigo E, et al. *Brain Inj.* 2005;19:711-724.

Suggested algorithm for the assessment of patients after traumatic brain injury *(Agha & Thompson, 2006)*



How should we test ?

Routine Basal Hormonal Screening Tests for Posttraumatic Hypopituitarism

Basal Hormone Test	Test Time
Serum cortisol (morning)	0900 hours
fT3*, free T_4, TSH	0900 hours
IGF-I	0900 hours
Follicle stimulating hormone (FSH), Luteinzing hormone (LH), Testosterone (in men) or 17 βE2 (in women)	0900 hours
Prolactin (PRL)	0900 hours
Urinary free cortisol (UFC)	24 hours
Patients with polyuria: Diuresis, urine density, Na^{++} and plasma osmolality	

*May be omitted per physician discretion.

Ghigo E, et al. *Brain Inj*. 2005;19:711-724.

Summary of Typical GH Provocative Tests

Provocative agent & dosage	Assay times (min)	Response (peak GH)
Insulin tolerance test (ITT)* **0.05-0.15 IU/kg regular insulin IV at 0 min***	0, +30, +45, +60, +75, +90	Normal: >5 µg/L Severe deficiency: <3 µg/L
Glucagon stimulation test **1 mg IM at 0 min**	0, +90, +120, +150, +180	Normal: >5 µg/L Severe deficiency: <3 µg/L
GHRH + Arginine **GHRH: 1 µg/kg IV at 0 min** **Arginine†: 0.5 g/kg (max.dose 30 g)**	0, +30, +45, +60	Normal: >16.5 µg/L Severe deficiency: <9 µg/L Normal BMI
GHRH + GHRP-6 **GHRH: 1 µg/kg IV at 0 min** **GHRP-6: 90 µg in single dose IV at 0 min**	0, +30, 45, +60, +90	Normal: >20 µg/L Severe deficiency: <10 µg/L

*The ITT is contraindicated in patients with CNS pathologies.

†Arginine HCl (30 g in 100 mL) to be administered as infusion over 30 min from 0 to +30 min.

Obese: severe deficiency:<4.2 µg/L

Ghigo E, et al. *Brain Inj*. 2005;19:711-724.

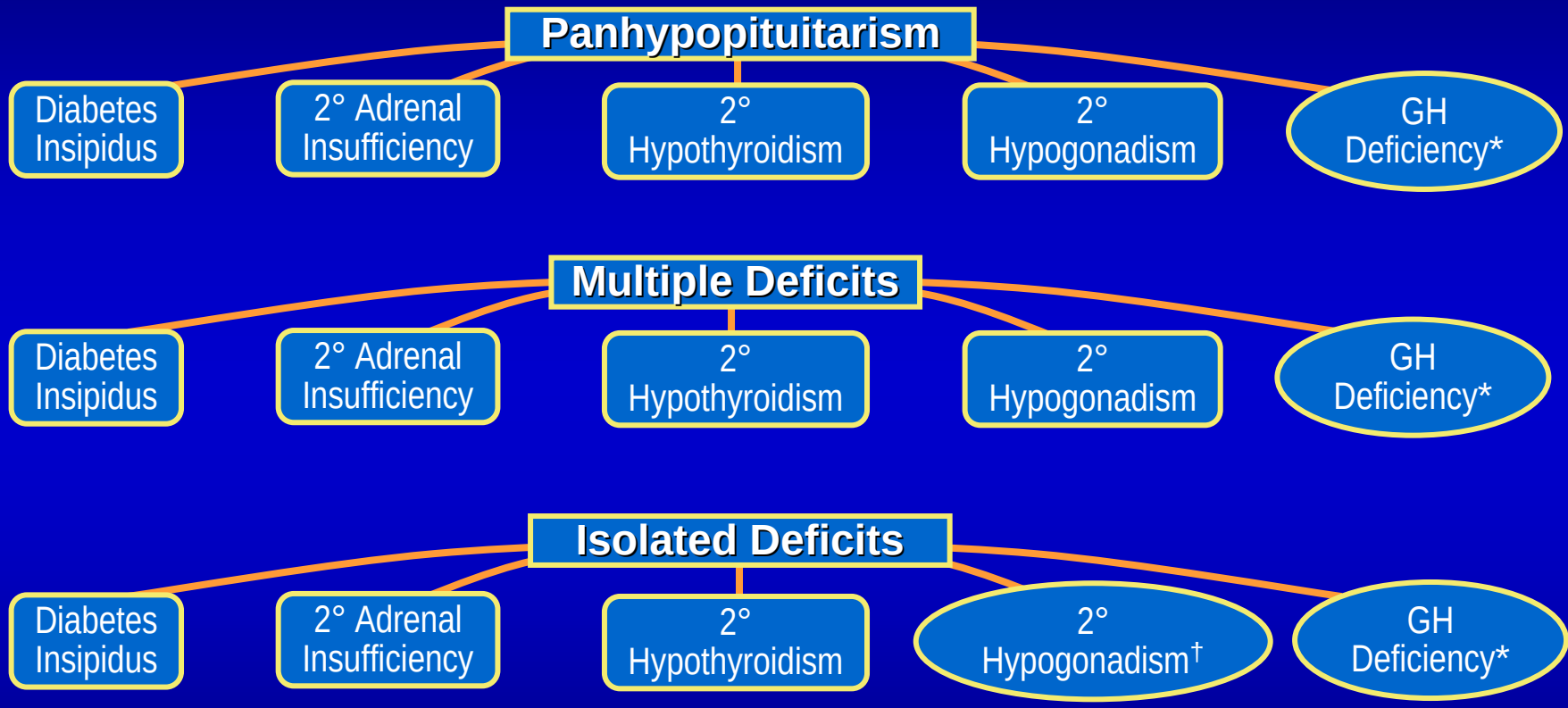
Who and how to treat ?

THERAPY: Suggestions from the Italian prospective study

1. When deficits were demonstrated, only **adrenal insufficiency, diabetes insipidus and thyroid insufficiency** were replaced.

2. On the other hand, it was agreed that other deficits, e.g. **gonadal deficit and GHD** had to be reconfirmed later on (at 1 year) under optimized replacement of other deficits, if any, and in order to avoid over-treatment of defects that would theoretically be transient, particularly when isolated.

Recommended Therapeutic Options for Patients Less Than One Year Post-injury Based on Type of Deficit



Note: These indications do not rule out any hormone replacement therapy (HRT) when definitely indicated.
*Replacement of other hormonal deficits can restore normal GH response to provocative testing; thus, GH deficiency needs to be confirmed after appropriate replacement of other hormone deficiencies.
†Isolated insufficiency of the gonadal axis could reflect functional stress-induced impairment and be transient. Patients should be retested before HRT is initiated.

Replace immediately

Replace as appropriate

Adapted from Ghigo E, et al. *Brain Inj*. 2005;19:711-724.

Conclusions

- Post-TBI hypopituitarism occurs frequently, and is under-diagnosed and under-treated
- Hormonal deficits may significantly contribute to the chronic disability of TBI and its physical, cognitive, health, and social sequelae
- Subjects at highest risk of hypopituitarism appear to be those with moderate-to-severe head trauma (GCS<13)
- Timely diagnosis of children and adolescents with posttraumatic hypopituitarism is critical since the burden of disease on their development may be extensive
- In addition to conventional HRT, the potential of GH treatment to enhance patient recovery can be anticipated based on results seen in adult patients with GHD due to other etiologies

Take at Home

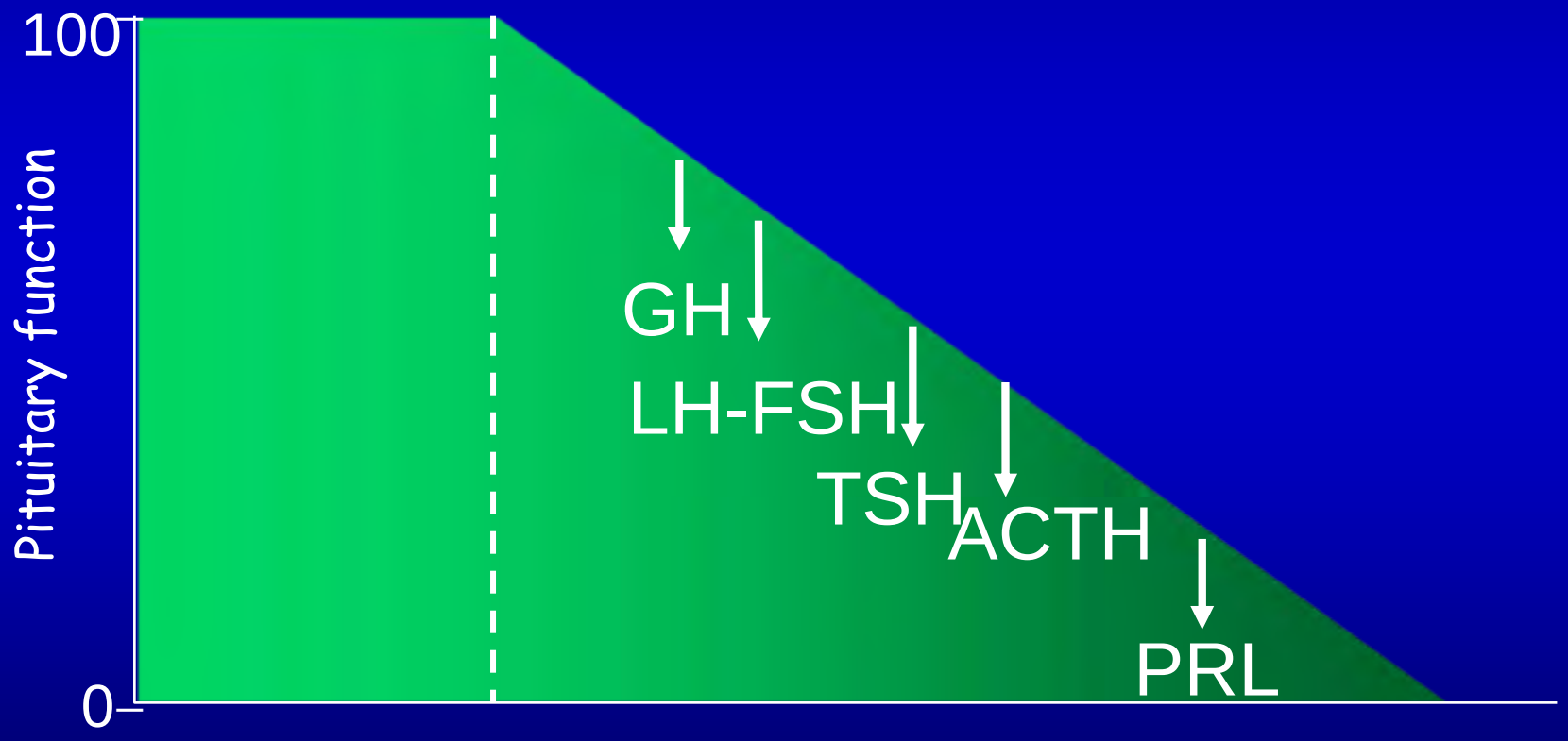
- TBI and SAH high risk to pituitary function
- Screened prospectively and retrospectively for PD
- Appropriate HRT when needed to improve QL and enhance the rehabilitation prospects
- It is indicated to increase awareness among physicians of the risk of TBI-induced endocrinopathies and the need for tests and HRT
- Team is necessary for screening (neurosurgeon, intensive care unit specialists, neurologists, rehabilitation physicians), but endocrinologists and internists must be actively share their expertise with other physicians.

Assessing the Efficacy of Hormonal Replacement

- Any assessment of the efficacy of HRT should be done in collaboration with an endocrinologist and according to the classical guidelines for hypopituitary deficiencies
- Suggested possible measures:
  - Fatigue: Fatigue Severity Scale (MFI 20) using a Visual Analog Scale
  - Emotion: Neurologic Changes of Personality Inventory (NECHAPI) and Visual Analog Mood Scale
  - Cognition: Digit Vigilance Task; CogState™
  - QoL: Assessment of GH Deficiency in Adults (AGHDA)

Ghigo E, et al. *Brain Inj*. 2005;19:711-724.

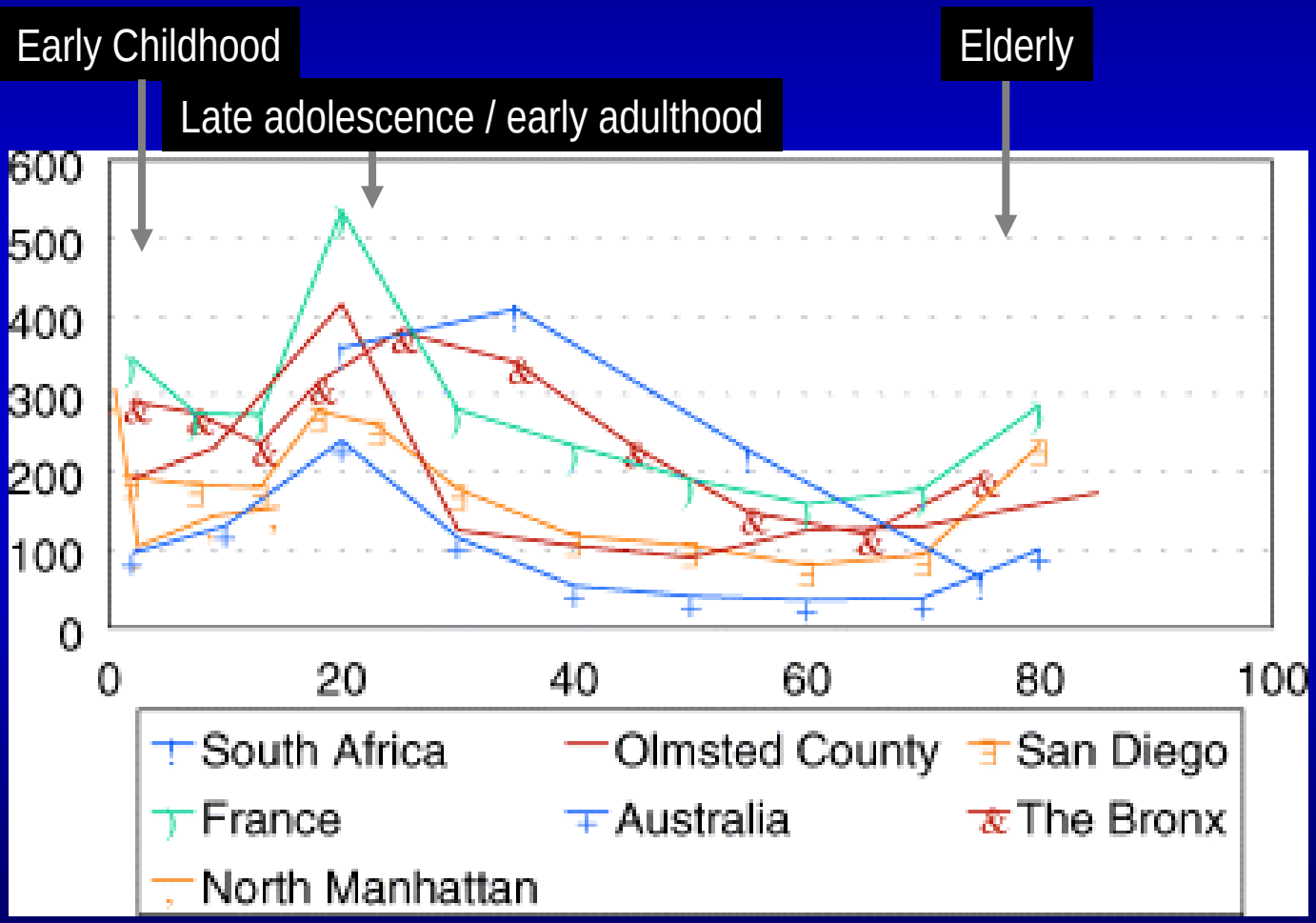
SCALA DI SUSCETTIBILITA' AL DANNO DELLE of pituitary endocrine function



Epidemiology of TBI

Incidence peaks:

Age-specific incidence of traumatic brain injury



Bruns J & Hauser WA 2003, Epilepsia 44:2

Special Article

Hypopituitarism Secondary to Head Trauma

Benvenga S, Campenni A, Ruggeri RM and Trimarchi F

JCE&M, 85: 1353, 2000

…After our initial observation of the first genuine case of posttraumatic isolated hypogonadotropic hypogonadism, namely the posttraumatic selective damage of the gonadotrophs, we became alerted about PHTH. Our experience with this patient proved to be fruitful, because it helped us to diagnose PHTH-rather than idiopathic hypopituitarism-in subsequent patients. We learned, in fact, that head trauma can be minor and had occured several years earlier, so that the patient may lose recollection of it.

…In addition to screening the literature from 1986 through 1998, we also screened the years 1970-1985……

Thus we bring the total of PHTH cases to 367.

Hypopituitarism following traumatic brain injury and aneurismal subarachnoid haemorrhage: a preliminary report

D.F. Kelly, I.T. Gaw Gonzalo, P. Cohan, N. Berman, R. Swerdloff, C. Wang
J Neurosurgery 93: 743-752, 2000

…Some degree of hypopituitarism appear to occur in approximately 40% of patients with moderate or severe head injury, with GH and gonadotroph deficiencies being most common…

0021-972X/01/$03.00/0
The Journal of Clinical Endocrinology & Metabolism

Vol. 86, No. 6
Printed in U.S.A.

Prevalence of Neuroendocrine Dysfunction in Patients Recovering from Traumatic Brain Injury*

STEVEN A. LIEBERMAN, ASRA L. OBEROI, CHARLES R. GILKISON, BRENT E. MASEL, AND RANDALL J. URBAN

Transition Learning Community (B.E.M.) and Departments of Internal Medicine (S.A.L., A.L.O., C.R.G., R.J.U.) and Neurology (B.E.M.), University of Texas Medical Branch, Galveston, Texas 77555

… pituitary hormone deficiencies were identified in a substantial proportion of patients with previous brain injury.

51.4% single abnormal axis

17.1% dual abnormalities

GH deficiency, found in 15% by glucagon stimulation testing, may compound the physical and psychological complication of traumatic brain injury and interfere with rehabilitation.

Hormone Replacement Therapy in Adults with TBI-mediated Deficiencies

Syndrome	Treatment	Monitoring Therapy
Hypothyroidism	Levothyroxine	Easily monitored; effective therapy may alleviate fatigue and improve cognitive function including initiation, lethargy, decreases in memory and dementia in the elderly
Secondary Hypoadrenalism	Hydrocortisone	Monitoring of dosing is subjective with no objective criteria; clinicians use weight, BP, and how patient feels to monitor effectiveness; therapy may alleviate fatigue, weakness, inability to respond to stress
Hypogonadism	GnRH Bromocriptine Testosterone Estrogen	Issues of fertility need to be differentiated from issues that simply require testosterone, such as decreased energy/muscle mass/libido, fatigue, depressed affect; administration of GnRH is normal treatment for FSH/LH deficiency and facilitates spermatogenesis
Growth Hormone Deficiency	rhGH	IGF-I and stimulation challenge used to assess GH levels; GHD is associated with increased mortality; effective therapy may return mortality risk to normal

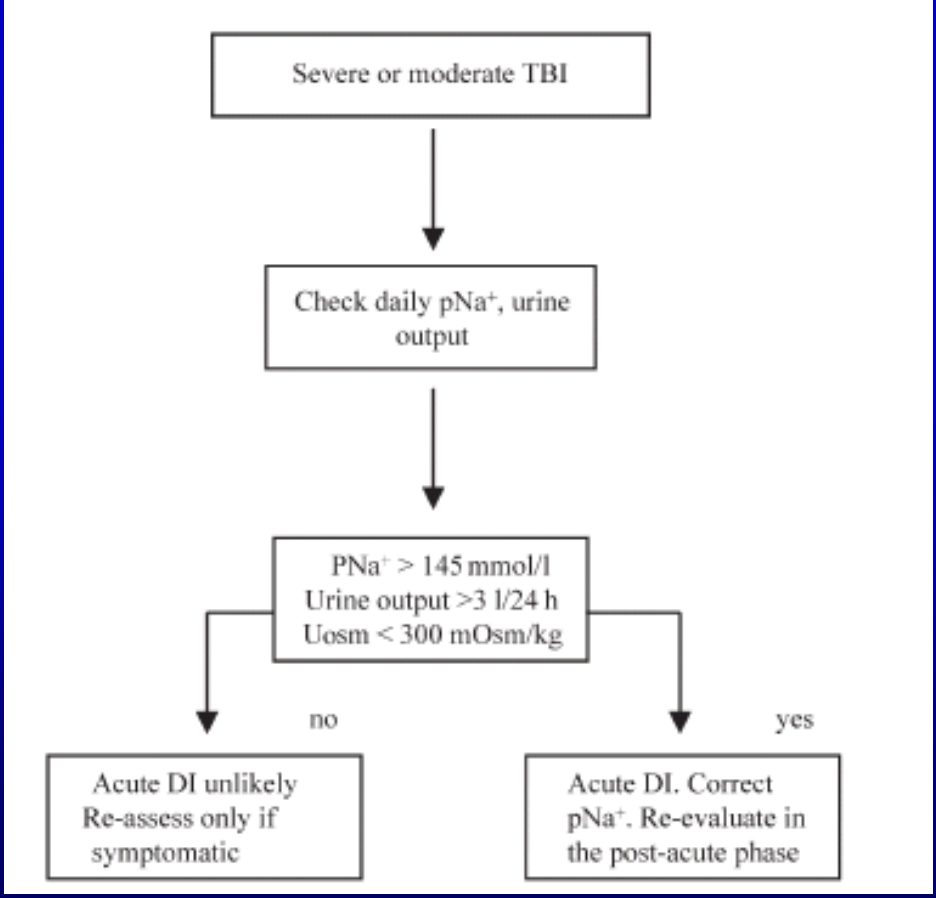
Elovic E. *J Head Trauma Rehabil*. 2003;18:541-543.
Elovic E. *J Head Trauma Rehabil*. 2004;19:184-187.

The natural history of post-traumatic neurohypophysial dysfunction

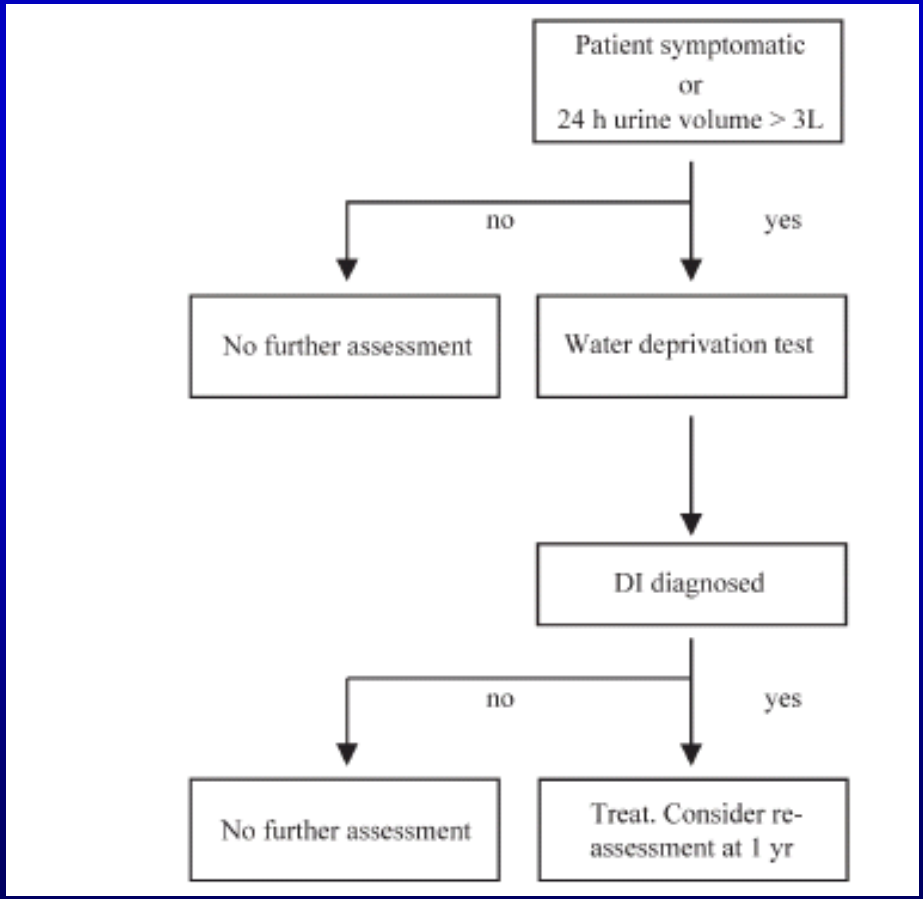
A. Agha, M. Sherlock, J. Phillips, W.Tormey and C. J Thompson

Eur J Endo152:371, 2005

DI in the acute phase



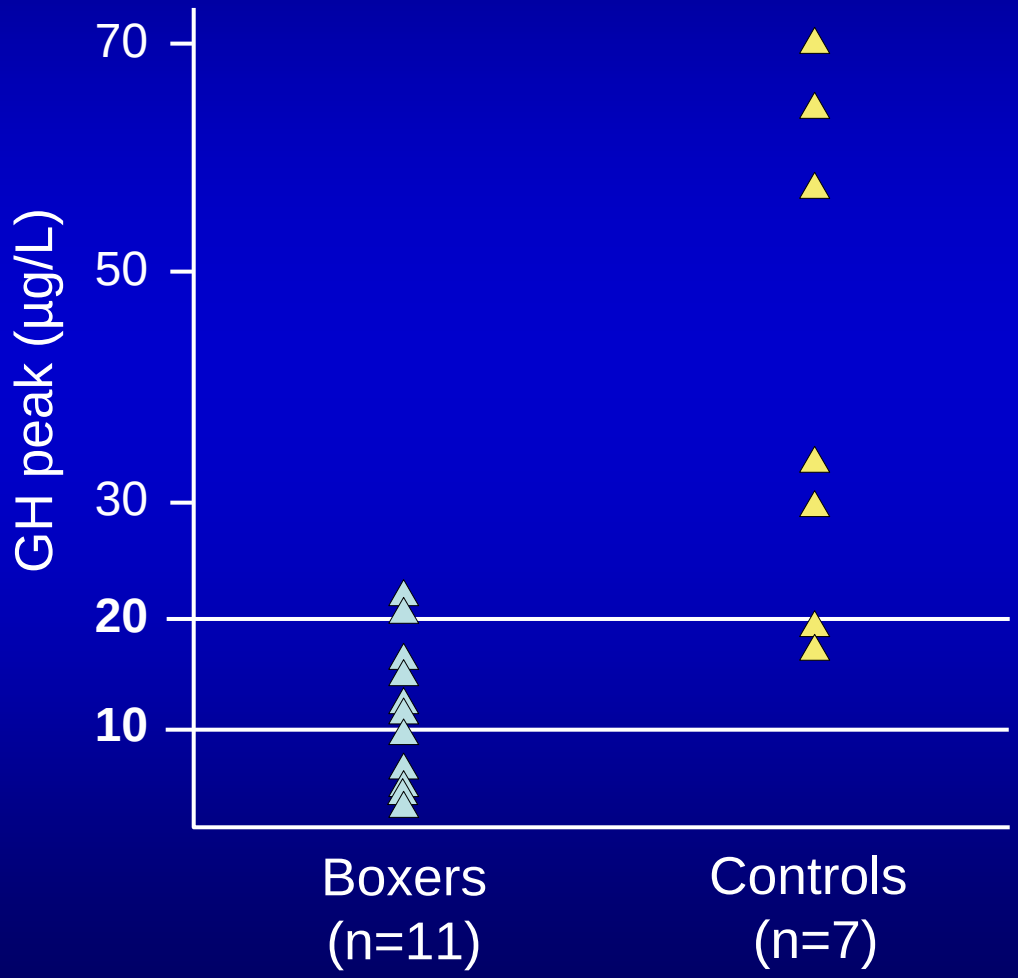
DI in the post acute phase



Chronic Trauma in sports as a Cause of Hypopituitarism. F. Kelestimur, Pituitary 2005

- Contact sports: boxing, soccer, football, ice hockey, and martial arts cause acute or chronic TBI (CTBI)
- 20% retired professional boxer developed chronic traumatic encephalopathy (CTE)
- This study show that amateur boxers had GHD in 45% (GHRH+GHRP-6 test)
- No correlation between peak GH levels and boxing duration

Chronic, Repetitive Head Trauma During Boxing Associated with Isolated GHD



- Individual GHRH+GHRP-6 stimulated GH peaks in controls and boxers
- Cut-off peak GH value for GHD was ≤10 µg/L
- Peak GH values ≥20 µg/L were considered normal

Kelestimur F, et al. *J Endocrinol Invest*. 2004;27:RC28-RC32.

Prospective Studies

Studies	Taniverdi (2006)	Aimaretti (2006)	Agha (2005)	Schneider (2006)
N° of cases	TBI=52	TBI =70 SAH=32	TBI=102	TBI=78
Timing	Acute phase 12 months	3 months 12 months	6-36 months	3 months 12 months
Test	GHRH+ GHRP6	GHRH+ Arginine		GHRH+ Arginine
Conclusion				

6th AME National Meeting

Verona, 27-29 october 2006

GHD in Adults. An Update at 15-yrs from the Beginning

GHD in Transition Age

Maria Rosaria Ambrosio

Università degli Studi di Ferrara

Dipartimento di Scienze Biomediche e Terapie Avanzate
Sezione di Endocrinologia
Direttore Prof. Ettore degli Uberti

TRANSITION

Definition

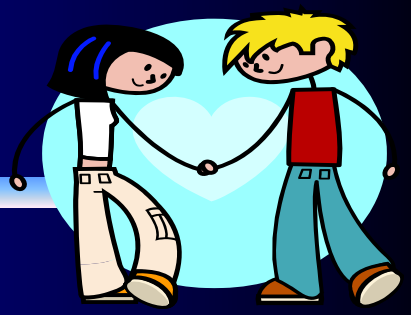
broad set of physical and psychosocial changes, arbitrarily defined as starting in late puberty and ending with full adult maturation

Duration

period from mid to late teens until 6–7 years after achievement of final height

Clayton PE et al Eur J Endocrinol 2005, 152:165

TRANSITION



Characteristics of the "transition" life phase

- Epiphyseal fusion
- Attainment of adult stature
- Attainment of adult muscle mass, especially in males
- Attainment of adult size of pelvic inlet (in female)
- Fertility
- Attainment of peak bone mass
- Physiological homeostasis

Rosenfeld RG et al Horm Res 2003, 60(1):74

TRANSITION

Body Composition in Severely GH-Deficient (GHD) Patients after Childhood GH Treatment: A Comparison with Adult Onset GHD Patients

Actual and height-normalized values for body composition assessed by DEXA

CO patients have 16–20% less height-normalized LBM, FM, and BMC compared with age-matched patients with AO GHD

Age (yr)		
Mean SD	20.9 ± 2.4 [a]	25.2 ± 3.0
Range	(18.0–27.3)	(18.8–29.7)
Age at diagnosis (yr)	8.7 ± 3.9 [a]	21.4 ± 3.4
Height SD score	1.18 ± 1.16 [a]	0.38 ± 1.12

Attanasio et al. J Clin Endocrinol Metab 2002 87:3368

TRANSITION

Among adult GHD patients,
those with childhood-onset GHD have:

Shorter stature
Lower IGF-1
Reduced lean body mass
Reduced total bone mineral content

↓

"maturational deficit" of body tissues

Attanasio et al. J Clin Endocrinol Metab 1997 82:82 and 2002 87:3368

TRANSITION

GH EFFECTS DURING HUMAN LIFE PHASES

childhood	one-dimensional longitudinal growth
transition	three-dimensional somatic development
adulthood	maintenance of normal body composition, metabolism and quality of life

Rosenfeld RG et al Horm Res 2003, 60(1):74

TRANSITION

Transitional care of GHD

- Should GH replacement be continued after reaching final height?
- What is the adequate management of patients treated with GH during childhood in transition phases?

TRANSITION

Reassessment of pituitary status

- GH secretion and IGF-1 levels reach a maximum at mid to late puberty and subsequently decline

- The GH replacement strategy differs in childhood from that adopted in adult life: in childhood all degrees of GHD are considered for replacement whereas in adult life only patients with severe GHD are currently treated

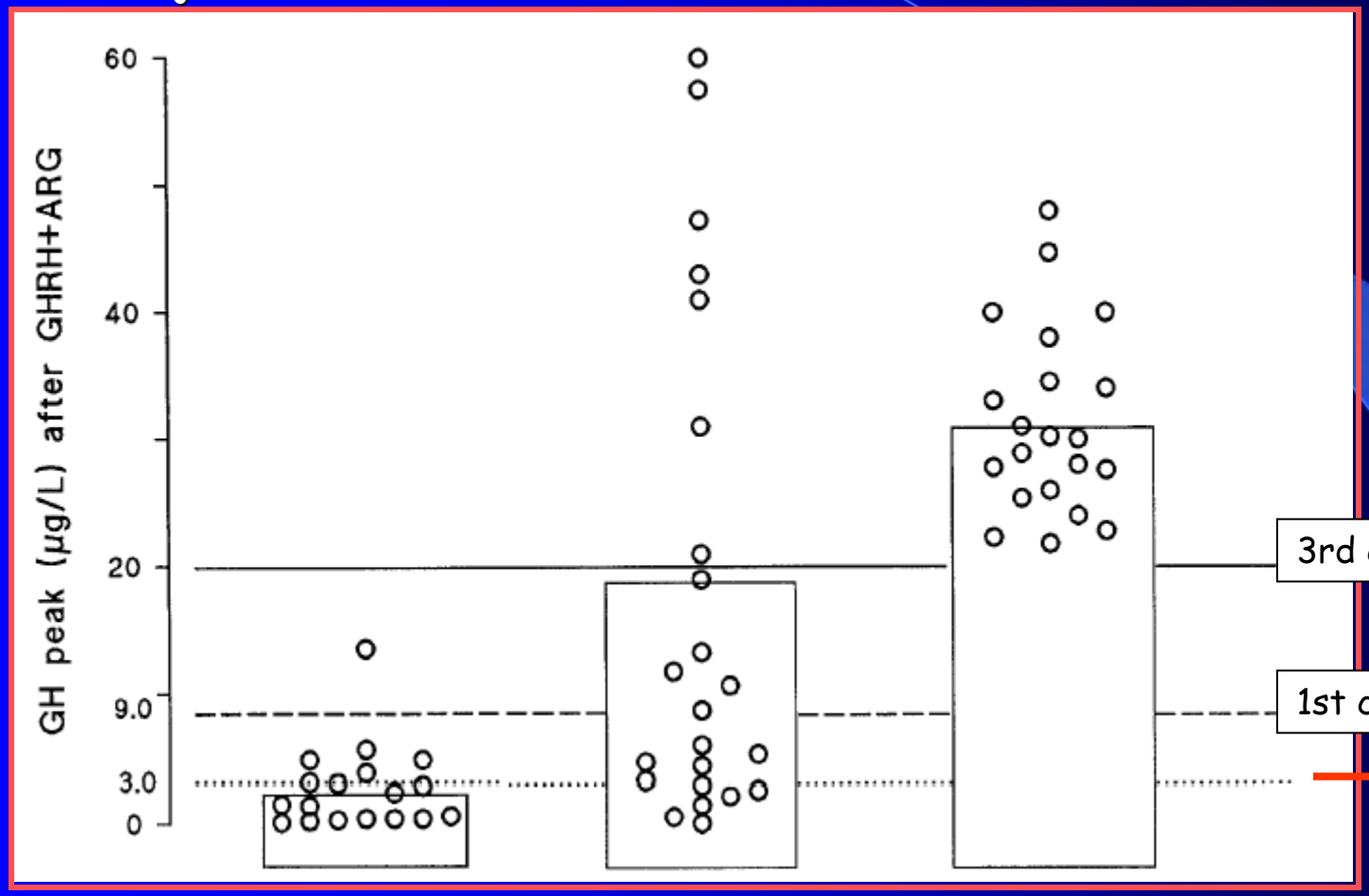
- Most patients diagnosed as GHD and treated with GH in childhood do not have permanent or complete GHD, "but rather have insufficient secretion of GH to support normal childhood growth"

Clayton PE et al Eur J Endocrinol 2005, 152:165
Quigley CA Curr Opi Endocrinol Diabetes 2003, 10:277

TRANSITION

Reassessment of pituitary status

Mean and individual GH peaks after GHRH+ARG test in subjects who had been treated with GH in childhood

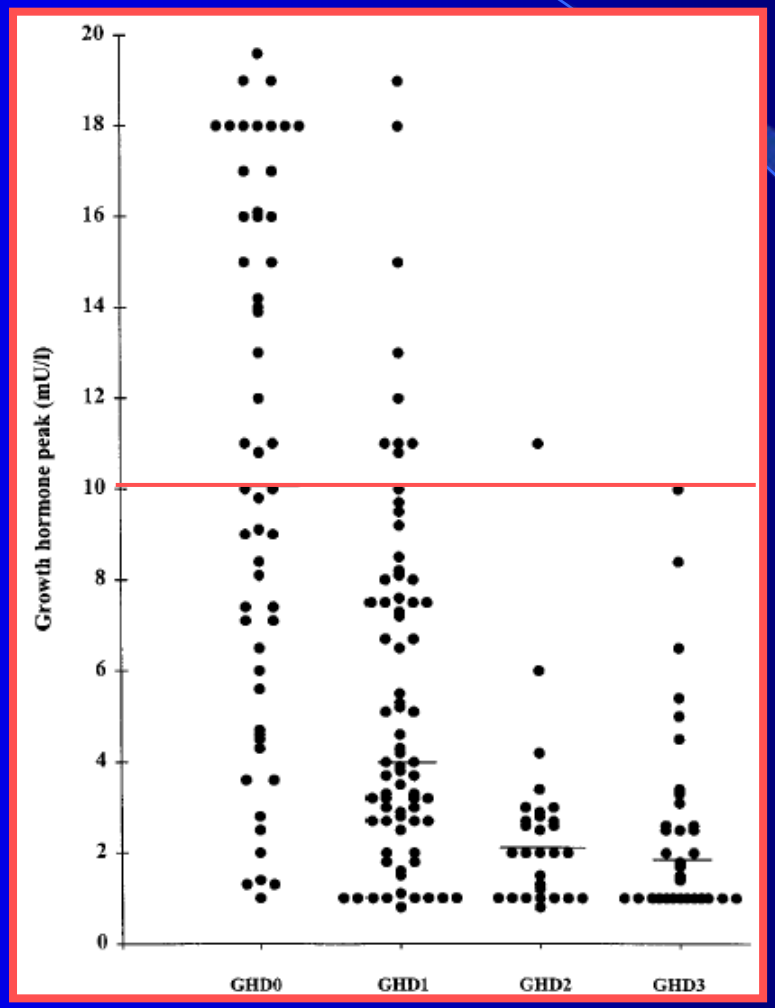


Aimaretti G et al J Clin Endocrinol Metab 2000, 85:3693

TRANSITION

Reassessment of pituitary status

Distribution of the peak serum GH levels in response to an ITT in 190 patients divided into groups according to the degree of hypopituitarism

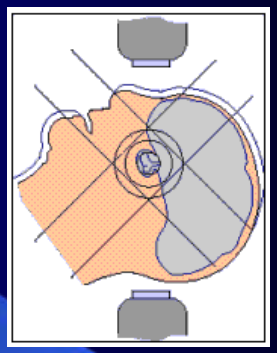


Toogood AA et al. Clin Endocrinol 1994, 41: 511

TRANSITION

Reassessment of pituitary status

Radiotherapy



GH status evolves with time after radiotherapy
Occurence of GHD depends on dose of irradiation

At retest

- 43% of children with partial GHD in childhood became severely GHD
- 64% of severely GHD children remained severely GHD
- 48% of all patients were not severely GHD

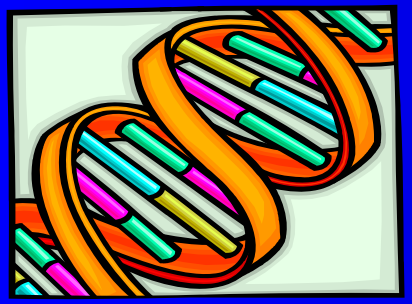
Patients with partial GHD at final height require follow-up and retesting, because they may become severe GHD in the future

Gleeson HK et al J Clin Endocrinol Metab 2004, 80:662

TRANSITION

Reassessment of pituitary status

Genetic GH deficiency



Persistent GHD into adulthood

TRANSITION

Reassessment of pituitary status

Criteria for severe GHD diagnosis during human life phases

Childhood

GH peak after provocative testing < 10 µg/L

Adulthood

GH peak after ITT < 3 µg/L

Transition

GH peak after ITT < 5 µg/L

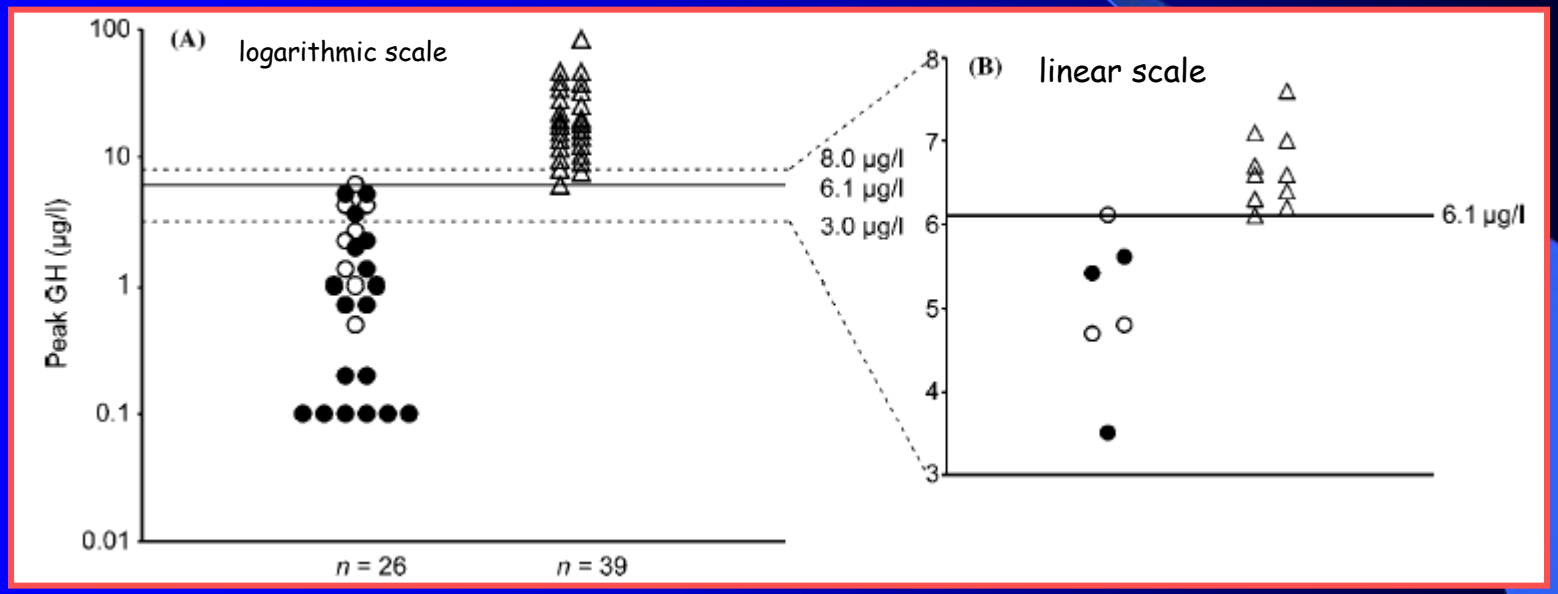
Standardization and quality control of GH assays are critical

Clayton PE et al Eur J Endocrinol 2005, 152:165

TRANSITION

Reassessment of pituitary status

Peak GH response after ITT



8 isolated GHD and 18 multiple pituitary hormone deficiency pts

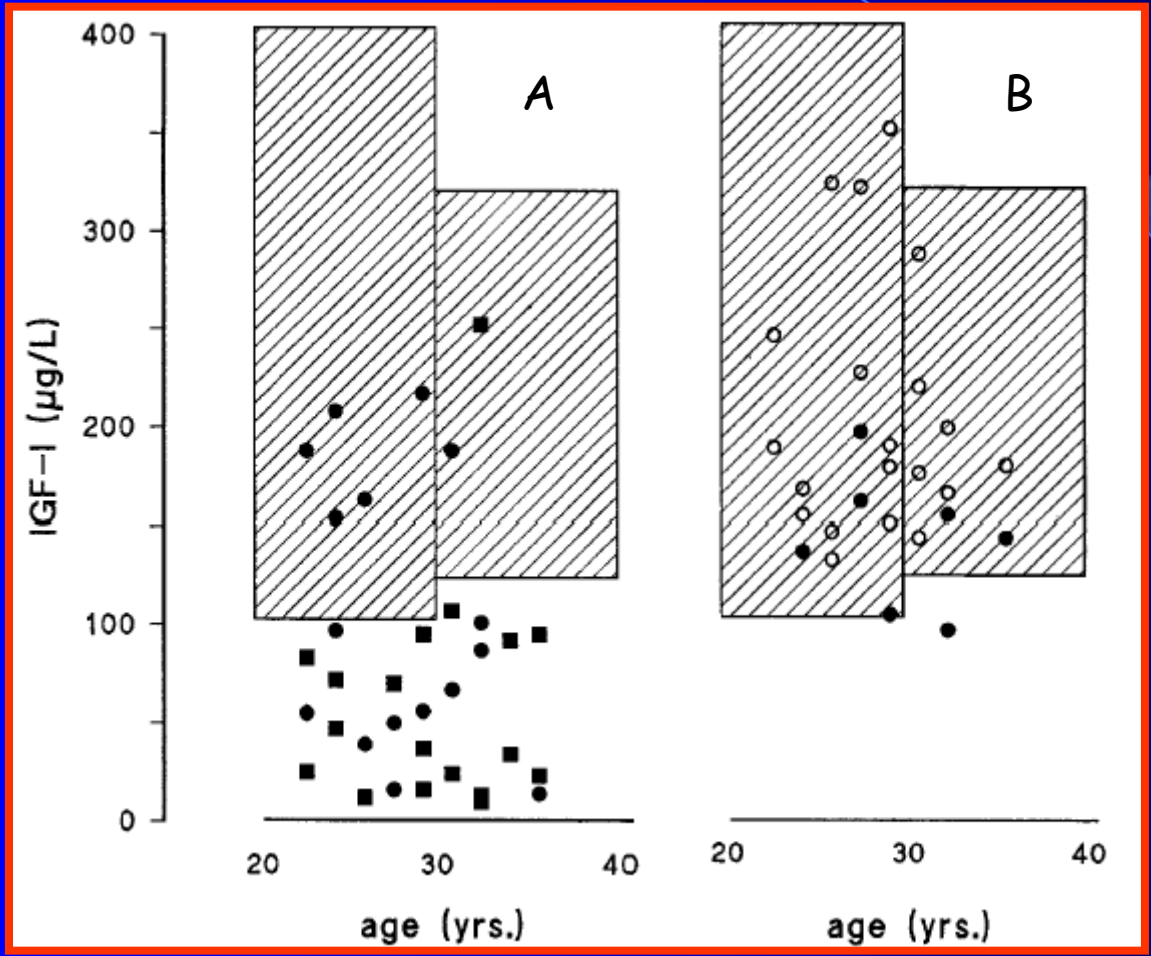
age- and sex-matched controls

Maghnie M et al Eur J Endocrinol 2005, 152:589

TRANSITION

Reassessment of pituitary status

Individual IGF-1 in subjects who had been treated with GH in childhood



■ organic GHD
● idiopathic GHD
○ GHNSD

(A) confirmed adult GHD
(B) not corfimed adult GHD

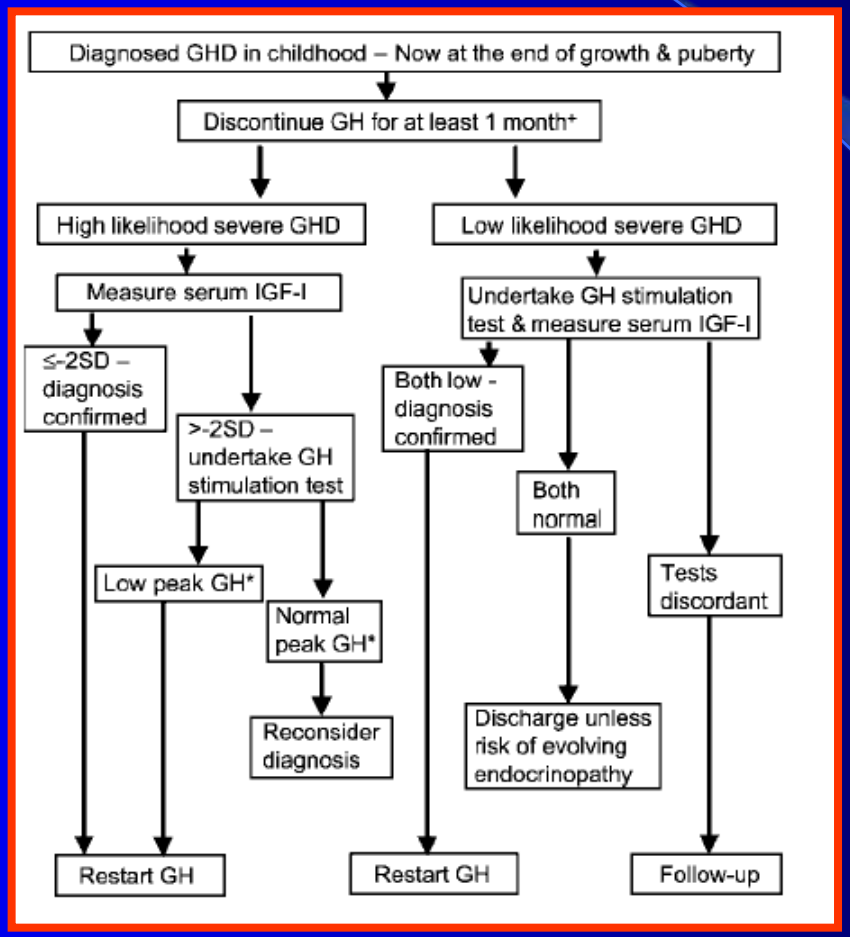
Aimaretti G et al J Clin Endocrinol Metab 2000, 85:3693

TRANSITION

Reassessment of pituitary status

The process of re-evaluation of GH and IGF-1 levels at the end of growth in patients with GHD diagnosed in childhood

*Peak GH , 5 μg/l



Clayton PE et al Eur J Endocrinol 2005, 152:165

GAZZETTA UFFICIALE
DELLA REPUBBLICA ITALIANA

GAZZETTA UFFICIALE n. 259 del 4-11-2004
Note AIFA 2004 (Revisione delle note CUF)

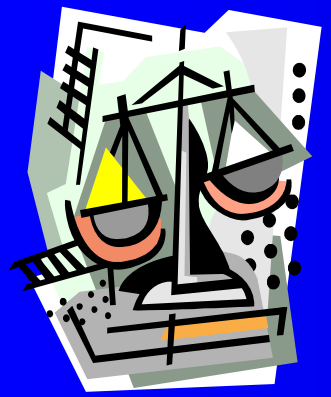
Revisione delle note riportate nel Decreto del 22 dicembre 2000

Nota 39

Motivazioni e criteri applicativi

Il trattamento con GH biosintetico può essere effettuato fino al raggiungimento della statura definitiva e deve essere proseguito in età adulta nei pazienti in cui sia stato riconfermato un deficit permanente di GH, **secondo i criteri applicabili in età adulta.**

TRANSITION



GHD: clinical endpoints

IGF-1

Body composition

Lipids

Cardiovascular function

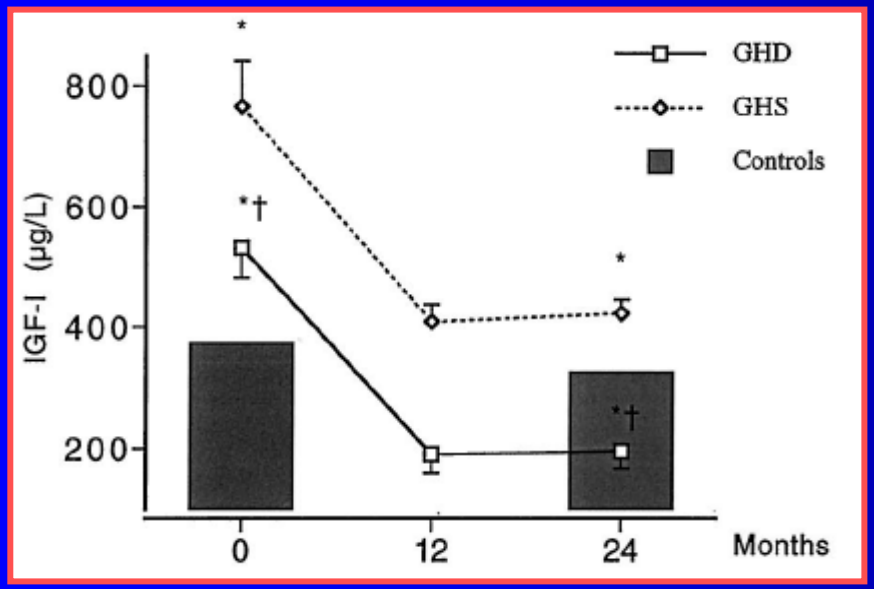
Bone

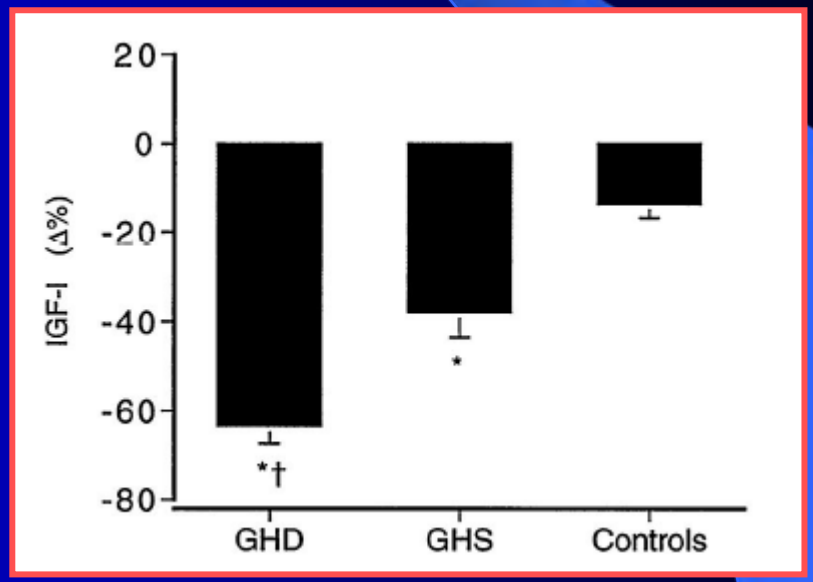
…Quality of life…

TRANSITION

Discontinuation of GH Treatment in GH-Deficient and GH-Sufficient Adolescent Patients Compared with Control Subjects

IGF-1



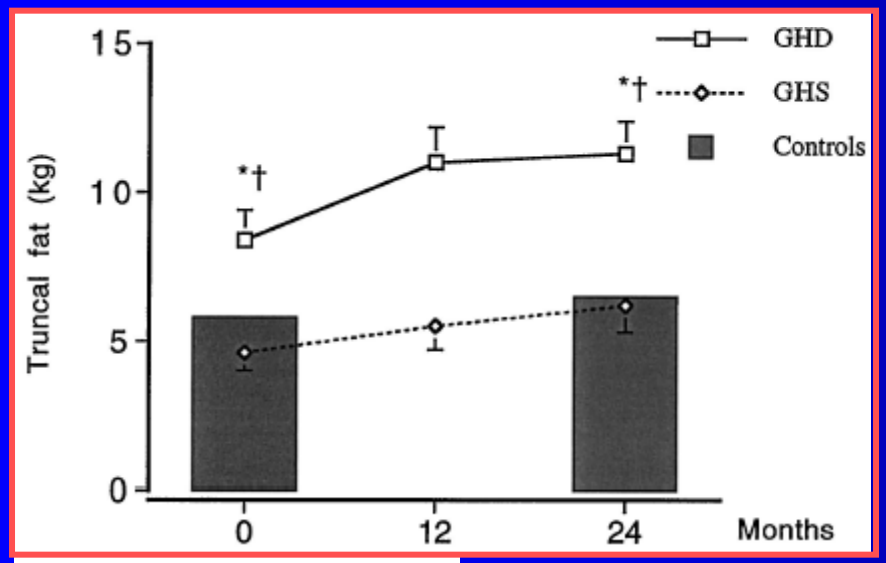


Johannsson G et al. J Clin Endocrinol Metab 1999; 84: 4516

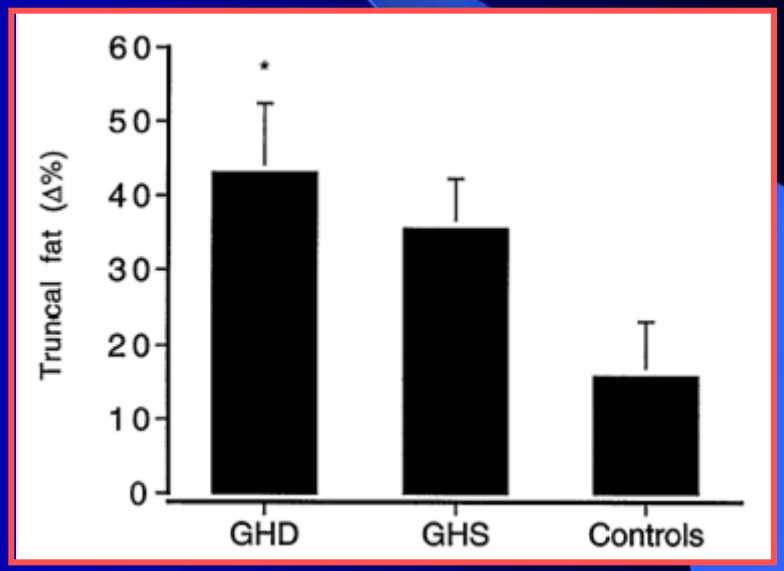
TRANSITION

Discontinuation of GH Treatment in GH-Deficient and GH-Sufficient Adolescent Patients Compared with Control Subjects

Truncal fat mass



*, $P<0.05$ vs. controls
†, $P<0.05$ vs. GHS group

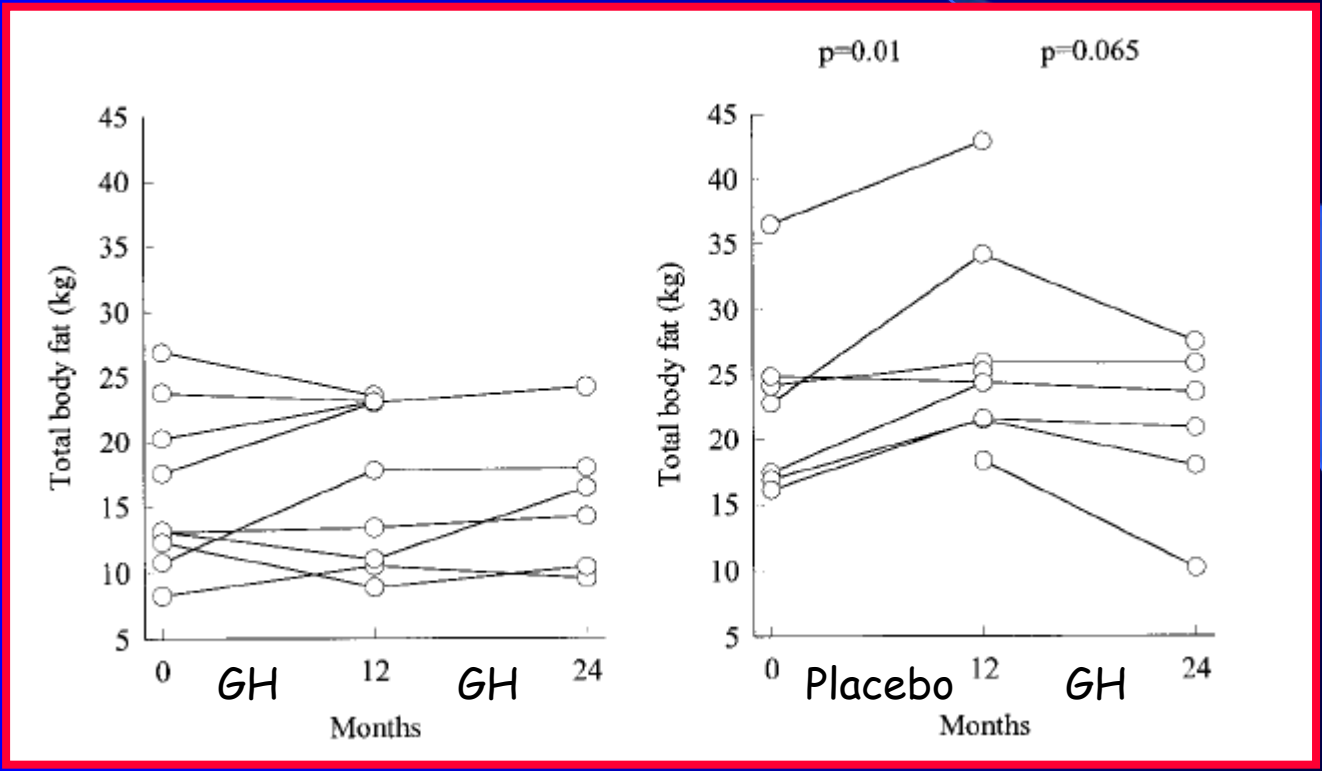


Johannsson G et al. J Clin Endocrinol Metab 1999; 84: 4516

TRANSITION

Continuation of GH Replacement in GH-Deficient Patients during Transition

Total body fat

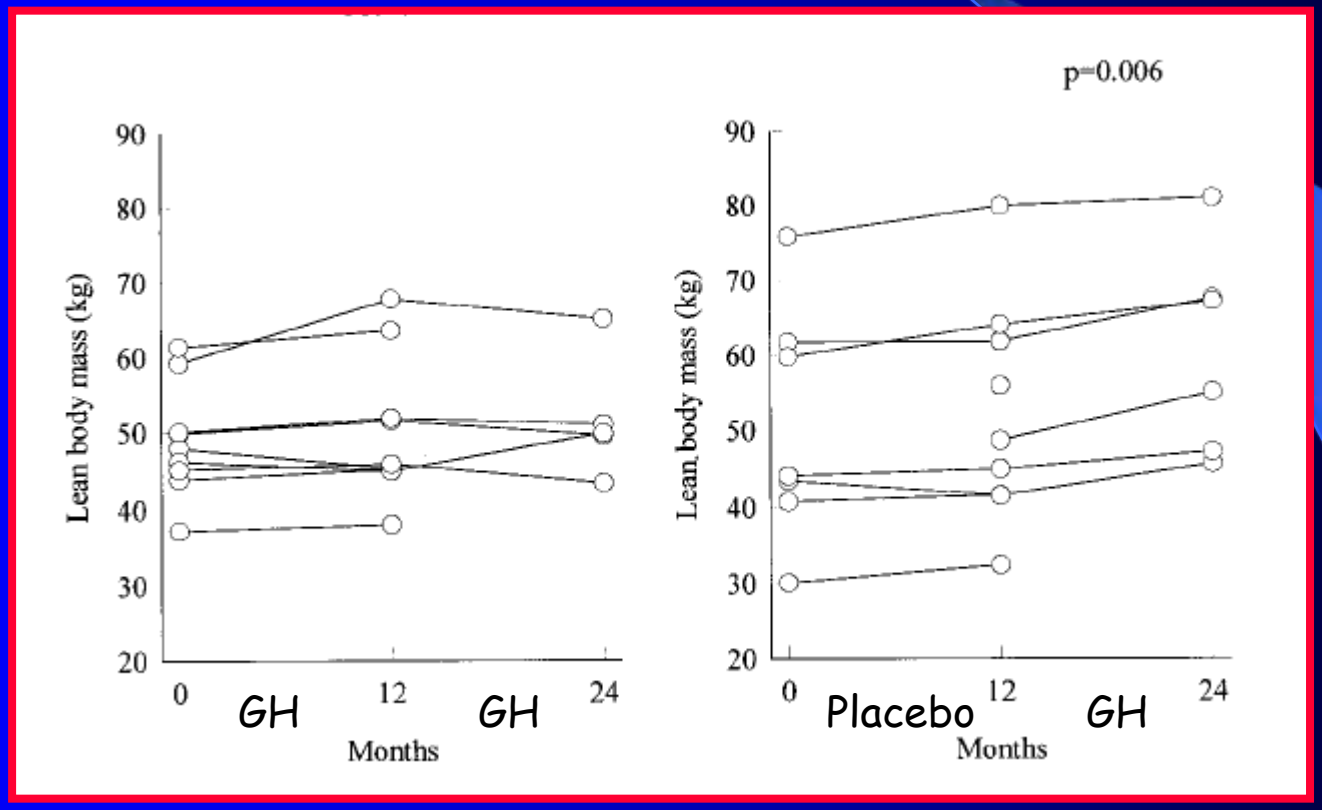


Vahl N et al. *J Clin Endocrinol Metab* 2000; 85: 1874

TRANSITION

Continuation of GH Replacement in GH-Deficient Patients during Transition

Lean body mass



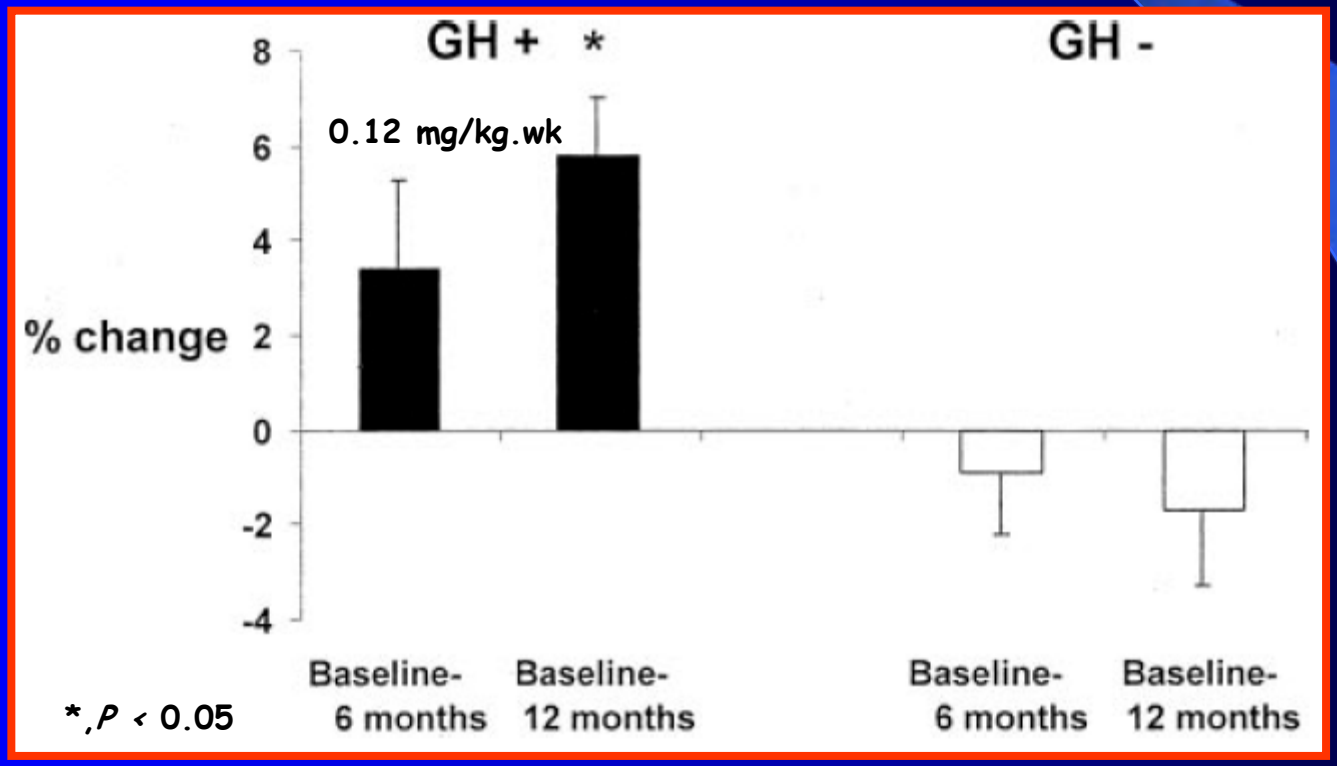
Vahl N et al. *J Clin Endocrinol Metab* 2000; 85: 1874

TRANSITION

Adolescents with Severe GH Deficiency at Completion of Linear Growth: Comparison of Continuation or Cessation of GH Therapy on Body Composition

Lean body mass

24 adolescents (13 males, 11 females) aged 17.0 ± 0.3, yr, mean ± SE

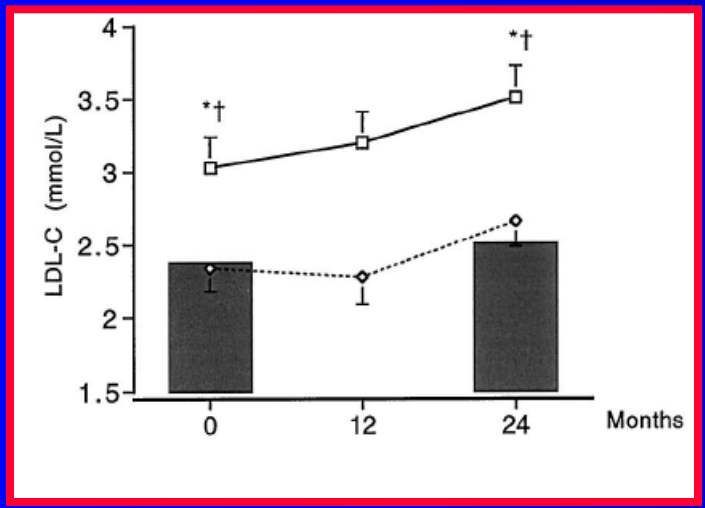


Carroll P V et al *J Clin Endocrinol Metab 2004 89:3890*

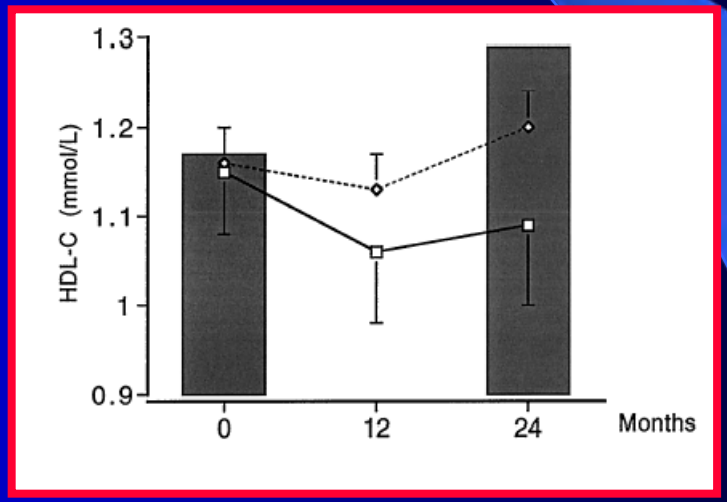
TRANSITION

Discontinuation of GH Treatment in GH-Deficient and GH-Sufficient Adolescent Patients Compared with Control Subjects

Serum LDL-C concentrations



Serum HDL-C concentrations



Johannsson G,et al. J Clin Endocrinol Metab 1999; 84: 4516

EFE 2006

TRANSITION

Adolescents with Severe GH Deficiency at Completion of Linear Growth: Comparison of Continuation or Cessation of GH Therapy on Metabolic Status

Serum lipids

24 adolescents (13 males, 11 females) aged 17.0 ± 0.3, yr, mean ± SE

- total cholesterol
- LDL cholesterol
- HDL cholesterol
- serum triglycerides

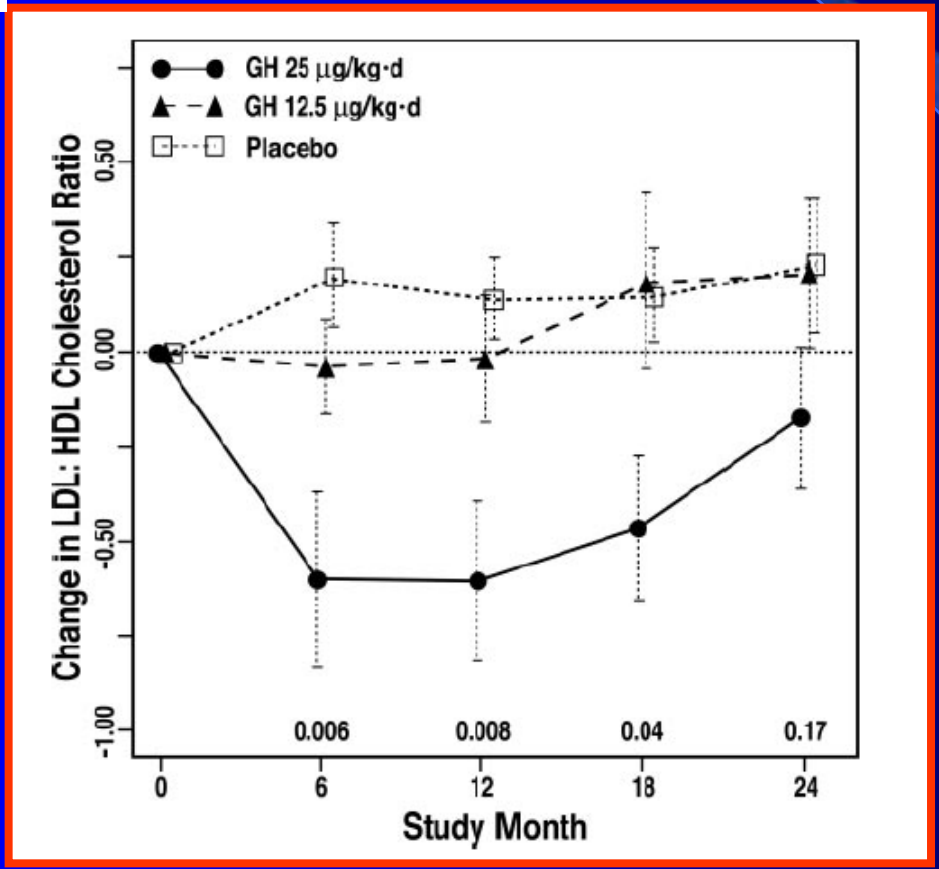
No changes occurred with either continuation (0.12 mg/kg.wk) or cessation of GH replacement

Carroll P V et al *J Clin Endocrinol Metab 2004 89:3890*

TRANSITION

GH Dose-Response in Young Adults with Childhood-Onset GH Deficiency

Serum lipids

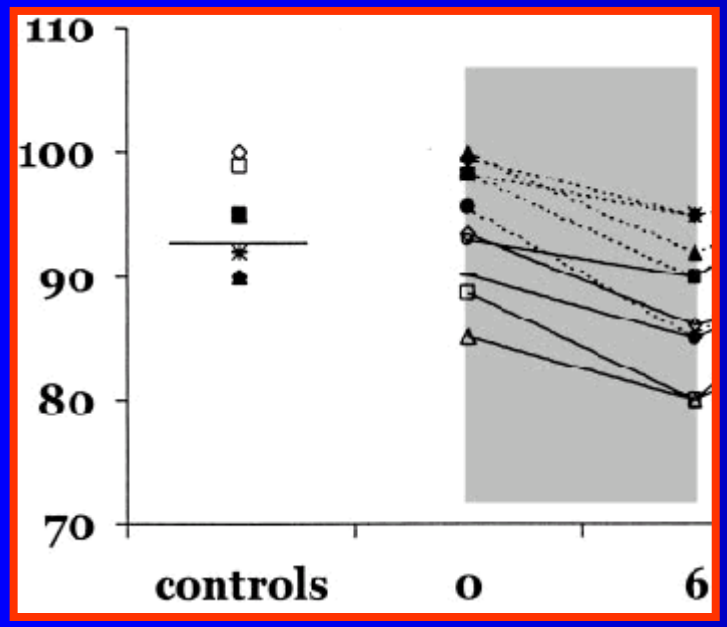


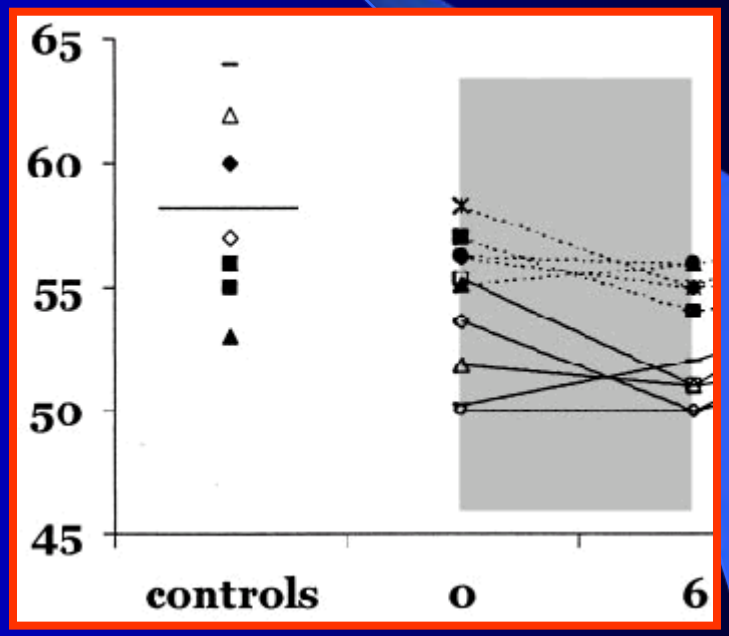
Underwood LE et al. J Clin Endocrinol Metab 2003,88:5273

TRANSITION

Discontinuation of GH Treatment in Adolescents GH Deficiency

Cardiac Function





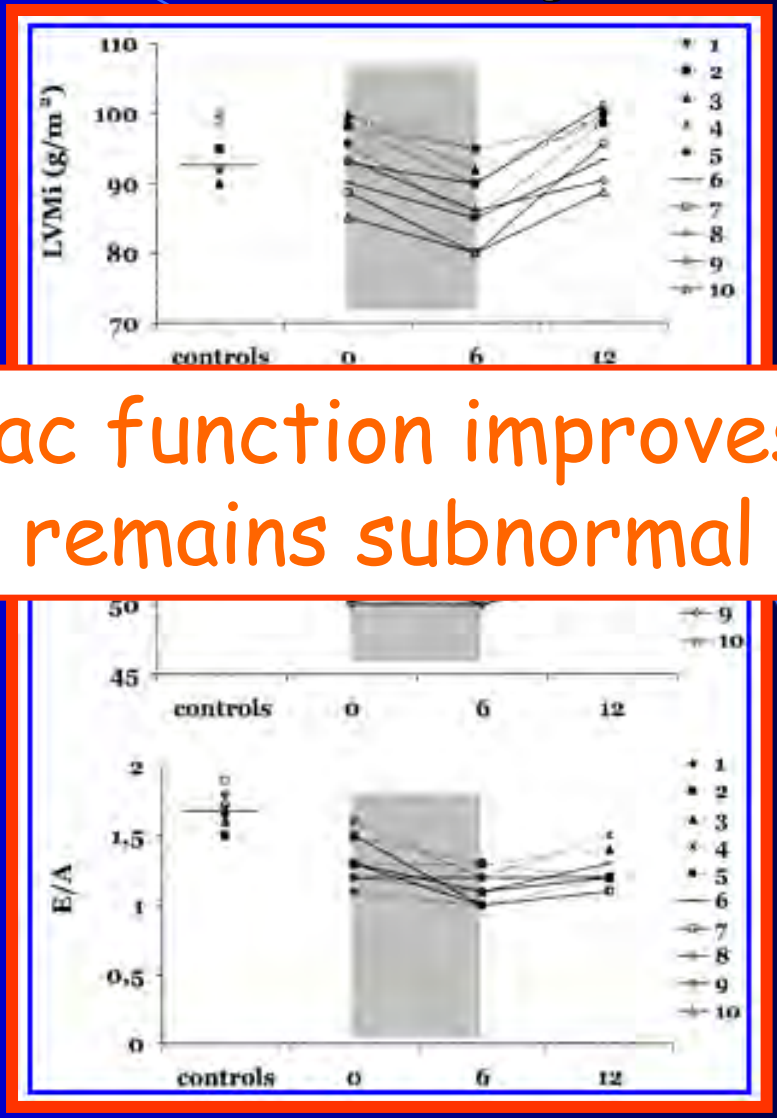
Colao A et al. J Clin Endocrinol Metab 2002; 87: 3650

TRANSITION

GH Replacement in GH-Deficient Patients during Transition

Cardiac Function

Left ventricular mass index



Cardiac function improves, but remains subnormal

Early/late mitral flow velocity ratio

GH dose
starting dose of 8–10 μg/kg.d
At the end of the study

	boys	girls
median	10 μg/kg.d	12 μg/kg.d
maximal	11 μg/kg.d	15 μg/kg.d

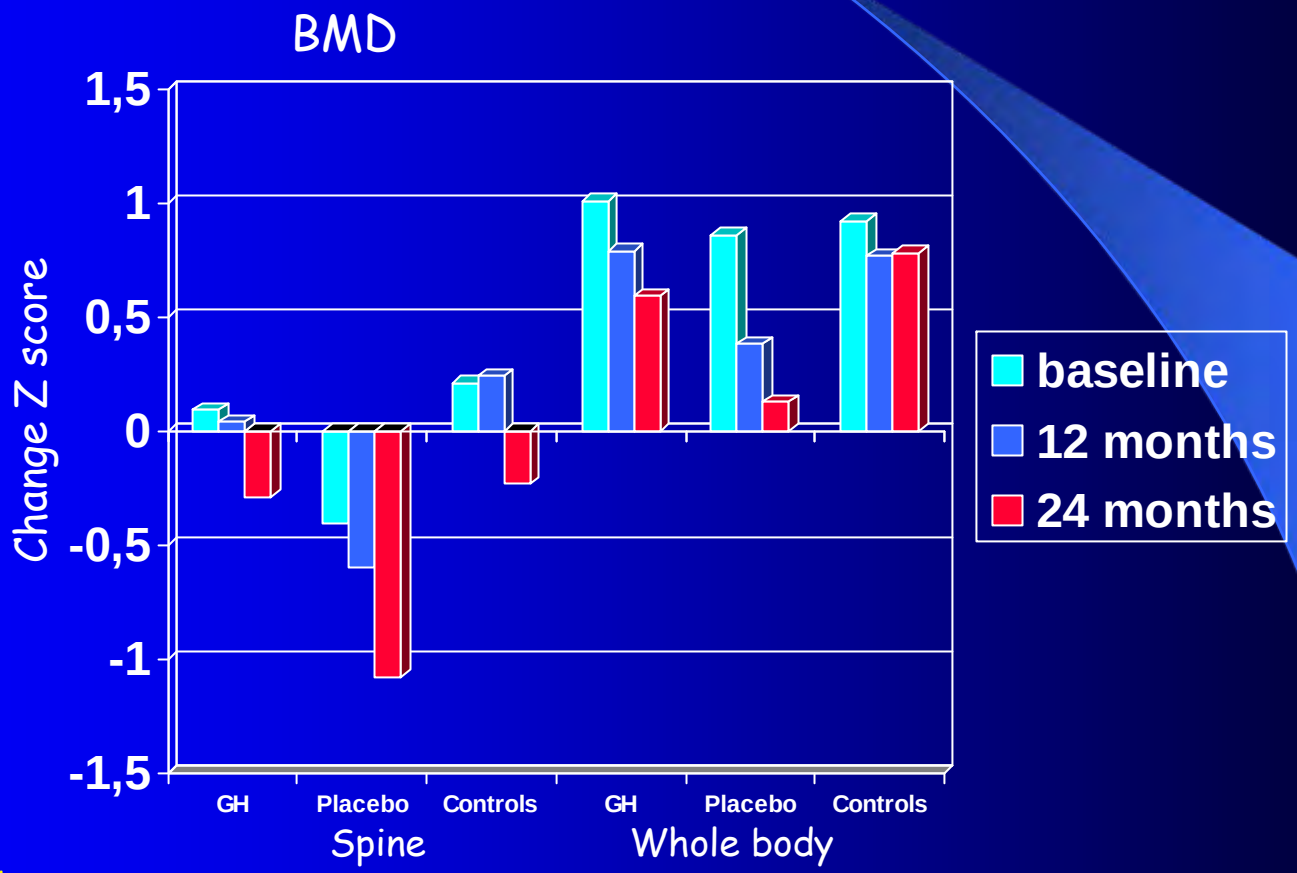
Colao A et al. J Clin Endocrinol Metab 2002; 87: 3650

EFE 2006

TRANSITION

GH Replacement in GH-Deficient Patients during Transition

Bone



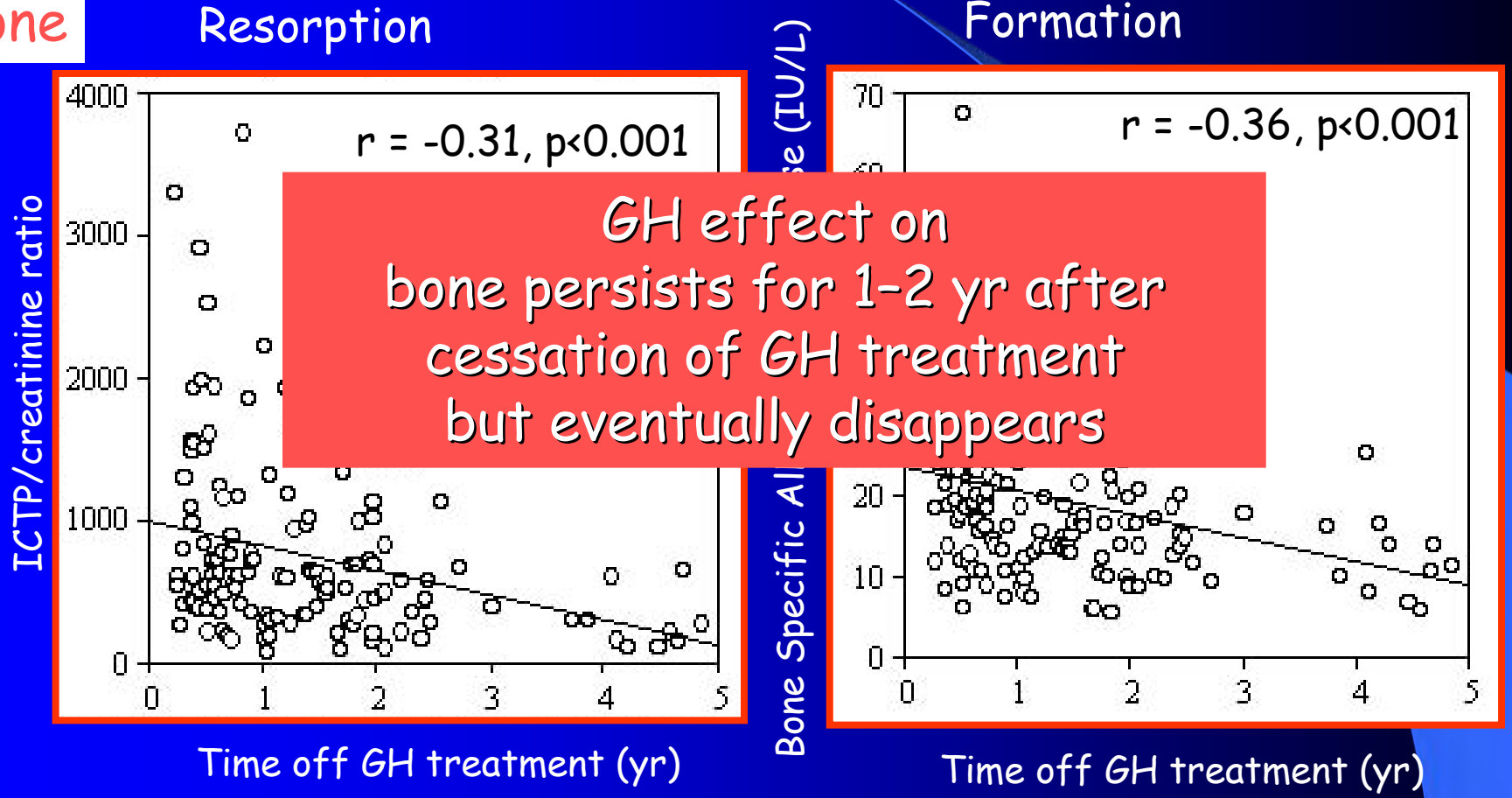
GH dose
20 μg/kg..d

Mauras N et al 2005, *J Clin Endocrinol Metab 2005,90:3946*

TRANSITION

Discontinuation of Growth Hormone (GH) Treatment

Bone



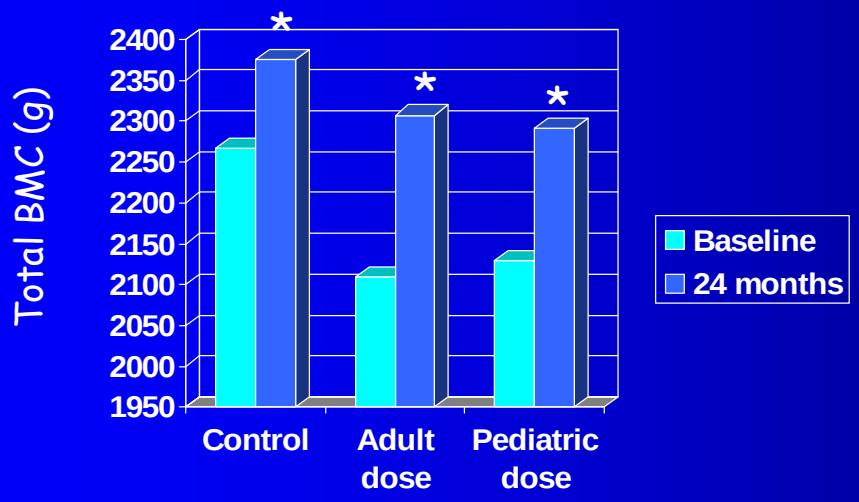
GH effect on bone persists for 1–2 yr after cessation of GH treatment but eventually disappears

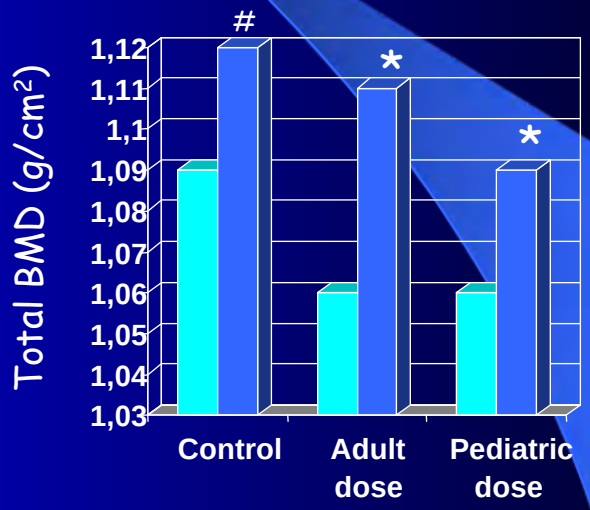
Shalet SM et al 2003, *J Clin Endocrinol Metab 2003,88::4124*

TRANSITION

GH Replacement in GH-Deficient Patients during Transition

Bone





\# p <0.01

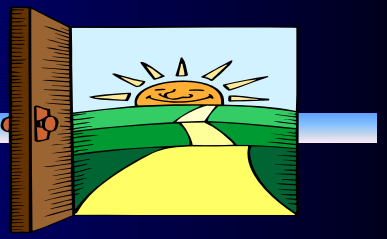
* p <0.001

Adult dose 12.5 µg/kg.d

Pediatric dosae 25.0 µg/kg.d

Shalet SM et al 2003, *J Clin Endocrinol Metab 2003,88::4124*

TRANSITION



Quality of Life

Adult GHD patients

CO patients showed
- less psychosocial distress
- less improvement in Nottingham Health Profile scores in response to GH replacement therapy

vs. AO patients

Attanasio AF et al. J Clin Endocrinol Metab 1997 ;82:82

Adolescent GHD patients

GH deficient patients after discontinuation of GH treatment showed
- greater impairment in the Psychological General Well-Being Index assessment in overall score and in the domains of depression and general health
- no difference in measurement of cognitive factors

vs. GH-sufficient patients

Wiren L et al. J Clin Endocrinol Metab 2001;86:3934

TRANSITION

Quality of Life

GH treatment did not cause significant changes in quality of life assessed by general healthy questionnaires

Mauras N et al. J Clin Endocrinol Metab 2005;90:3955

Vahl N et al. J Clin Endocrinol Metab 2000;85:1874

TRANSITION

Quality of Life in Childhood Onset Growth Hormone-Deficient Patients in the Transition Phase from Childhood to Adulthood

QoL questionnaire (QLSM-H)

- specifically developed for patients with adult GHD and hypopituitarism
- validated for adult patients

In CO GHD patients, scores for :

- ability to become sexually aroused
- ability to tolerate stress
- ability to concentrate
- self-confidence
- physical endurance
- body shape

were significantly lower than in the normal population

Attanasio AF et al. J Clin Endocrinol Metab 2005 90:4525

TRANSITION

Quality of Life

Baseline to 2-yr changes in total QLS-H SD score and individual items SD scores

QLS-H item	Control (n = 13)	GH treated (n = 42)	P^b
Total score	0.00 ± 0.80	0.12 ± 0.89	0.385
P value[a]	0.652	0.822	
Ability to become sexually aroused	0.06 ± 0.73	***0.23 ± 0.78***	0.368
P value[a]	0.688	***0.038***	
Ability to tolerate noise	−0.33 ± 1.27	0.00 ± 1.06	0.611
P value[a]	0.508	0.776	
Ability to tolerate stress	−0.04 ± 0.68	0.00 ± 0.98	0.992
P value[a]	0.875	0.871	
Body shape	−0.12 ± 0.78	***0.46 ± 1.26***	0.106
P value[a]	0.676	***0.035***	
Concentration	0.13 ± 0.70	−0.18 ± 1.06	0.422
P value[a]	0.641	0.316	
Ability to cope with own anger	−0.21 ± 0.93	0.01 ± 0.95	0.550
P value[a]	0.492	0.969	
Initiative/drive	−0.07 ± 0.89	−0.11 ± 1.07	0.766
P value[a]	0.945	0.717	
Physical endurance	0.30 ± 0.73	0.20 ± 1.24	0.704
P value[a]	0.232	0.524	
Self confidence	0.27 ± 0.95	0.02 ± 0.98	0.296
P value[a]	0.334	0.900	

P^a vs baseline
P^b control vs GH treated

GH treatment increased QLS-H score only for sexual arousal and body shape

Attanasio AF et al. J Clin Endocrinol Metab 2005 90:4525

EFE 2006

TRANSITION

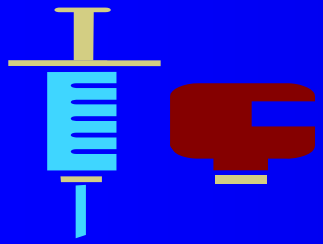
Quality of Life

- Discontinuation of GH replacement therapy at final height does not associate with a rapid decline in QoL in patients remaining GH deficient
- GHD questionnaires may preferentially detect QoL issues in AO patients of an older age range
- Available instruments may not be sensitive enough for younger CO patients, specifically for those in the transition phase

Quality of life measure is not a useful parameter for continuing GH replacement during transition

TRANSITION

What is the appropriate GH dose during transition?

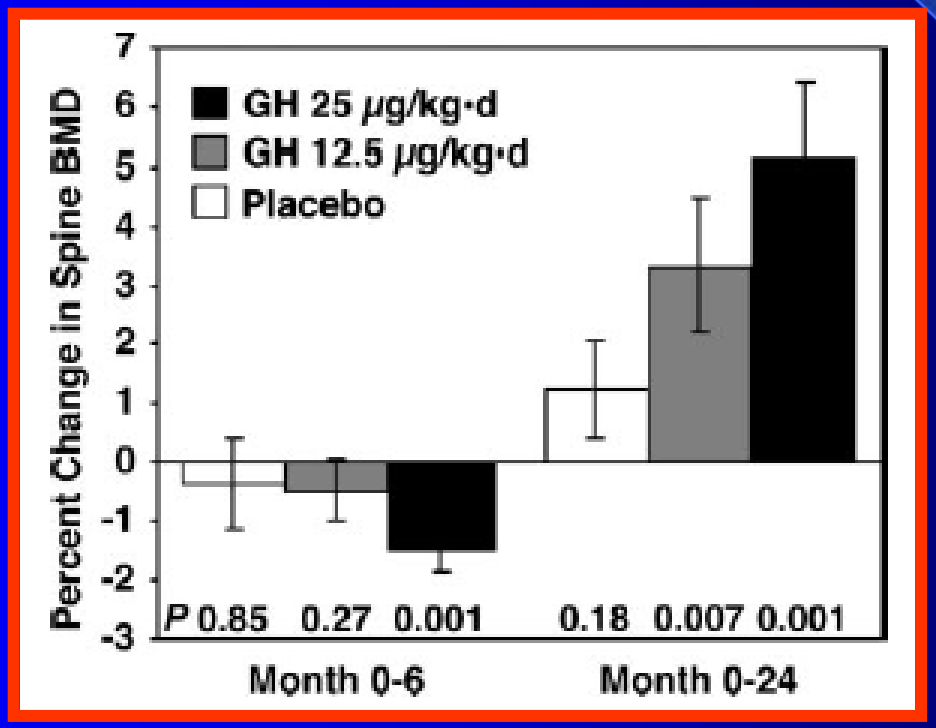


TRANSITION

Dosing of GH

Bone

GH Dose-Response in Young Adults with Childhood-Onset GH Deficiency



39 males, 25 females
Age (yr) 23.8 ± 4.2

Dose response:
Month 0–6, *P* 0.035
month 0–24, *P* 0.018

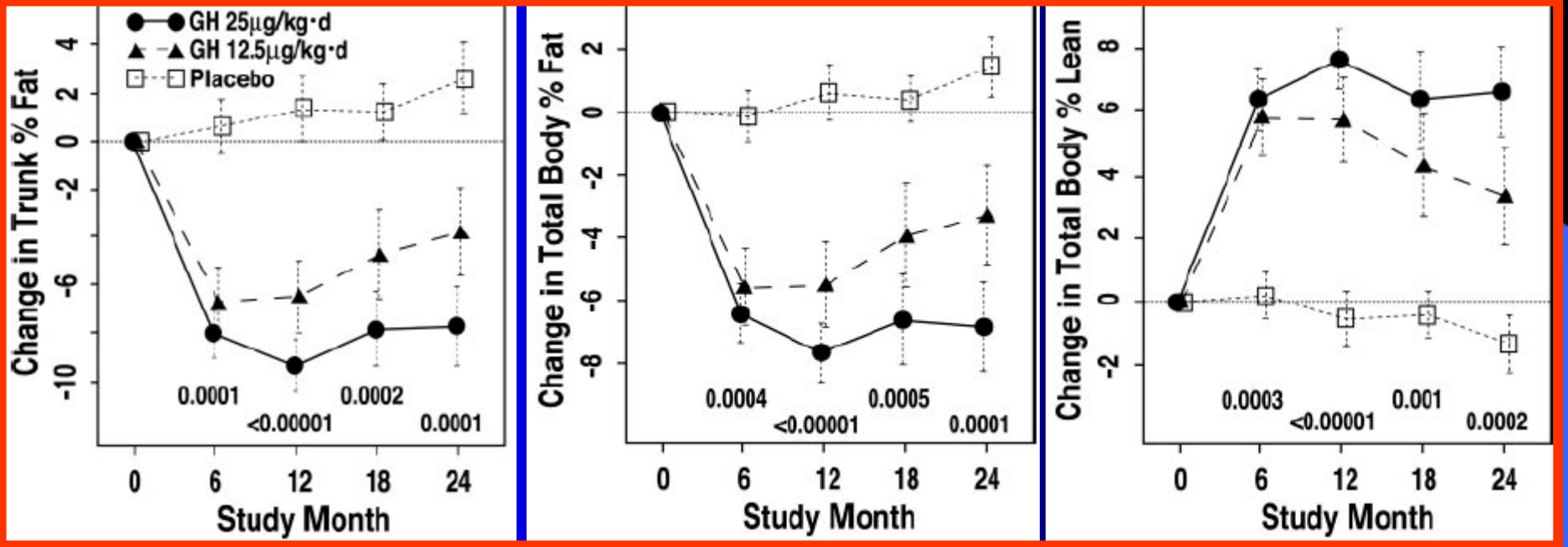
Underwood LE et al. J Clin Endocrinol Metab 2003,88:5273

TRANSITION

Dosing of GH

Body Composition

GH Dose-Response in Young Adults with Childhood-Onset GH Deficiency



39 males, 25 females
Age (yr) 23.8 ± 4.2

Underwood LE et al. J Clin Endocrinol Metab 2003,88:5273

TRANSITION

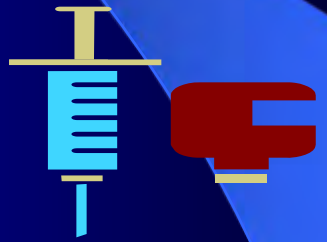
Dosing of GH After Completion of Linear Growth

ESPE 2003:

Restart at 0.2-0.5 mg/d (if previous GH discontinued 1-3 mo)

Titrate on the basis of IGF-1 level

Maximum dose: 2.0 mg/d



Clayton PE et al Eur J Endocrinol 2005, 152:165

AACE 2003:

Start at 0.4-0.8 mg/d

Increase by 0.2–0.4 mg/d every 4-6 wks

Maintenance dose: 1.2 – 2.0 mg/d

Endocrine Practice 2003, 9:65

TRANSITION

IGF-1

at present
is the best biochemical marker of GH responsiveness
is mandatory as a safety marker

The GH dose should be adjusted to achieve IGF-1 levels within but not exceeding the upper normal range (IGF-1 SDS: 0 to +2)

Serum IGF-1 levels should be monitored every 6 months

Fasting
Malnutrition
Hepatic failure
Inflammatory bowel disease
Renal failure
Hypothyroidism

→ LOW IGF-1

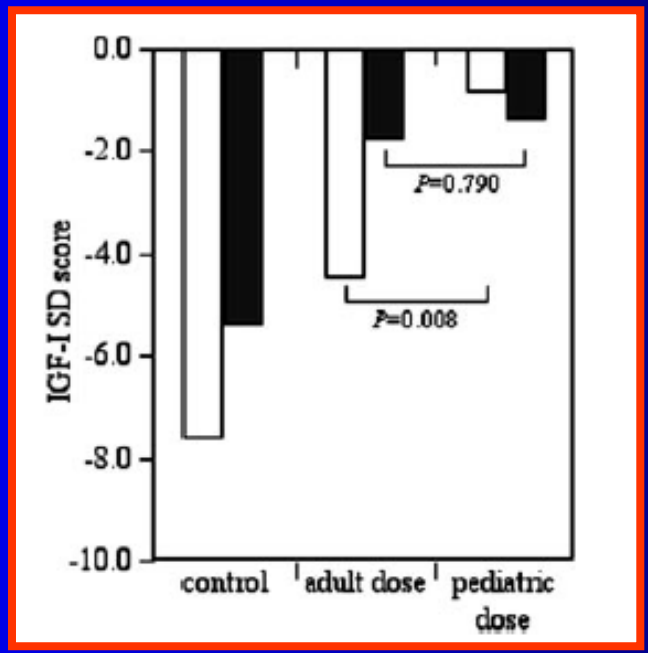
Clayton PE et al Eur J Endocrinol 2005, 152:165

TRANSITION

Continuation of GH Replacement in GH-Deficient Patients during Transition

Serum IGF-1 SD score after 2 yr with no treatment (control) or GH treatment at an adult or pediatric dose in female (■) and male (■) CO GHD patients

	Age (yr)
Control (n°32)	→ 19.9±3.1
Adult dose (n°58)	→ 19.4±2.7
Pediatric dose (n°59)	→ 19.6±32.8



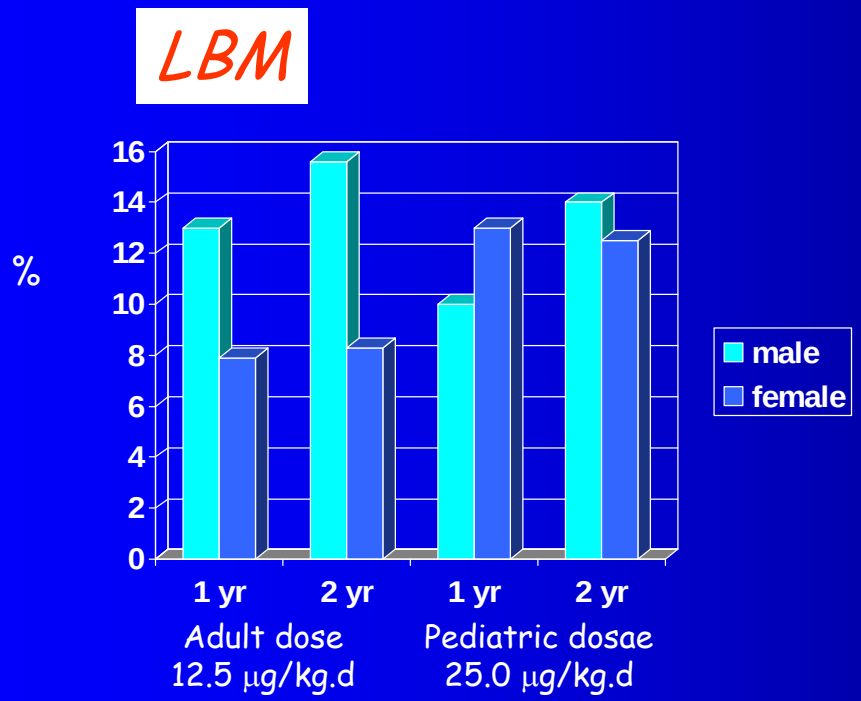
Attanasio AF et al. J Clin Endocrinol Metab 2004 89:4857

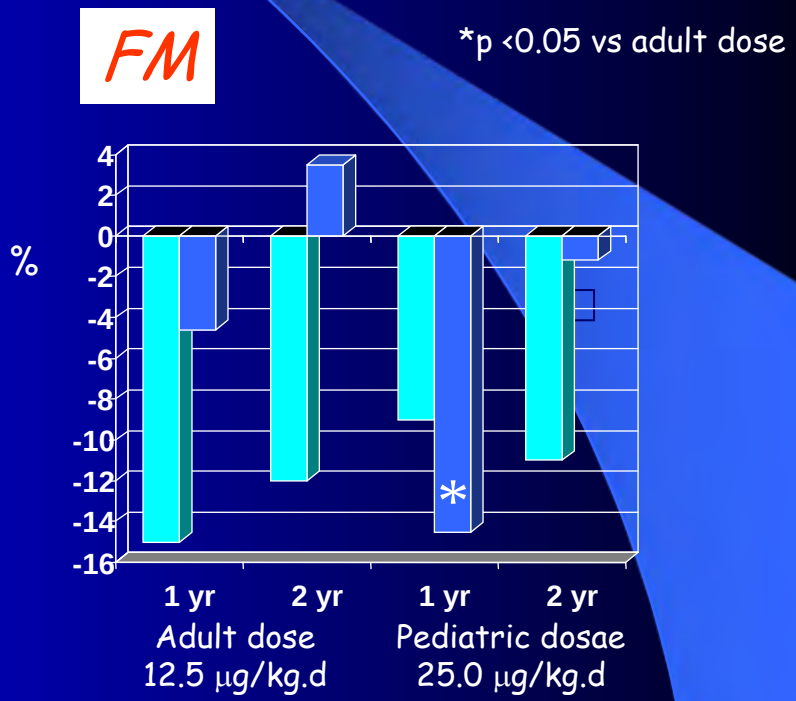
TRANSITION

Continuation of GH Replacement in GH-Deficient Patients during Transition

Changes from baseline to yr 1 and 2 for females and males

*p <0.05 vs adult dose



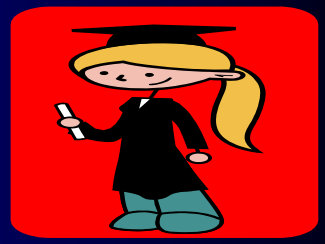


Females may require a higher dose, still in the pediatric range

Attanasio AF et al. J Clin Endocrinol Metab 2004 89:4857

TRANSITION

Dosing of GH After Completion of Linear Growth



Women generally require higher GH doses than men,
in particular those treated with oral estrogen replacement

The dose and route of oestrogen administration influence

IGF-1 generation

and

therefore GH dose requirement

Clayton PE et al Eur J Endocrinol 2005, 152:165

TRANSITION

Transition care

Transition care requires a dedicated service with contributions from paediatric and adult endocrinologists skilled in the management of hypopituitarism and GHD

Local resources will determine the precise format of the service

Patient education is an implicit part of the transition program. This educational process should start at the time of diagnosis in childhood, when the patient and family are informed, not only of the linear growth-stimulating effect of GH, but also of its life-long effects on body composition and metabolism

Clayton PE et al Eur J Endocrinol 2005, 152:165

TRANSITION

Conclusion

Assessment and treatment of patients in this phase of life should acknowledge that these patients are not just "older children" or "younger adults" but that they are a unique and separate group with distinct and different needs

THANK YOU !!!

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De Paola Grazia
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GHD in Elderly

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GHD in elderly is somatopause?

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How Do Hormones Change with Normal Aging?

- Estrogens- decrease to very low levels over a 1-3 year period at menopause (between ages 45-55)
- Testosterone (T)- Gradual decline from age 30 onward reaching low (hypogonadal) levels in >50% of men by age 65
- Adrenal Steroids-
  - Active adrenal hormones (cortisol and aldosterone) change little
  - DHEA, steady decrease with age to very low levels in both sexes
- Thyroid- not much change in healthy men and women, but increased prevalence of hypothyroid disease in older persons.
- Insulin- loss of sensitivity to insulin action with aging and obesity

- **Growth Hormone (GH)- Gradual decrease in secretion (and circulating IGF-I levels) from age 45-90**

Clinical features of Growth Hormone Deficiency in adults

- Increased weight and body fat mass
- Decreased lean body mass
- Decreased exercise capacity
- Decreased muscle mass and strength
- Reduced cardiac performance
- Reduced bone density and increased fracture rate
- Poor sleep
- Impaired sense of well-being

Similarities of Changes in Body Composition, Muscle Strength, Aerobic Capacity and Metabolic Variables with Aging and in Hormone Deficiency

	Aging	Low GH	Low T	High Cortisol	Low E2
Lean Body Mass Muscle Strength	↓	↓	↓	↓	–
Aerobic Capacity	↓	↓	↓	↓	–
Percent Body Fat	↑	↑	↑	↑	↑
Total and LDL Cholesterol	↑	↑	↑	↑	↑
Insulin sensitivity Glucose tolerance	↓	↓	↓	↓	–

Somatopause

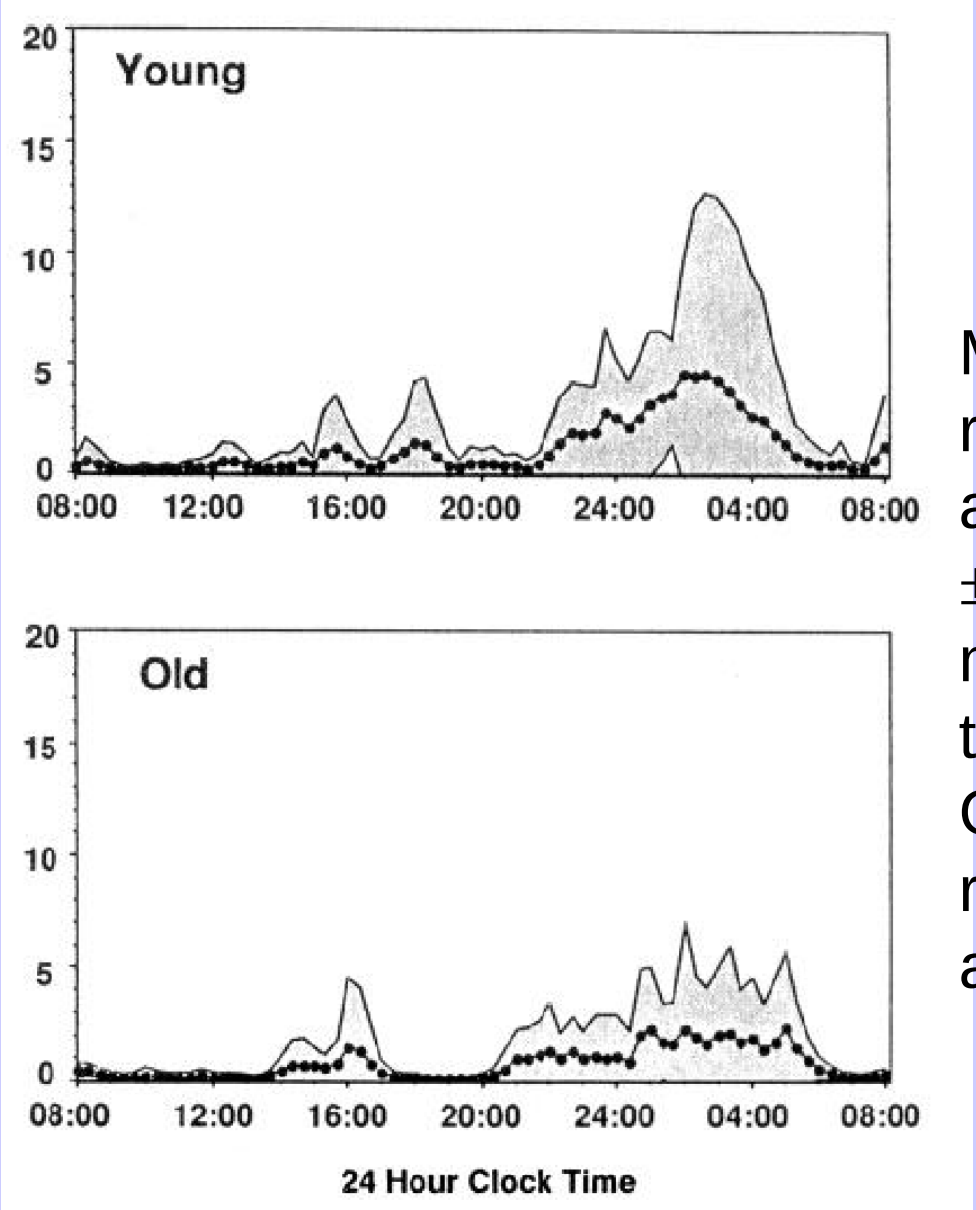
On the average, for a normal body mass index, each decade of increasing age attenuated the GH production rate by 14% and the GH half-life by 6%.

(*Iranmanesh, JCEM 1991*).

In the elderly men the mean basal plasma GH level was similar to that in the young men, but the total GH peak area as well as the amplitude of the peaks were significantly (p less than 0.01) lower than those in young men during both the day and the night.

Plasma SM-C levels were significantly lower in the elderly men and were correlated with the total integrated GH levels and total GH peak areas, but not with basal plasma GH levels, suggesting that the GH peaks determine SM-C levels and that the decreased GH secretion in elderly men has biological significance.

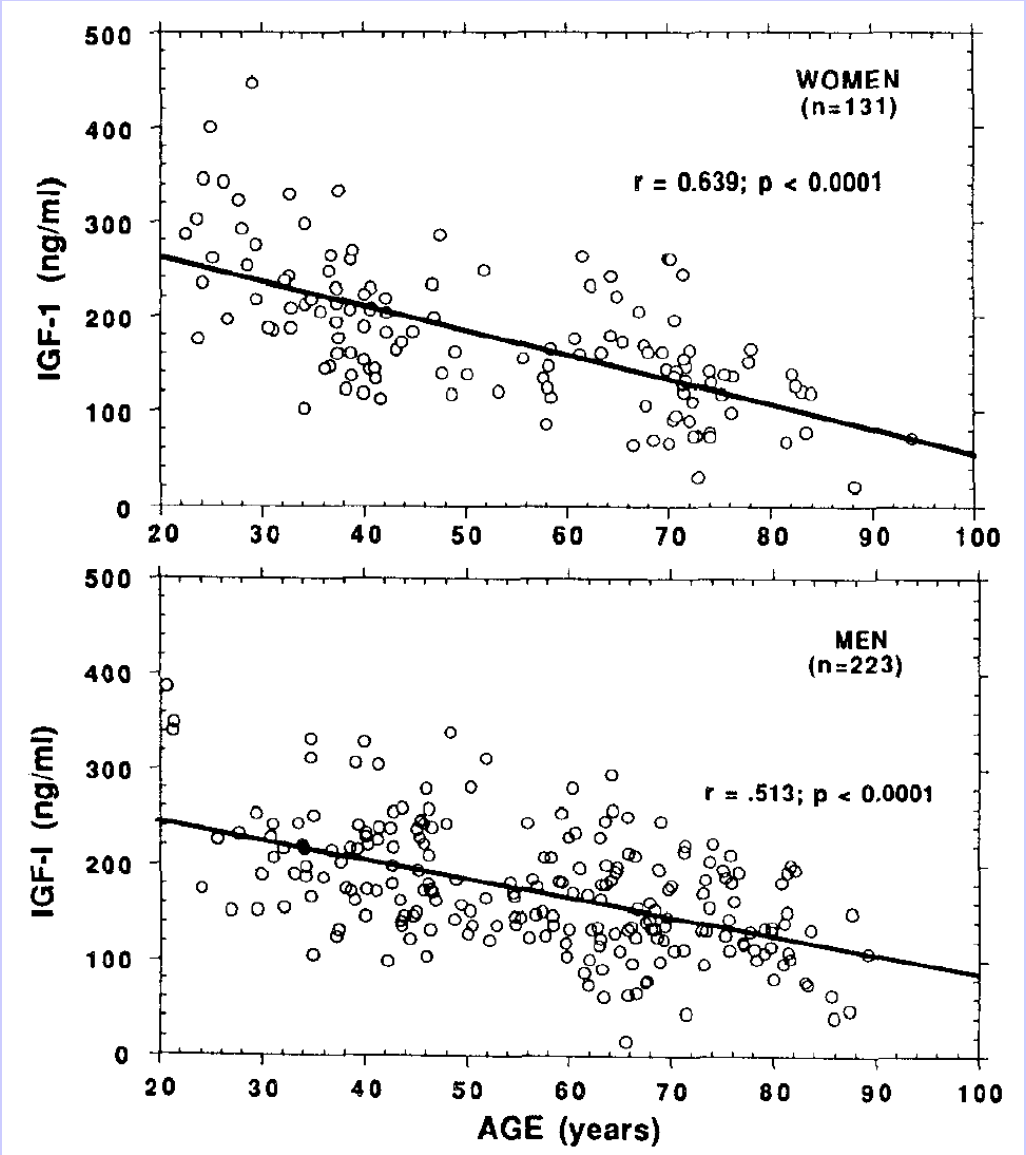
(Vermeulen, JCEM 1987).



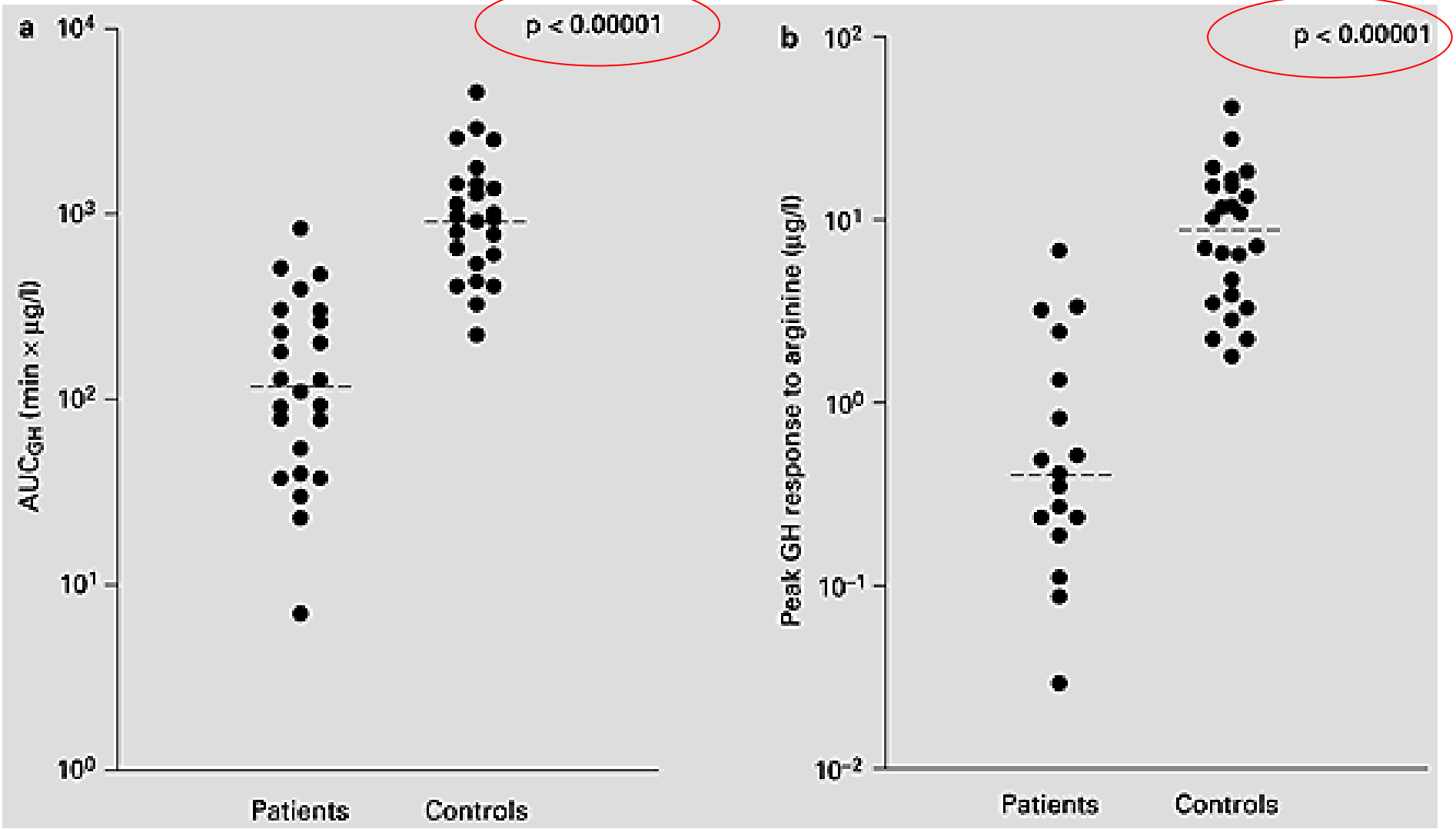
Mean (± 1SD) 24 h GH release in nine young (mean age 26±4 yr) and 10 old (68 ± 6 yr) men sampled at 20 min intervals, demonstrating the normal diurnal pattern of GH secretion and the reduced nocturnal peak amplitude in the older men.

(Corpas, Endocrine Rev. 1993)

IGF-I levels in normal women and men in the Baltimore Longitudinal Study on Aging; the decrease with age in mean (± 1 SD) IGF-I is shown by decade

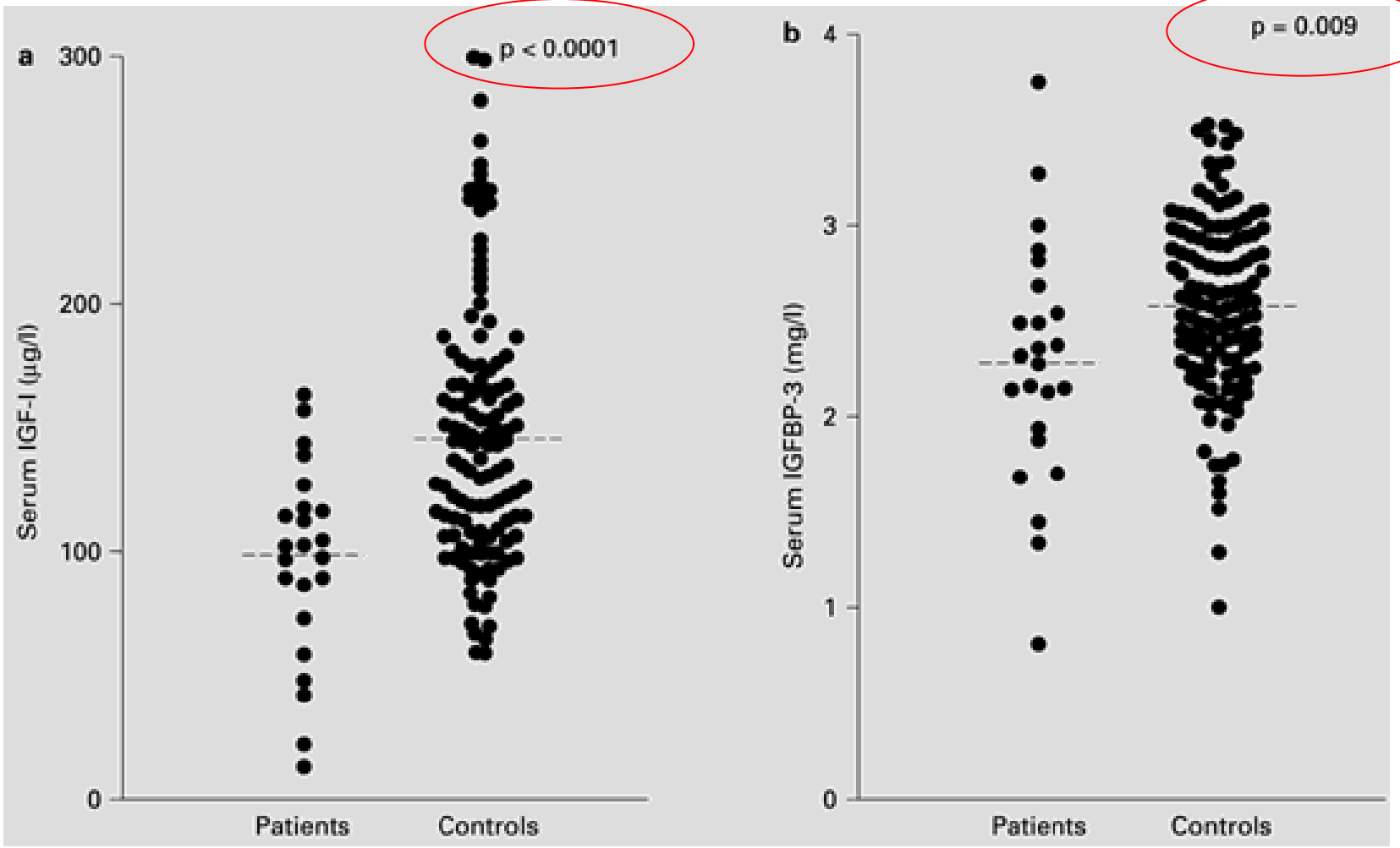


(Corpas, Endocrine Rev. 1993)



GH secretion in 24 patients with hypothalamic-pituitary disease and 24 control participants. **a** Area under the curve of the 24-hour GH profile (20-min sampling) and **b** peak GH response to arginine. Median values are indicated by horizontal bars.

(Toogood, Horm Res 2003)



Serum concentrations of IGF-I (**a**) and IGFBP-3 (**b**) in 24 patients with hypothalamic-pituitary disease compared with data from 125 control individuals aged over 60 years. Median values are indicated by horizontal bars.

(Toogood: Horm Res, 2003)

Mass, kg	Patients (n = 21)	Controls (n = 24)	p
Total fat	27.5 (19.2–50.2)	21.2 (8.8–49.2)	0.0047
Total lean	50.9 (27.0–69.2)	51.6 (32.4–60.5)	0.8
Arms, fat	3.3 (2.0–8.3)	2.4 (0.8–7.1)	0.033
Legs, fat	7.3 (4.2–16.4)	5.6 (2.4–17.1)	0.021
Trunk, fat	15.7 (10.0–24.1)	12.4 (5.1–23.2)	0.009
Arms, lean	6.7 (2.8–8.6)	6.5 (3.5–8.1)	0.9
Legs, lean	16.2 (8.8–22.5)	17.1 (10.6–21.0)	0.4
Trunk, lean	24.4 (12.5–35.2)	24.8 (15.3–29.9)	0.96

Values are expressed as median (range).

Fat and lean mass measured in elderly patients with hypothalamic-pituitary disease and elderly controls

(Toogood: Horm Res, 2003)

	Patients (n = 21)	Controls (n = 24)	p
Vertebrae L2–L4	0.80 (–2.83 to 2.95)	1.10 (–2.87 to 2.64)	0.68
Femoral neck	0.27 (–1.48 to 3.43)	0.25 (–2.29 to 3.26)	0.89
Femoral trochanter	0.46 (–2.14 to 3.37)	0.50 (–2.4 to 3.8)	0.98
Ward's triangle	0.10 (–1.58 to 3.94)	0.47 (–2.45 to 3.31)	0.96

Values are expressed as median (range).

Age-specific standard deviation scores at each site measured in elderly patients with hypothalamic-pituitary disease and elderly controls

(Toogood: Horm Res, 2003)

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Normal elderly subjects

vs

Diagnosis of GHD in elderly

Appropriate clinical context

and

Basal IGF-I and GH stimulation test!

Consensus Guidelines GHRS ***J Clin Endocrinol Metabol, 1998***

CAUSES OF GHD

- Acquired
  - Trauma
    - Perinatal
    - Postnatal
  - Central nervous system infection
  - Tumors of hypothalamus or pituitary
    - Pituitary adenoma
    - Craniopharyngioma
    - Rathke's cleft cyst
    - Glioma/astrocytoma
    - Germinoma
    - Metastatic
    - Other
  - Infiltrative/granulomatous disease
    - Langerhans cell histiocytosis
    - Sarcoidosis
    - Tuberculosis
    - Hypophysitis
    - Other
  - Cranial irradiation
  - Surgery
  - Idiopathic

(Molitch, JCEM, 2006)

	Age >65 years	Age <65 years	p
Patients, n	170	1,395	
Age, years	69.1 (65.6–74.1)	47.9 (31.4–60.3)	<0.0001
Males, %	61.8	51.0	0.008
Females, %	38.2	49.0	0.008
Pituitary adenoma, %	77.1	57.9	<0.001
Craniopharyngiomas, %	4.7	11.7	<0.01
Other pituitary/hypothalamic tumours, %	3.5	4.0	ns
Cranial tumours, %	0.0	2.7	na
Treated malignancies, %	0.0	0.4	na
Other causes, %	8.2	15.1	<0.05
Idiopathic, %	6.5	8.2	ns
Duration of pituitary disease, %	5.4 (1.3–23.3)	4.5 (0.96–18.9)	0.051
Number of additional deficiencies, %			0.38
0	5.3	10.0	<0.05
1	12.4	13.1	ns
2	22.4	15.7	<0.05
3	48.8	40.4	<0.05
4	11.2	20.9	<0.05
Peak GH on stimulation test, ng/ml	Male: 0.33 (0.07–2.40)	Male: 0.42 (0.10–2.20)	0.15
	Female: 0.23 (0.03–1.90)	Female: 0.60 (0.10–2.70)	<0.0001
IGF-I SDS	Male: –1.60 (–3.19 to +0.28)	Male: –1.76 (–4.36 to +0.27)	0.67
	Female: –1.78 (–3.81 to 0.06)	Female: –2.37 (–4.84 to –0.22)	0.04

Baseline clinical characteristics of male and female patients aged over and less than 65 years

(Monson Hormone Research, 2003)

* Includes a histiocytosis X, a pituitary apoplexy, a dysgerminoma, and a hypophysitis.
ap<0.05 vs. young GHD patients

The cause and type of the pituitary deficiency in the study population of 24 elderly patients and 24 younger patients with adult onset GH deficiency. Values are presented as the mean (range), the mean (SEM), or as number.

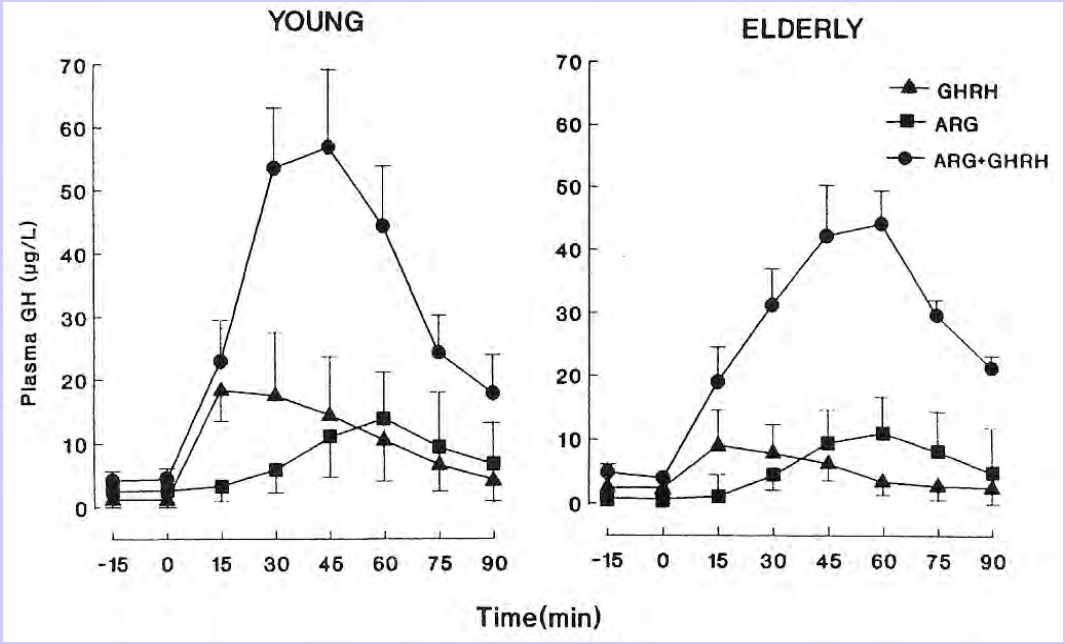
(Franco JCEM 2006)

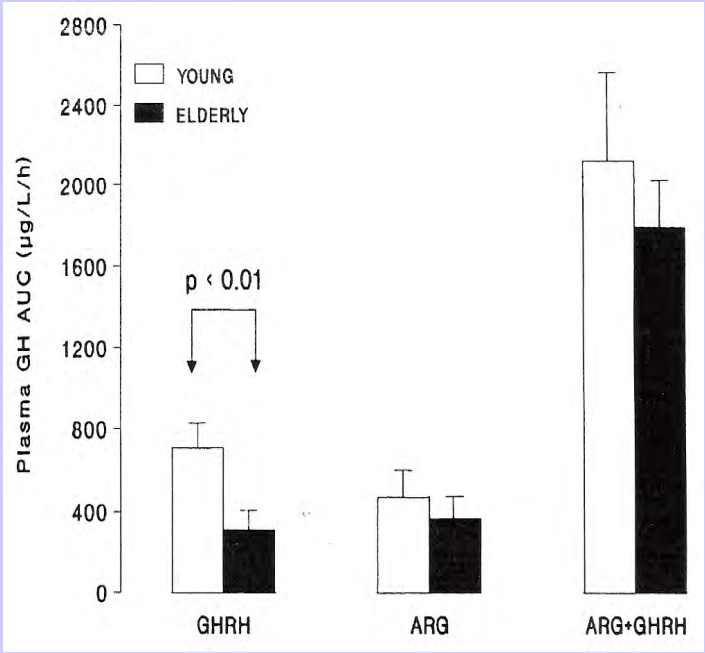
Baseline status	Elderly patients	Young patients	Total
Age (years; mean and range)	68 (65-75)	37 (27-46)	
Gender (all/men/women)	24/15/9	24/15/9	48/30/18
Body height (m)	1.70 (0.02)	1.74 (0.02)	
Body weight (kg)	81.2 (2.9)	85.5 (2.8)	
BMI (kg/m2)	28.1 (0.9)	27.9 (0.9)	
Waist circumference (cm)	99.2 (2.3)	97.0 (2.2)	
Waist:hip ratio	0.97 (0.01)	0.94 (0.01)	
Duration of hypopituitarism (years)	9.3 (1.8)[a]	4.1 (1.0)	
Type of pituitary deficiency			
Non-secreting pituitary adenoma	14	11	25
Hormone-secreting pituitary adenoma	7	4	11
Craniopharyngioma	1	1	2
Empty sella	2	2	4
Sarcoidosis	0	2	2
Other pathology *	0	4	4
Additional pituitary hormonal deficiencies			
0	2	3	5
1	4	2	6
2	3	3	6
3	15	16	31
Total number of deficiencies	55	56	111

Etiology of GHD in elderly (>65 years)

	Elgzyri Clin Endo,2004	*Colao Pituitary, 1998*	*UCSC 1998-2005* *Not Pub.*
•NFPA	24	16	20
•FPA		1	
•Prolattinomas	1		1
•Iidiopatic	2		
•Cystis	1		
•Empty sella	1		2
•Encephalitis	1		
•Craniopharyngiomas	1	2	4
•NFPA+ meningiomas	1		
•Sheehan			1
TOTAL	**31**	**19**	**28**

Growth hormone (GH) responsiveness to combined administration of arginine and GH-releasing hormone does not vary with age in man





(Ghigo J Clin Endocrinol Metab. 1990)

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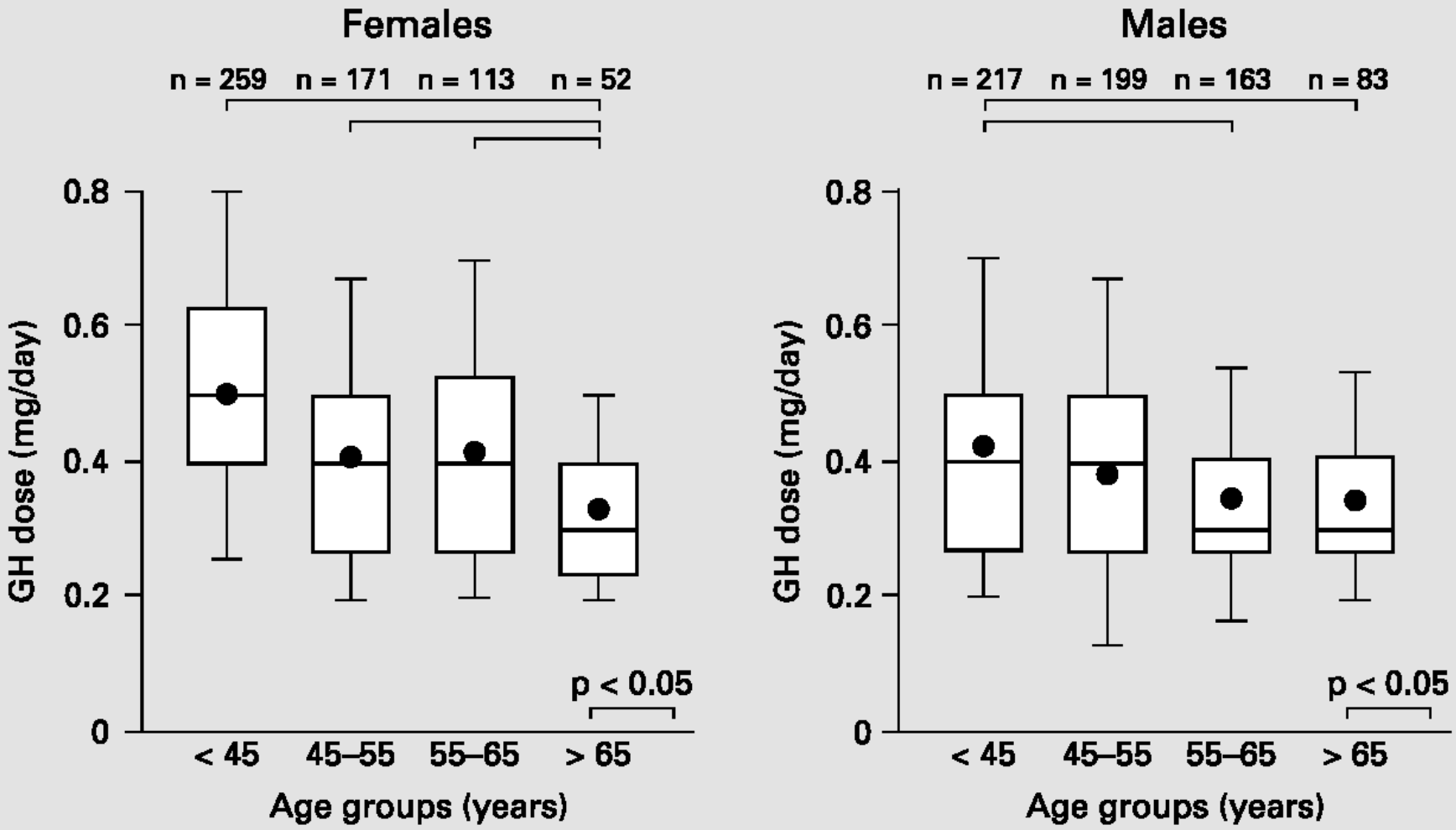
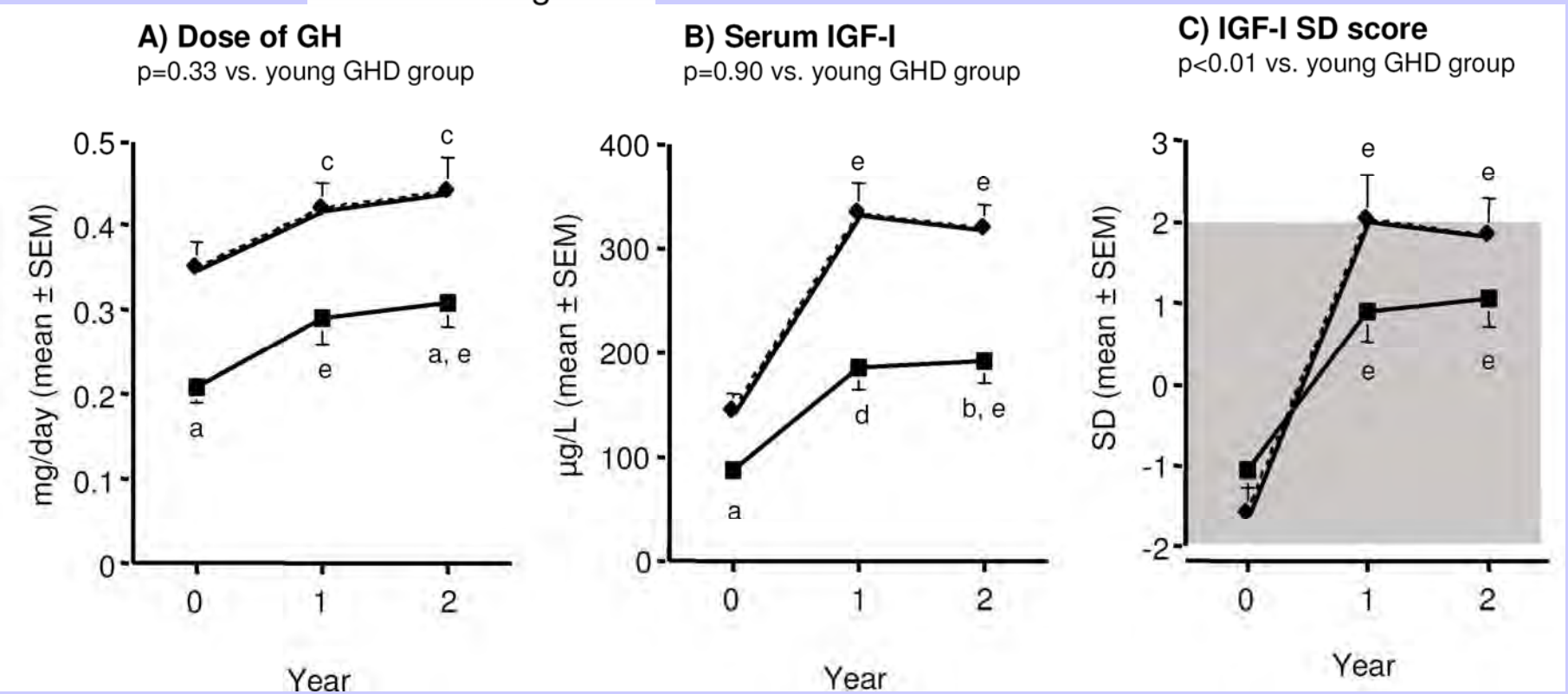


The dose of GH administered to patients in different age groups after 1 year of GH replacement therapy. Data are shown as mean, median and 10th–90th percentiles.

(Monson Hormone Research, 2003)



A) Dose of GH B) serum IGF-I concentration and C) IGF-I SD score in 24 elderly GHD patients above 65 years of age and 24 younger GHD patients (mean age 37; range 27-46 years). The vertical bars indicate the SE for the mean values shown. Between-group p-values (0-2 years) are based on an analysis of the percent change or change from baseline (for the dose of GH the analysis was based on the percent change from the dose prescribed at the baseline visit), whereas other p-values are based on an analysis of the absolute values. The shadowed area in C) represents ± 2 SD.a $p<0.01$; b $p<0.001$ [vs. young GHD adults at the same timepoint (baseline or study end)].c $p < 0.05$; d $p<0.01$ e $p<0.001$ (vs. baseline).

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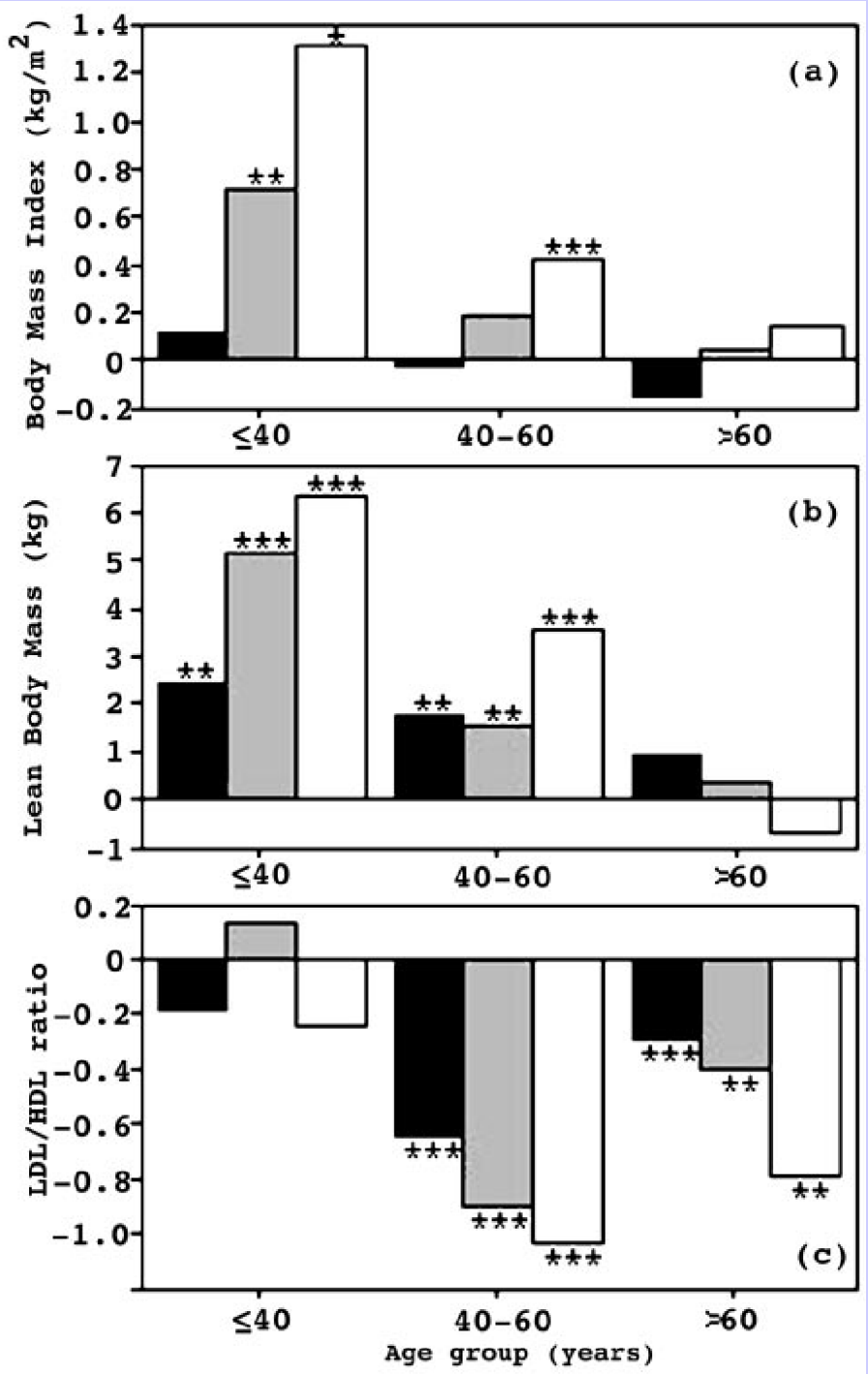
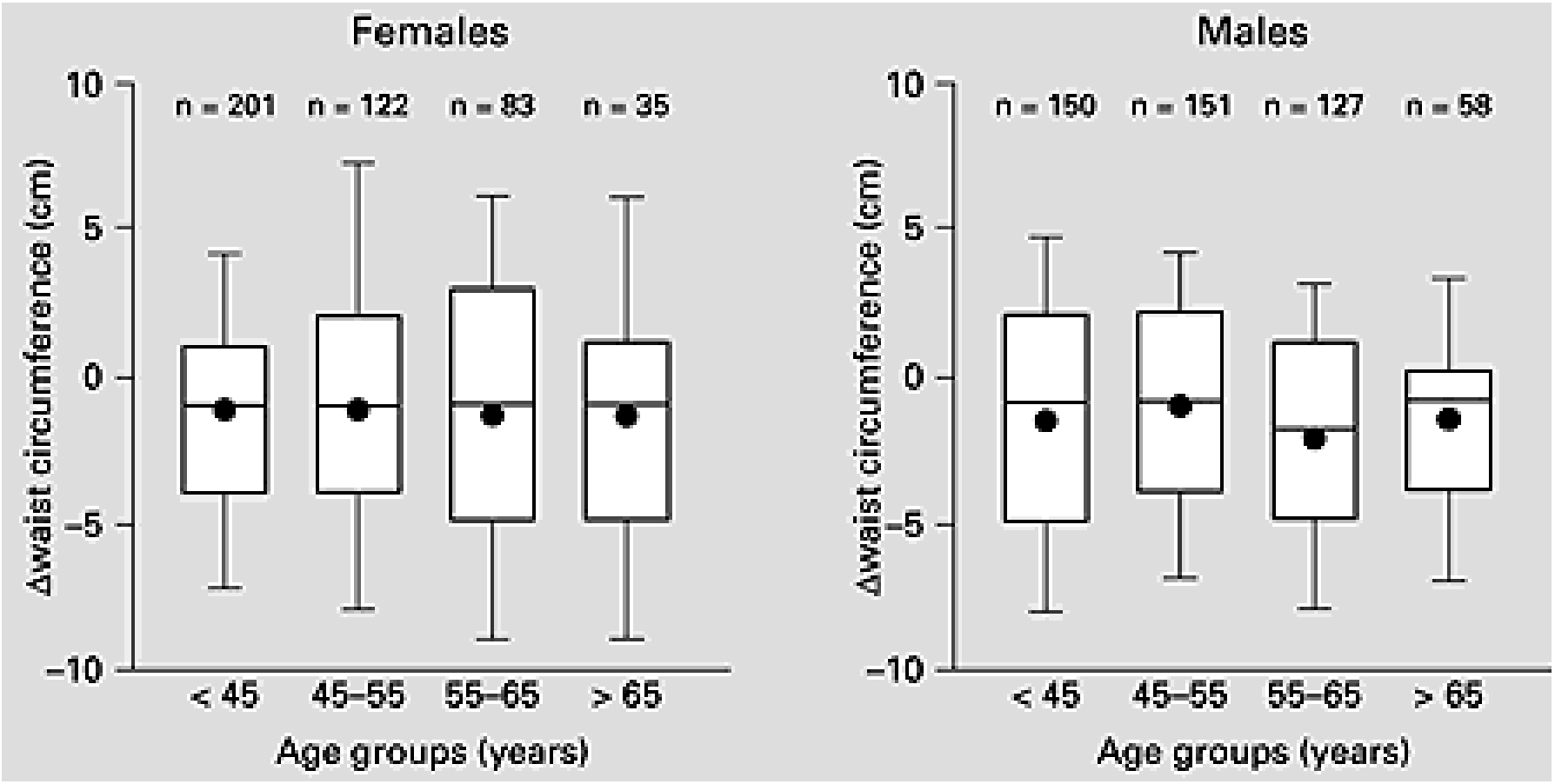
Mean changes from baseline in body mass index (*A*), lean body mass (*B*), and LDL/HDL ratio (*C*) after 1 yr (*black bars*), 2 yr (*gray bars*), and 3 yr (*white bars*) of GH treatment of AO GHD patients, by age groups.p< 0.05; **, *P*<0.01; ***, *P*<0.001 for change from baseline.

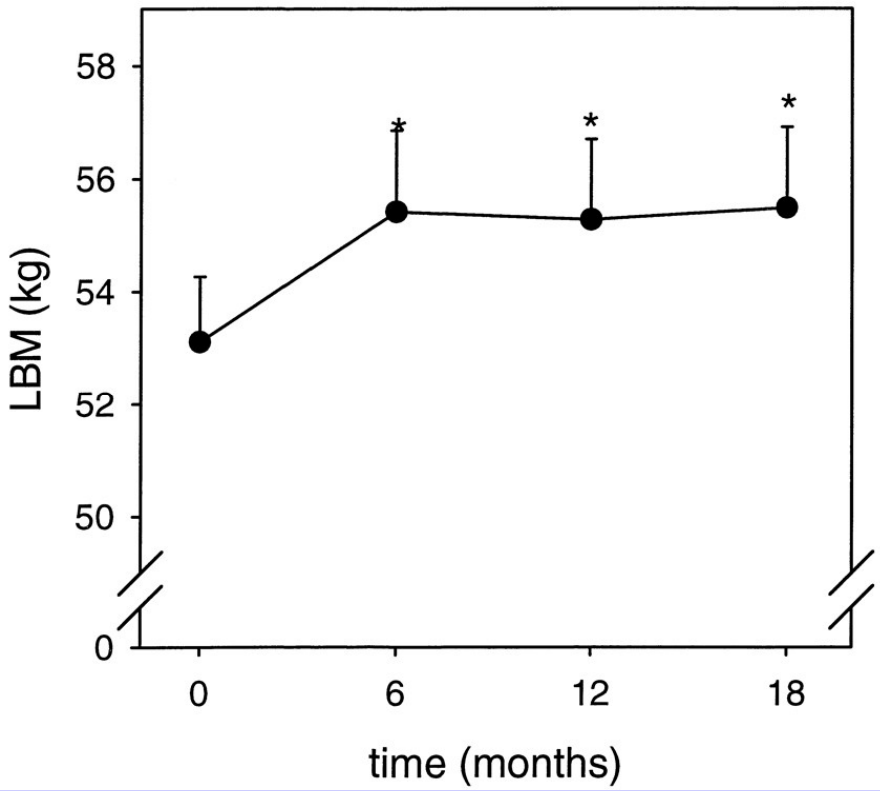


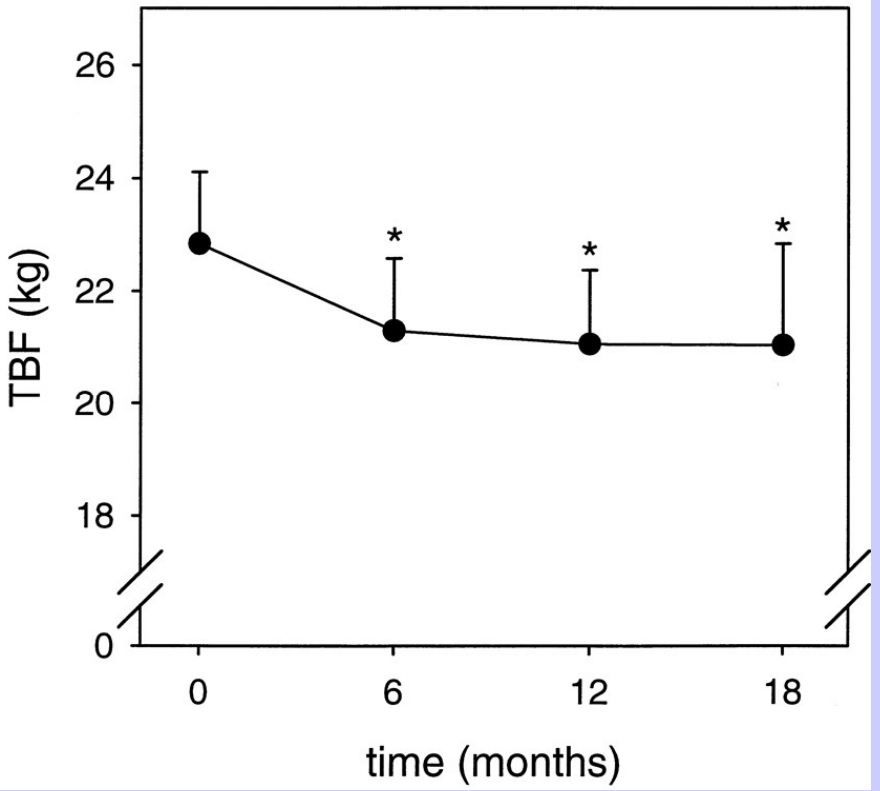
(Attanasio J Clin Endocrinol Metab 2002)



Change in waist circumference in patients in different age groups after 1 year of GH replacement therapy. Data are shown as mean, median and 10th–90th percentiles.

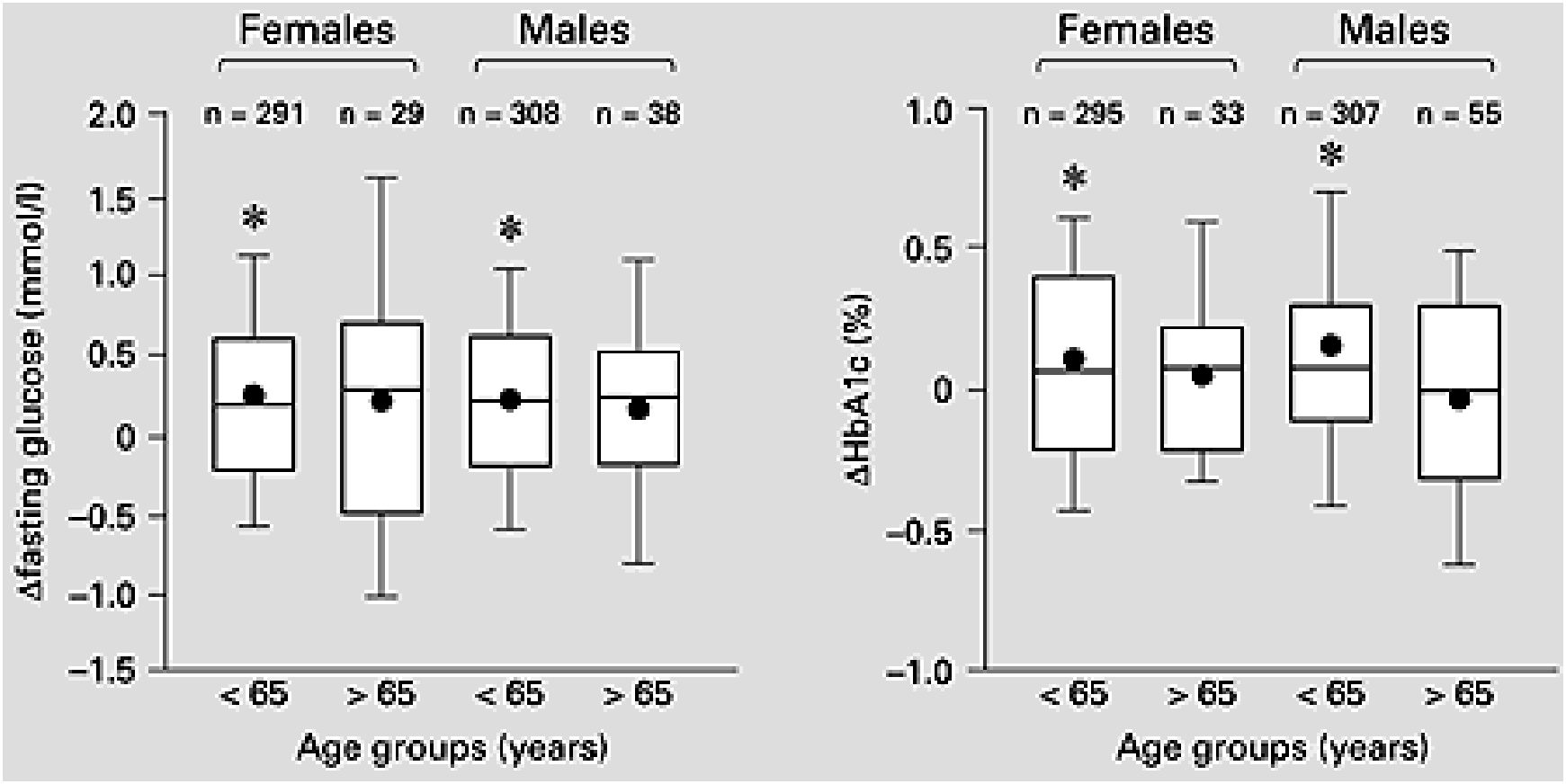
(Monson Hormone Research, 2003)





LBM and TBF (mean 6 SEM) before (n = 23) and after 6 (n = 23), 12 (n = 23), and 18 (n = 14) months in males, aged 60–79 yr, with GHD. *P<0.05.

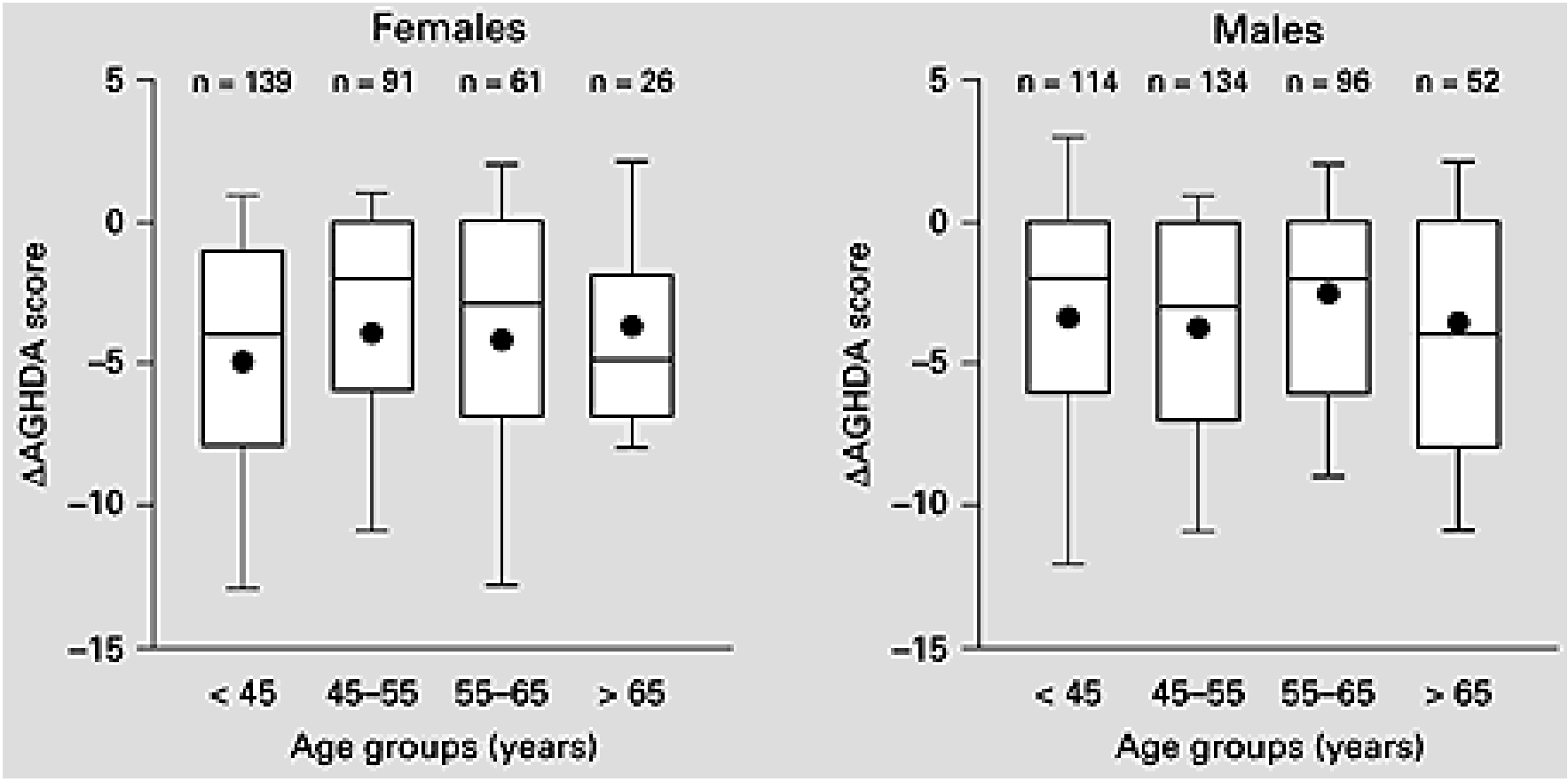
(Fernholm, JCEM 2000)



Change in indices of glucose metabolism in patients aged <65 or >65 years after 1 year of GH replacement therapy. Data are shown as mean, median and 10th–90th percentiles.

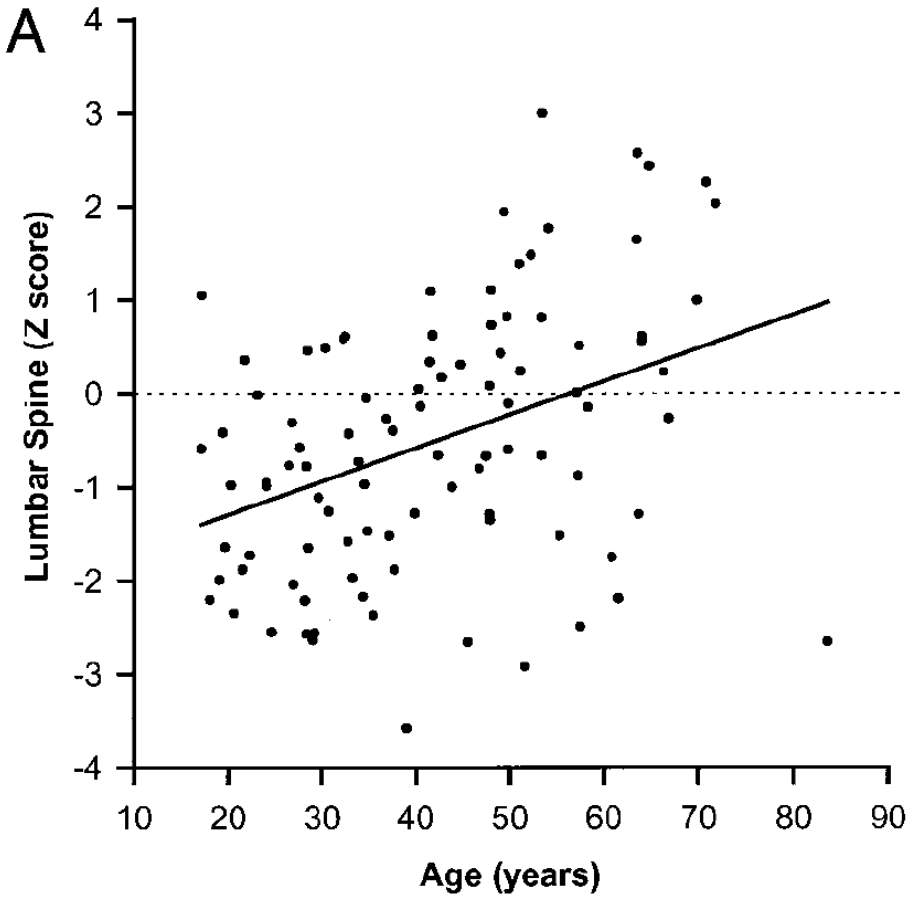
* p<0.0001 vs. baseline.

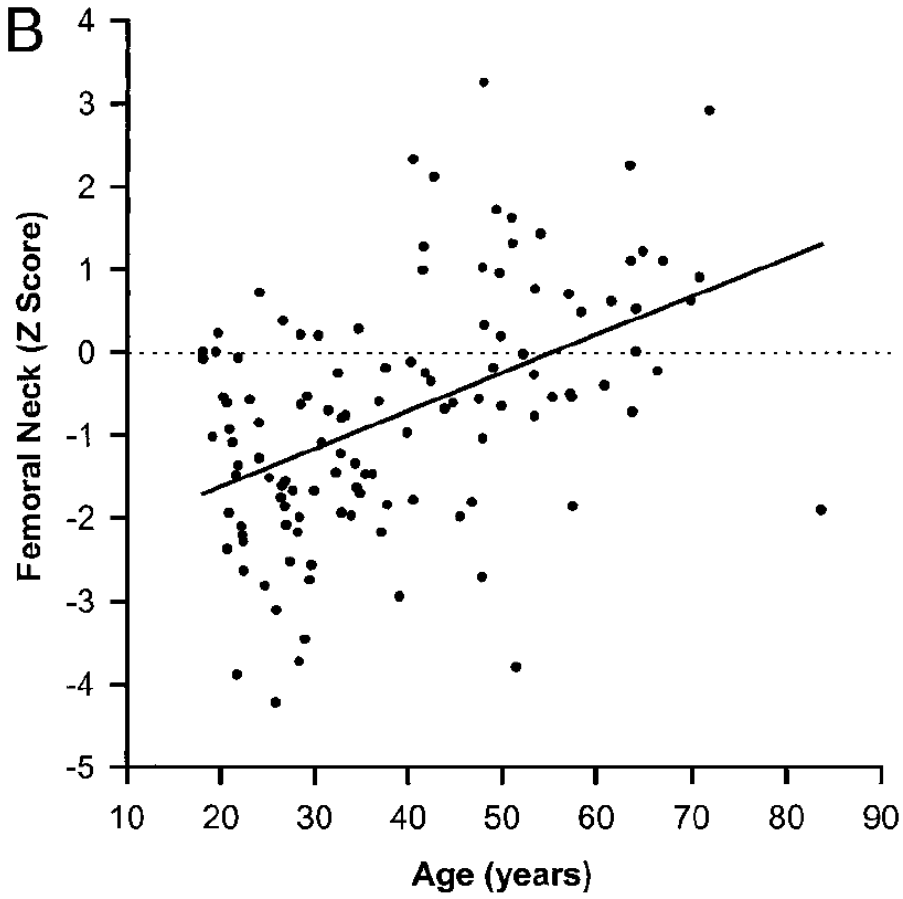
(Monson Hormone Research, 2003)



Change in QoL-AGHDA scores in patients in different age groups after 1 year of GH replacement therapy. Data are shown as mean, median and 10th–90th percentiles.

(Monson Hormone Research, 2003)

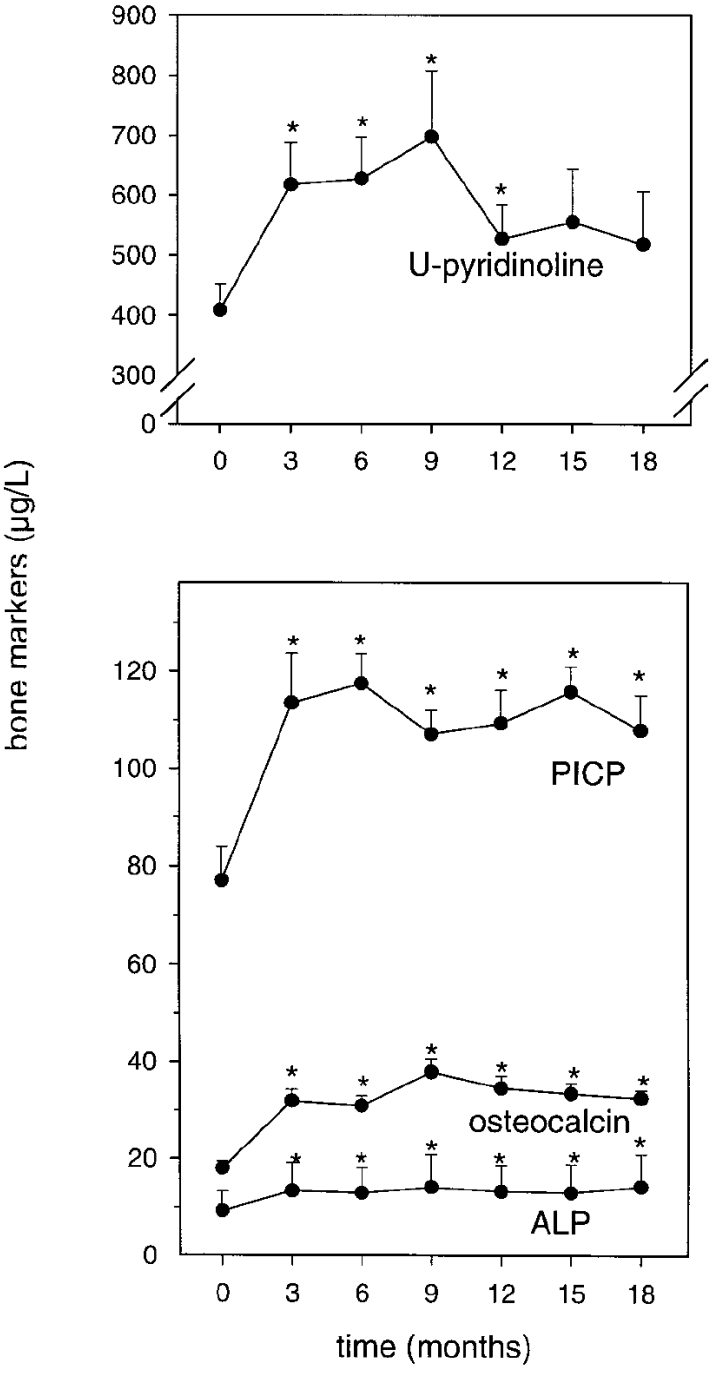




The relationship between BMD and age in 125 adults with severe GHD the lumbat ar spine (A) and femoral neck (B). BMD is represented in age-related SD scores (Z scores).

(Murray, JCEM 2004)

Markers for bone metabolism (mean 6 SEM) in serum (ALP, osteocalcin, PICP, and urinary pyridinoline) before and during GH replacement therapy (n = 28 for 0–12 months; n = 15 for 15 and 18 months) in patients with GHD, aged 60–79 yr. *, *P*<0.05.



PICP = Carboxyl-terminal propeptide of type I procollagen

(Fernholm, JCEM 2000)

Effects of GH replacement therapy on cardiac parameters in GH-deficient elderly patients during a 6-month placebo-controlled period

	Placebo			GH		
	Basal	Month 6	*P* basal *vs* month 6	Basal	Month 6	*P* basal *vs* month 6
VTI, cm	21 (13–31)	20 (14–28)	NS	22 (17–28)	22 (14–27)	NS
AV-plane movement, mm	12·7 (8·9–15·2)	12·5 (7–16·7)	NS	12·6 (10–15·3)	12·2 (10–14)	NS
Fractional shortening percentage	35 (26–48)	36 (14–47·5)	NS	34 (15·6–45)	38 (20·5–48)	NS
EF slope, mm/s^2	281 (161–1060)	296 (192–684)	NS	250 (152–492)	167 (176–492)	NS
E wave, cm/s	66 (47–117)	71 (48–120)	NS	64 (44–86)	60 (45–80)	NS
E/A ratio	0·9 (0·6–1·2)	0·9 (0·7–1·5)	NS	0·9 (0·6–1·5)	0·8 (0·7–1·8)	NS
S/D ratio	1·4 (0·9–1·7)	1·3 (0·7–1·6)	NS	1·6 (1–2·4)	1·4 (1·1–1·8)	NS
LVIDd, mm	50 (40–62)	51 (40–61)	NS	50 (41–62)	50 (42–62)	NS
LVIDs, mm	31 (21–45)	34 (25–49)	NS	34 (25–42)	33 (26–44)	NS
Posterior wall dimension, mm	9 (7–13)	11 (6–13)	NS	11 (7–15)	11 (7–15)	NS
Septum dimension, mm	11·2 (9–15·6)	11 (9–14·4)	NS	11·6 (7–14·2)	11·3 (7–14·5)	NS
Left atrial dimension, mm	37 (29–48)	36 (27–48)	NS	38 (31–45)	38 (32–44)	NS
Heart rate at rest, bpm	70 (47–102)	66 (45–110)	NS	58 (48–75)	67 (50–86)	0·029
Heart rate at max exercise, bpm	147 (112–179)	138 (113–177)	NS	142 (102–162)	148 (107–160)	0·05
Max work load, Watts	129 (70–210)	140 (80–120)	NS	150 (105–180)	160 (110–210)	0·012

VTI, aorta outflow tract integral; EF slope, the diastolic closing motion of the mitral valve leaflets; E wave, rapid filling wave; E/A ratio, rapid filling wave/atrial filling wave; S/D ratio, pulmonary vein systolic wave/pulmonary vein diastolic wave; LVIDd and LVIDs, left ventricular interior diameter at diastole and systole, respectively. Values are given as median and range.

(Elgzyri, Clin Endocr;2004)

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Contraindication of GH therapy

Absolute contraindication

1) Active malignancy
2) Benign intracranial hypertention
3) Proliferative diabetic retinopathy

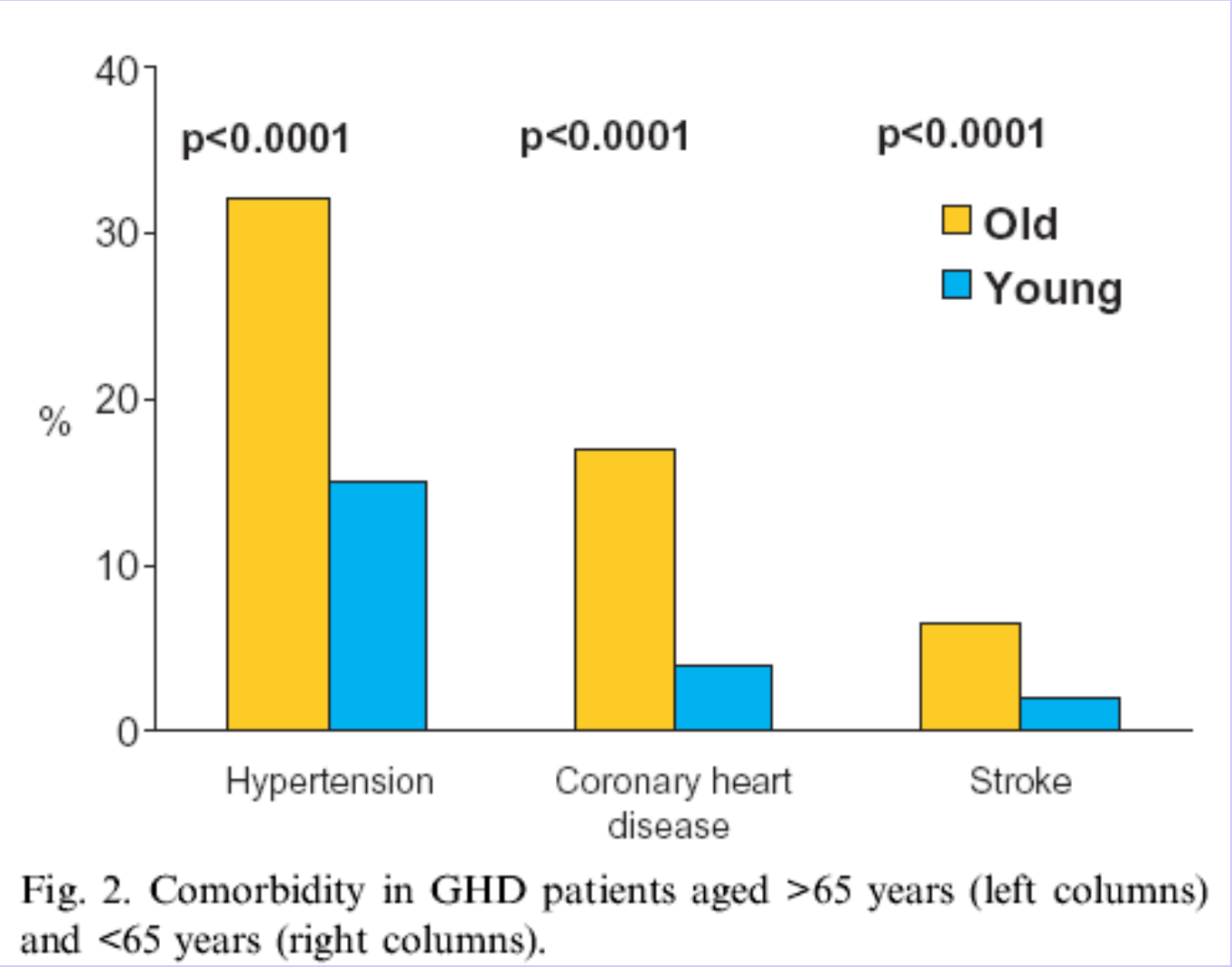

Fig. 2. Comorbidity in GHD patients aged >65 years (left columns) and <65 years (right columns).

(Feld-Rasmussen, KIMS, GH&IGFR, 2004)

Fig. 6. Total incidence of adverse events per 1000 of GH treatment in older patients (left columns) and younger patients (right columns).

(Feld-Rasmussen, KIMS, GH&IGFR, 2004)

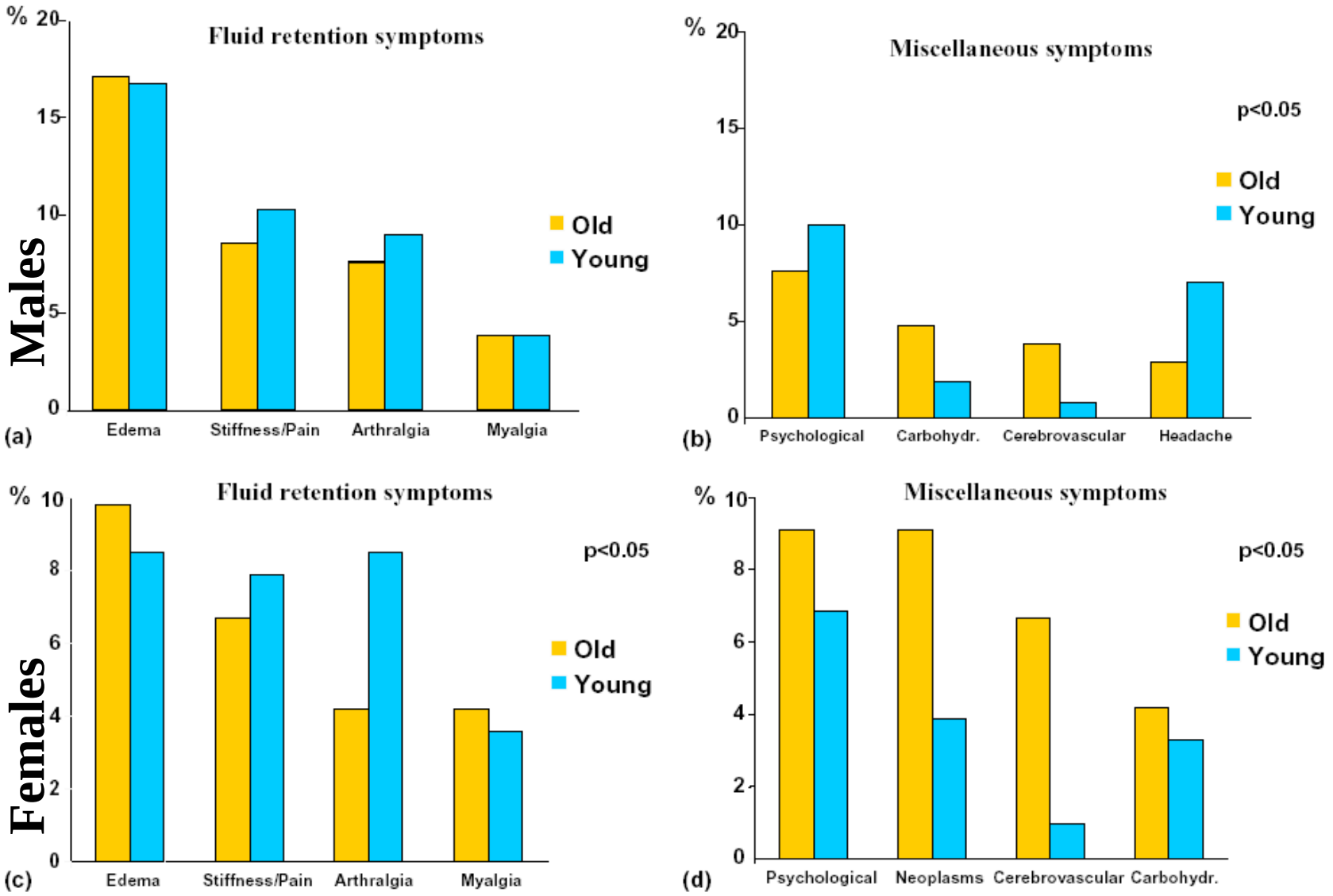

Fig. 7. (a–d) Subclassification of adverse events in male and female GHD patients >65 years (left columns) and <65 years (right columns).

(Feld-Rasmussen, KIMS, GH&IGFR, 2004)

GH/IGF-I axis and cancer risk

>> IGF-I levels

<< IGFBP-3 levels

In normal subjects, were associated with

- ✓ **breast cancer** in premenopausal
- ✓ **Prostate cancer**
- ✓ **Colorectal cancer**

- ✓ **Breast cancer** in premenopausal

However….

(Renehan, Lancet, 2004)

Clinical Endocrinology (2006) **64**, 115–121

REVIEW ARTICLE

Does growth hormone cause cancer?

P. J. Jenkins*, A. Mukherjeet and S. M. Shalett

"Extensive study of cancer survivors treated with GH has failed to demonstrate an increase in tumour recurrence and de novo cancers but a small increase in second malignant neoplasms. One long-term follow-up study of children treated with human pituitary GH suggested an increase in colorectal cancer and lymphoma, but surveillance data from many thousands of children and adults treated with GH have not shown any increase in cancer risk"

Thanks!

Neurosurgery
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Giulio Maira

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Alfredo Pontecorvi

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Neuroradiology
Cesare Colosimo

6th AME National Meeting

Italian Association of Clinical Endocrinologists

3rd Joint Meeting with AACE

American Association of Clinical Endocrinologists

La presentazione è stata svolta dal laptop del relatore

Verona, ITALY October 27-29, 2006

Associazione Nazionale Infermieri in Endocrinologia

Società Italiana di Medicina di Laboratorio