

Hypopituitarism: An Update

Karen K. Miller, M.D.

Chief, Neuroendocrine Unit, Massachusetts General Hospital (MGH)

Director, MGH Neuroendocrine and Pituitary Tumor Clinical Center

Professor of Medicine, Harvard Medical School

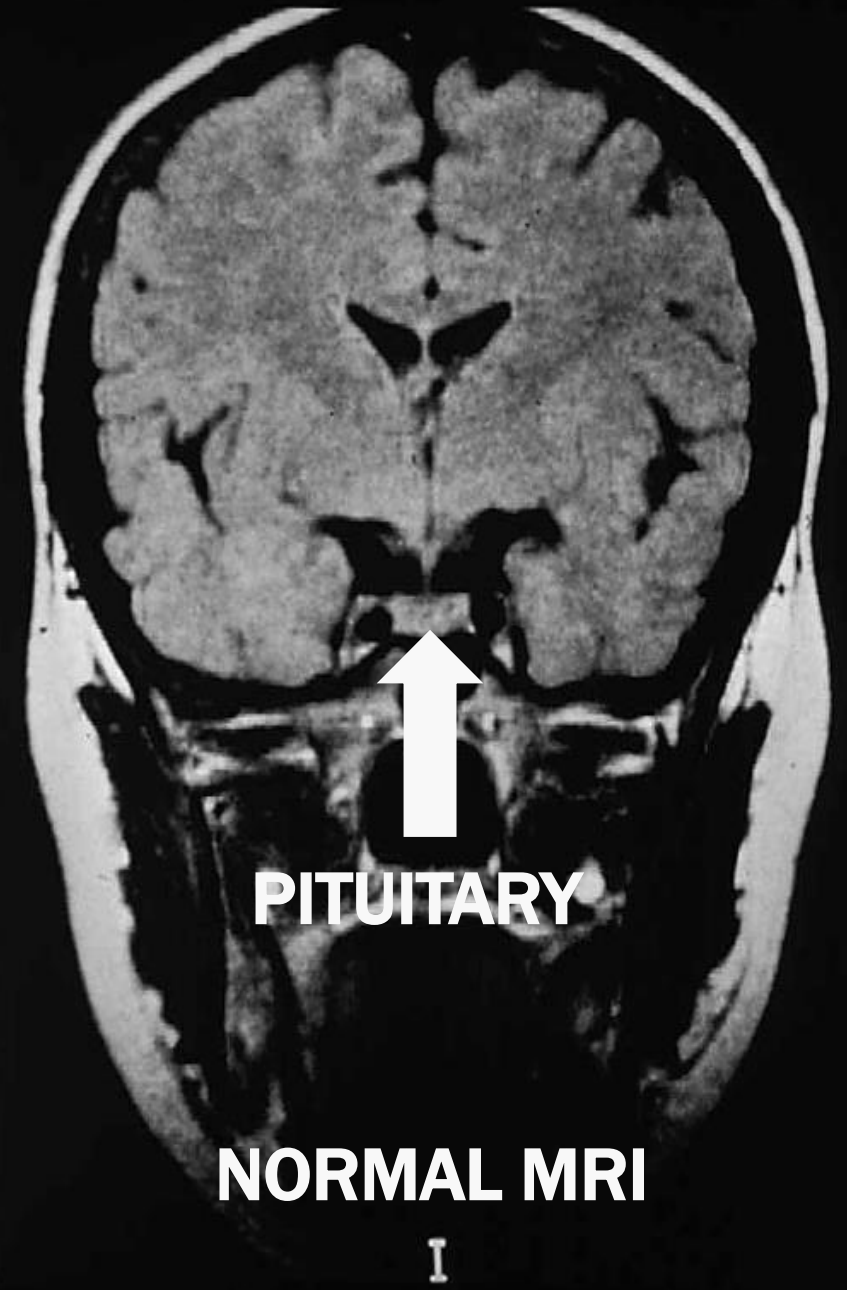
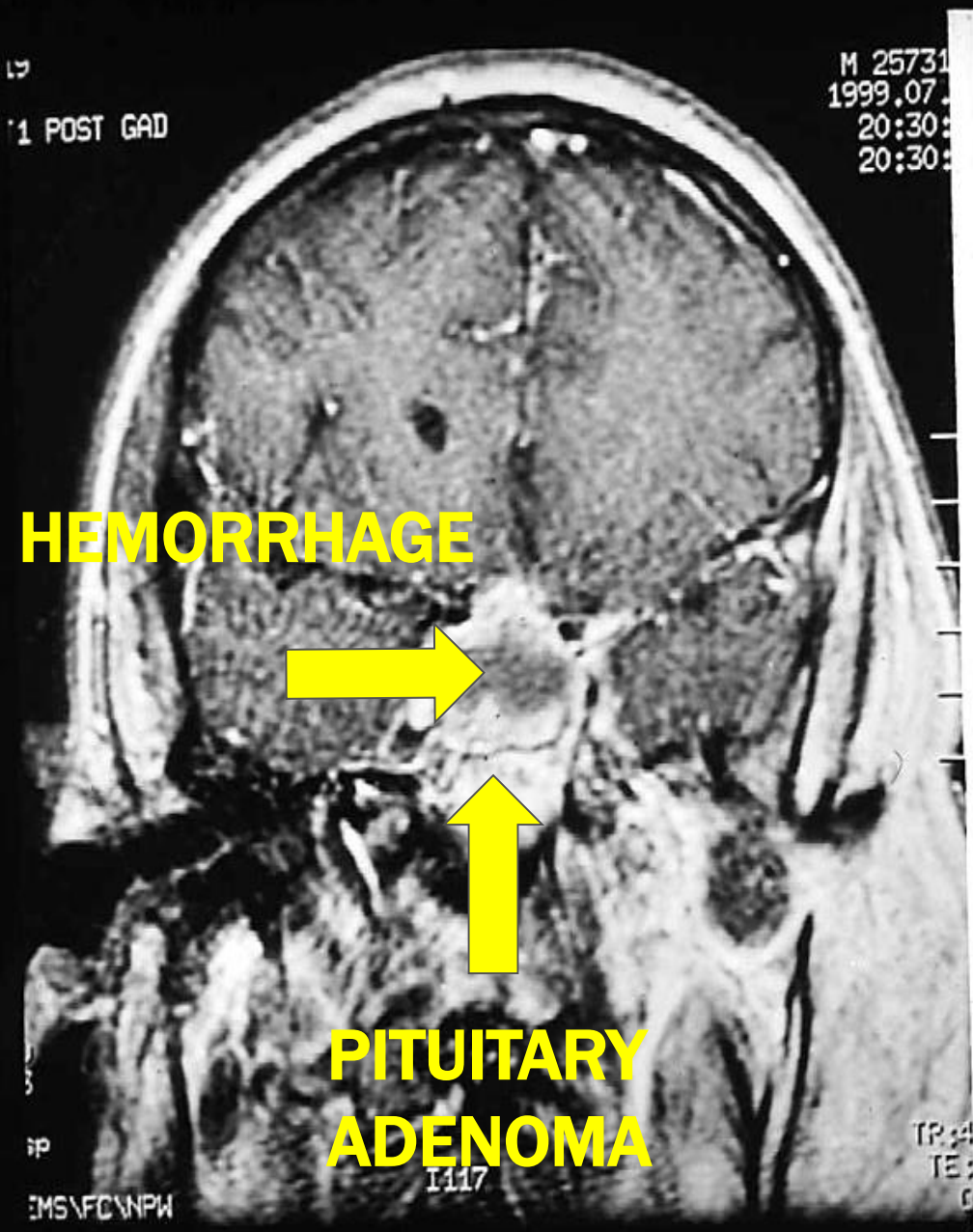
Dr. Miller has no relevant conflicts to declare.

Hypopituitarism Case

- **72-year-old man admitted to outside hospital with abdominal pain, nausea, vomiting, fever, headache and hypotension**
- **Treated with antibiotics, IV fluids and pressors**
- **Developed obtundation, hyponatremia (Na^+ 124 meq/L), meningismus, and cranial nerve III, IV and VI palsies**
- **Transferred to MGH**

Hypopituitarism Case

- Intubated, placed on antibiotics for presumed basilar meningitis
- Head CT: remarkable for a sellar mass
- Cortisol = 1.8 mcg/dl (50 nmol/L)
- Stress dose steroids administered
- Pressors were discontinued, and the patient was extubated
- A head MRI was performed



Hypopituitarism Case

- **Diagnosis:** pituitary apoplexy with hemorrhage in a macroadenoma
- **Treatment:** Transphenoidal surgical decompression
- **Pathology:** NF pituitary adenoma
- **Clinical course:**
 - Cranial nerve palsies resolved
 - Panhypopituitarism developed
 - Doing well on hormone replacement therapy

Topics

- **Causes of Hypopituitarism**
- **Central Hypothyroidism**
- **Central Adrenal insufficiency**
- **Central Hypogonadism**
- **Growth Hormone Deficiency**

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Etiologies Of Hypopituitarism

- **Pituitary tumors and treatment**
- **Suprasellar/hypothalamic tumors**
 - Craniopharyngioma
- **Infiltrative disease**
 - Sarcoid
 - Lymphocytic hypophysitis
- **Infarction**
 - Sheehan's syndrome
 - Apoplexy
- **Congenital**
- **Post-trauma/SAH**
- **Ipilimumab**
- **Opioids**

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Traumatic Brain Injury (TBI) and Subarachnoid Hemorrhage (SAH): Pooled Data from 19 Studies (1137 Patients)

- **Prevalence of hypopituitarism chronically**
 - **TBI: 27.5%**
 - **SAH: 47%**
 - **Adrenal insufficiency: 8% (TBI); 21% (SAH)**
- **Associated with impaired QOL and metabolic abnormalities**

Ipilimumab

- **Anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) therapy**
- **Complicated by autoimmune hypophysitis with panhypopituitarism in 17% of cases**
 - **Likely an underestimate**
- **Much lower incidence with nivolumab and/or pembrolizumab (0.5%)**

Treatment of Ipilimumab-Induced Hypopituitarism

- Hormone replacement
 - No need to d/c ipilimumab
- High-dose glucocorticoids not needed to treat hypophysitis but often used to treat autoimmune colitis
- Development of hypophysitis positively predicts survival (19.4 vs. 8.8 mos)
- Recovery of pituitary function in only 24%

Opioid-Induced Hypopituitarism

Systematic Review and Meta-analysis

- **52 studies including 18,428 subjects**
- **Patients with chronic pain, on maintenance for addiction treatment, and healthy volunteers**
- **Hypogonadism in 63% (99.5% of studies in males only)**
- **Adrenal insufficiency 15-24% (depending on diagnostic criteria used)**
- **Thyroid and GH axes do not appear to be affected**

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Free T4 Target in Treatment of Central Hypothyroidism

As we cannot use the TSH to target therapy, what should be the free T4 level target?

Free T4 Target in Treatment of Central Hypothyroidism

- Data suggest that central hypothyroidism is often under-treated
 - Doses are lower than in primary hypothyroidism, resulting in low-normal free T4 levels
 - Higher doses (~ 1.6 µg/kg in one study) may improve BMI and lipid profile
- A 2018 study in patients with primary hypothyroidism suggests that increasing L-T4 dose within the normal range does not result in objective benefit in weight, body composition quality of life, mood or cognition

Goller K *et al.*, *Exp Clin Endocrinol* 2004; Samuels *et al.* *JCEM* 2018; Slawik *et al.*, *JCEM* 2007;

Data Suggest We Should be Cautious about Free T4 Levels in the High-Normal Range

- **10,318** participants of the Rotterdam Study were included – not a study of hypopituitarism
- Higher free T4 levels, even within the normal range, were associated with an increased risk of sudden cardiac death (hazard ratio, **2.28** per **1 ng/dL** free T4, 95% CI, **1.31-3.97**)
- The absolute **10-year** risk of sudden cardiac death increased from **1-4%** in euthyroid patients with higher free T4 levels
- Goal: free T4 in the mid-normal range?

What is an Appropriate Free T4 Goal?

- None of these studies were in hypopituitary patients
 - TSH not elevated, and therefore T4 to T3 conversion is less than in primary hypothyroidism
- Goal: free T4 in the mid-normal range?
 - Except in those with contraindications such as cardiac issues or anxiety disorders

Apoplexy Case: Central Hypothyroidism

- **Timing: 6 weeks after apoplexy**
- **Lab results**
 - **TSH: 1.35 mIU/L (0.5-5 mIU/L)**
 - **Free T4: 0.7 ng/dl (0.9-1.8 ng/dl) (9.0 with a normal range of 11.6-23.2 pmol/L)**
 - **T3: 63 ng/dl (60-181 ng/dl) (0.97 with a normal range of 0.92-2.79 nmol/L)**
- **Replacement therapy: L-thyroxine**
 - **Mid-normal free T4**
 - **TSH <0.01 mIU/L (0.5-5 mIU/L)**

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Diagnostic Issues

- “Low-dose” 1 mcg cort-stim
 - In theory, superior for diagnosing mild central adrenal insufficiency
 - Controversial and technically challenging
 - 2 meta-analyses using mostly same data
 - Opposite conclusions
 - If center has experience with 1 mcg test, likely clinically equivalent to 250 mcg
 - We use traditional 250 mcg test

Dorin RI *et al.*, *Ann Intern Med*, 2003

Kaslauskaite R *et al.*, *J Clin Endocrinol Metab* 2008

Central Adrenal Insufficiency: Diagnosis

- **Insulin Tolerance Test (ITT)**
 - **Gold standard**
 - **Hypoglycemia stimulates entire HPA axis**
 - **Useful to diagnosis acute and chronic adrenal insufficiency, as well as growth hormone deficiency**
 - **Contraindicated in elderly, cv disease, seizures, serious psychiatric disease**
 - **Physician must be present**
 - **We do not use it any longer**

Other Diagnostic Tests for Adrenal Insufficiency

- **Glucagon testing**
 - High rate of false positives
 - Resulting in misdiagnosing as many as **51%** of healthy patients as having adrenal insufficiency
- **Free cortisol (blood or saliva)**
 - If standardized, may be useful for patients on oral estrogen or in ICU

Other Diagnostic Tests for Adrenal Insufficiency

- Recent studies suggest that a cut-off serum free cortisol by LC/MS/MS and equilibrium dialysis of 1 mcg/dl is roughly equivalent to a total cortisol of 18 mcg/dl
 - May be a guide in patients with impaired liver synthetic capacity in particular, but use with caution

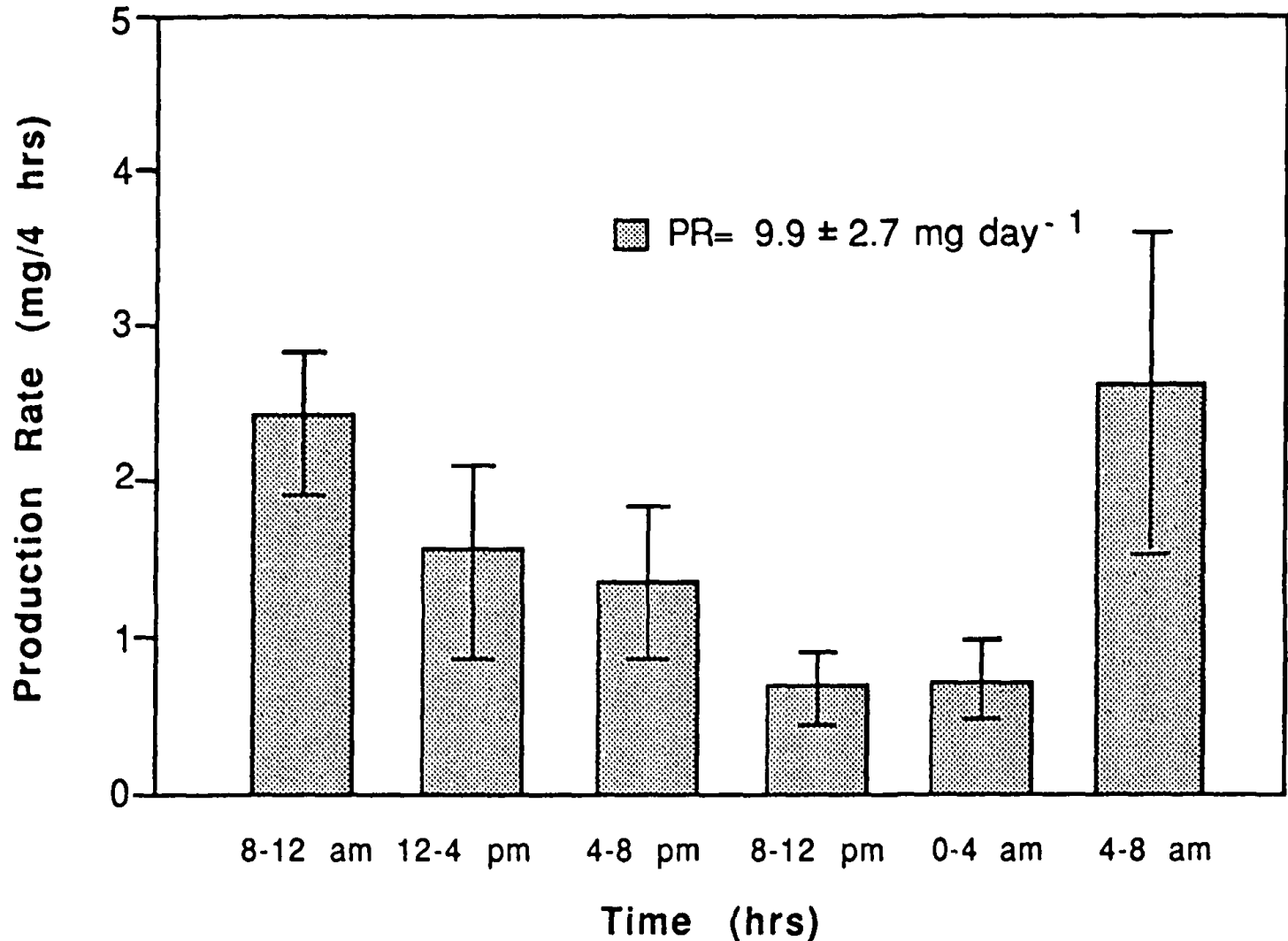
Central Adrenal Insufficiency: Treatment

- Differs from 1^o adrenal insufficiency
 - Mineralocorticoid (fludrocortisone) replacement not necessary
 - Glucocorticoid requirements may be lower, and therefore a once-daily medium-acting glucocorticoid can be used

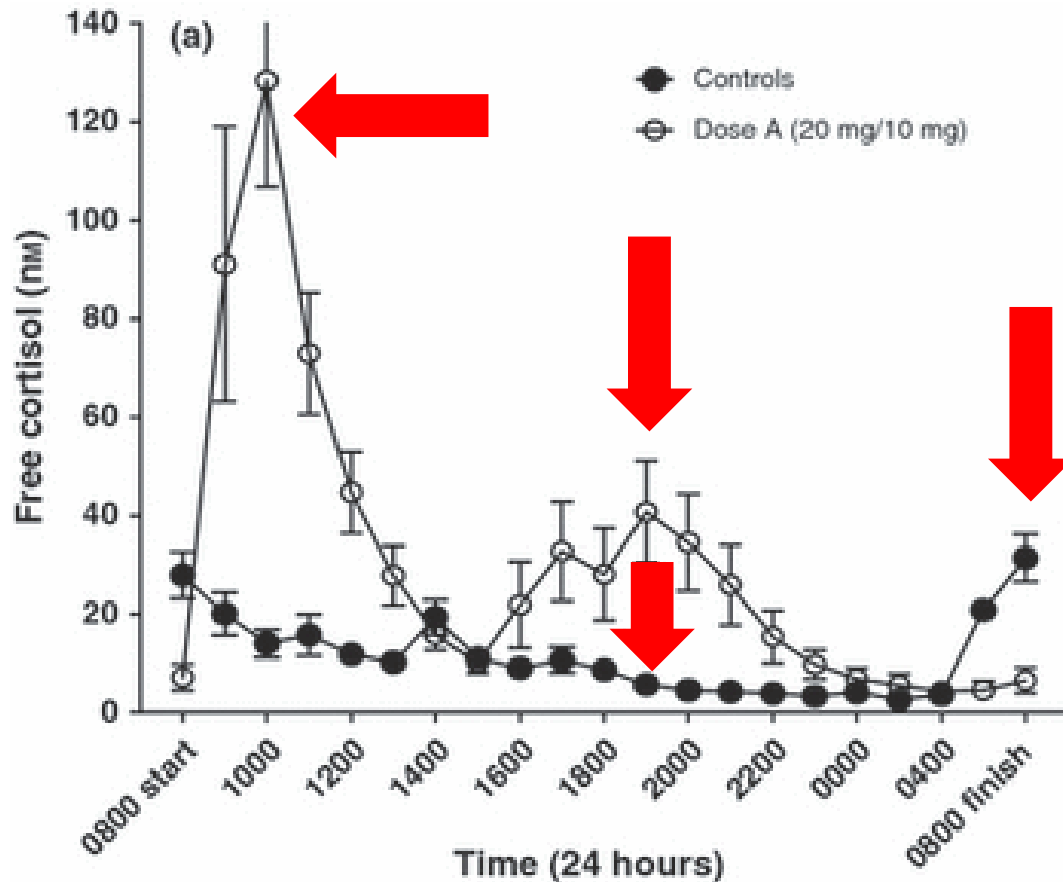
What is the Proper Replacement Dose and Timing of Dosing?

- Probably lower than we think
- Cortisol production rate
 - 9.9 ± 2.7 mg/day (0.027 ± 0.007 mol/day)
 - 5.7 mg/m²/day (0.016 mol/m²/day)

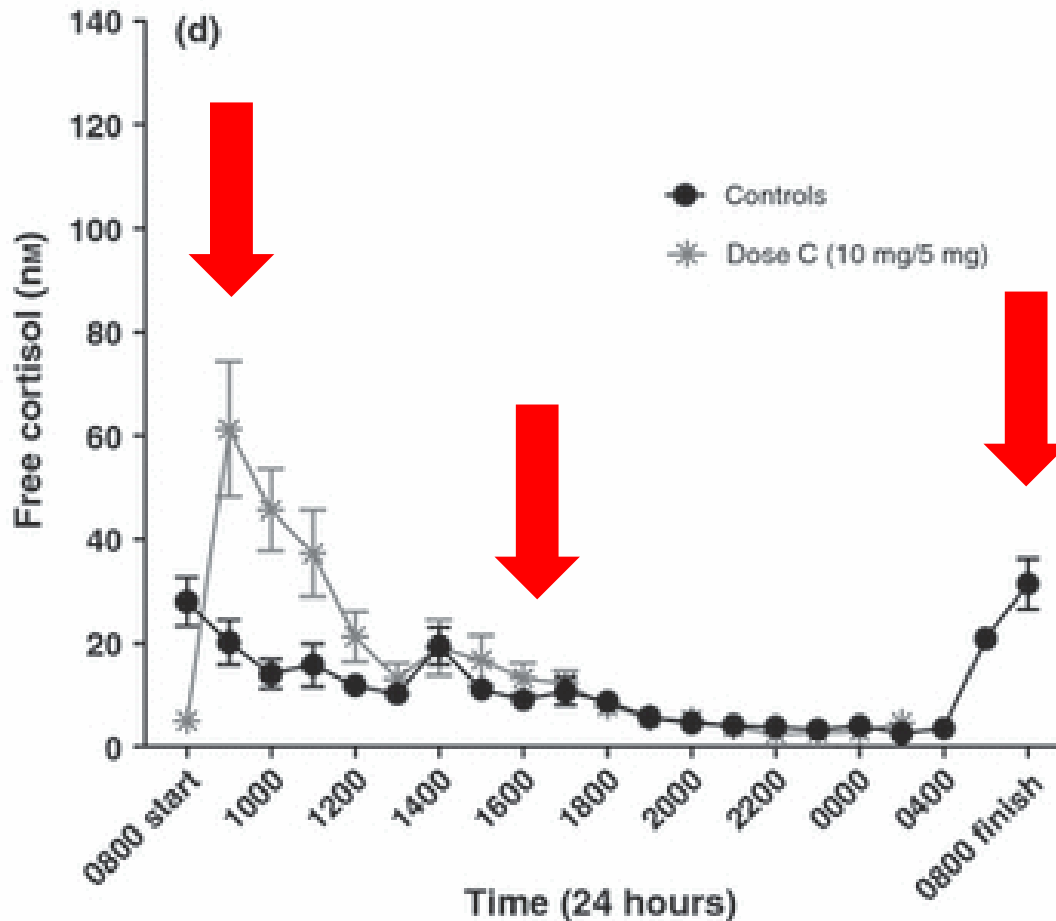
Diurnal Variation



Hydrocortisone (HC) 30 mg in Divided Doses is Supraphysiologic



HC 10 mg (8 am)/5 mg (2 pm) more Closely Mimics Physiologic Cortisol Secretion



Important to Individualize Regimen

- Significant range in individual glucocorticoid requirements: incompletely understood
 - Degree of glucocorticoid deficiency
 - Endogenous variability in metabolism (which can also be affected by medications, e.g. anticonvulsants)
 - Differences in glucocorticoid sensitivity
 - Glucocorticoid receptor polymorphisms

Treatment Options other than Hydrocortisone (HC)

- Once daily medium half-life glucocorticoid (e.g. prednisone or prednisolone 2-5 mg daily)
 - Advantage: afternoon dose is not necessary for patients with central adrenal insufficiency

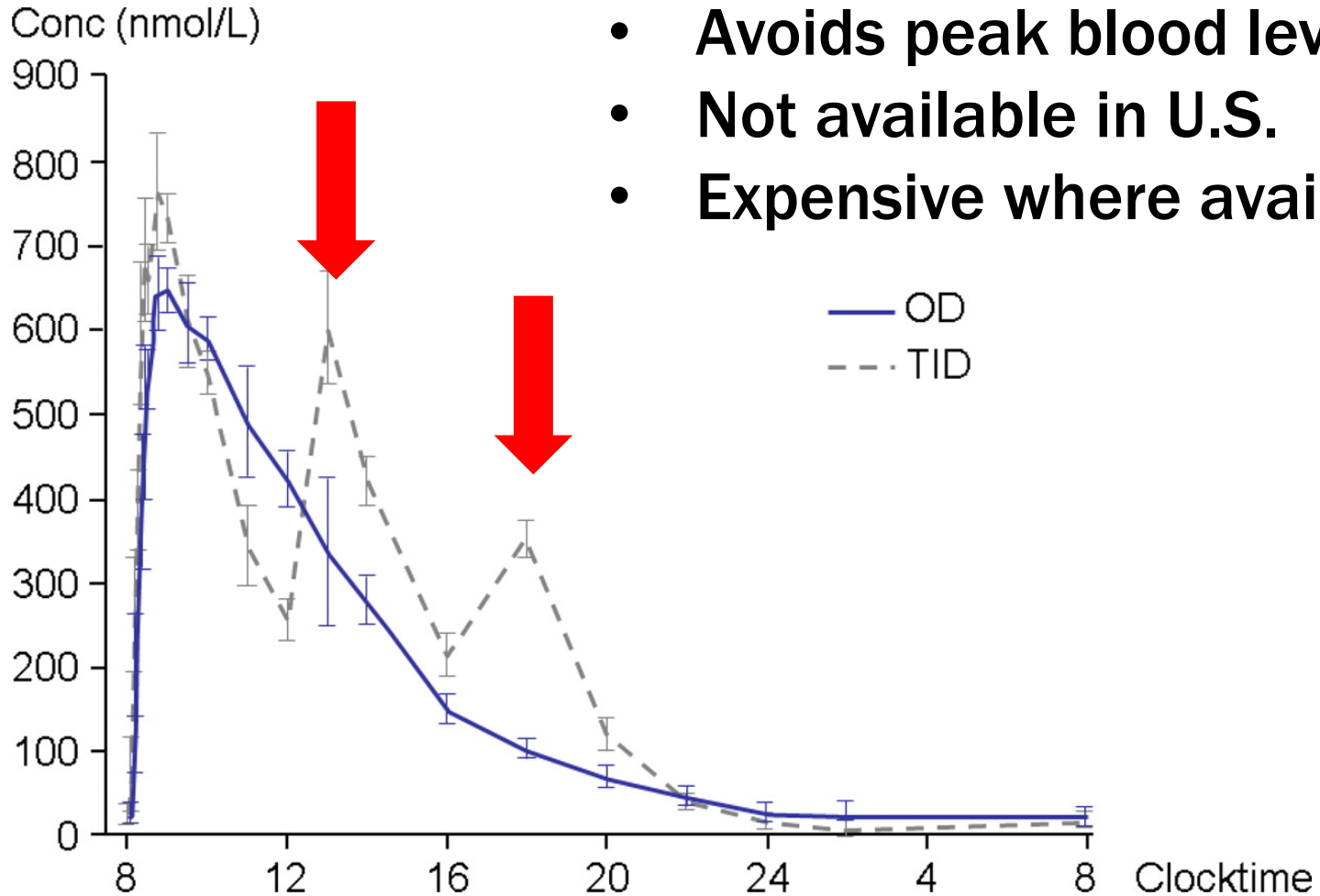
Is a Prednisone/Prednisolone Less Safe than Hydrocortisone?

- **2 studies**
 - No difference in CV risk markers: mean 3.7 mg dose prednisolone vs. 20.5 mg hydrocortisone
 - Higher LDL and total cholesterol, but no difference in HbA1c, triglycerides, BMI, blood pressure or waist circumference: mean 5.0 mg dose prednisolone vs. 21.5 mg hydrocortisone
- **Dose likely the important variable**
 - Very long-acting compounds (eg dexamethasone) may be more likely to cause iatrogenic Cushing's

Once daily dual-release hydrocortisone

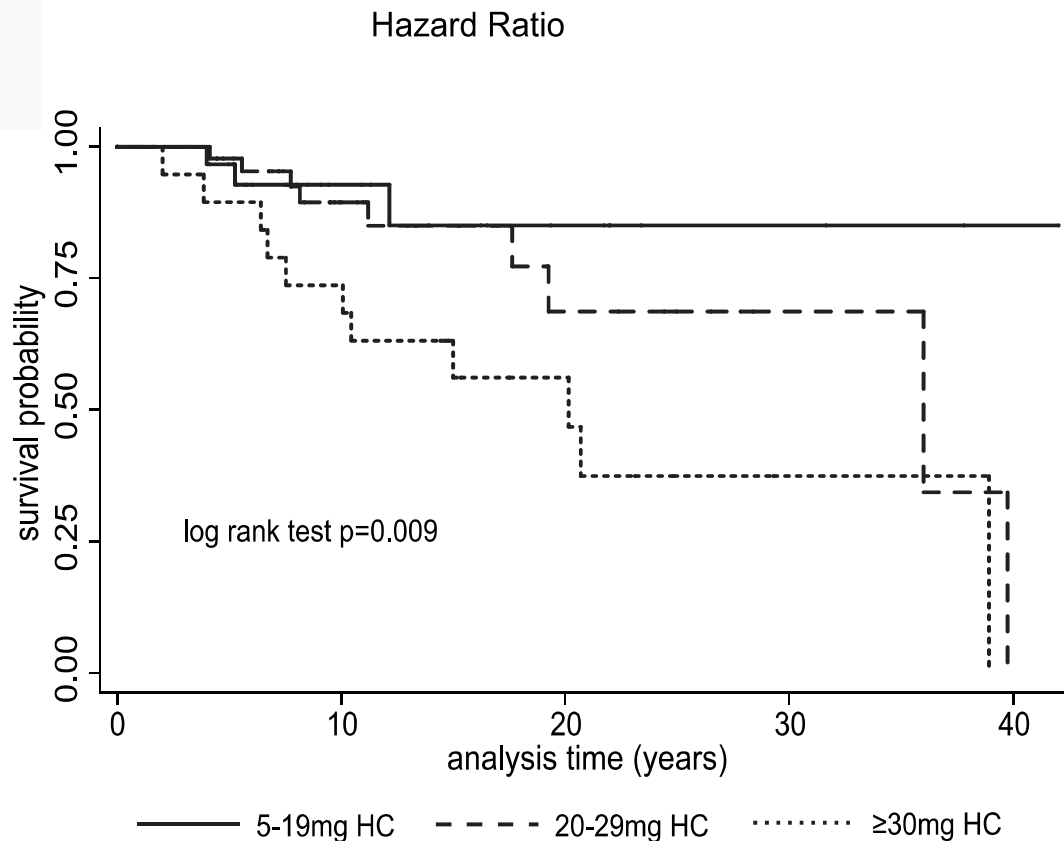
- **Approved in Europe**
- **Equivalent dose given once daily resulted in lower BMI, blood pressure and glucose metabolism compared with same dose given in 3 divided doses**

Once-Daily HC (solid line) vs. TID Comparable Dosing (dotted line)



- Avoids peak blood levels
- Not available in U.S.
- Expensive where available

Increased mortality observed (in patients with non-functioning adenomas) receiving ≥ 30 mg/day



2017 study suggests there may be an increased mortality in patients receiving >20 mg/day hydrocortisone

Hammarstrand C *et al* EJE 2017

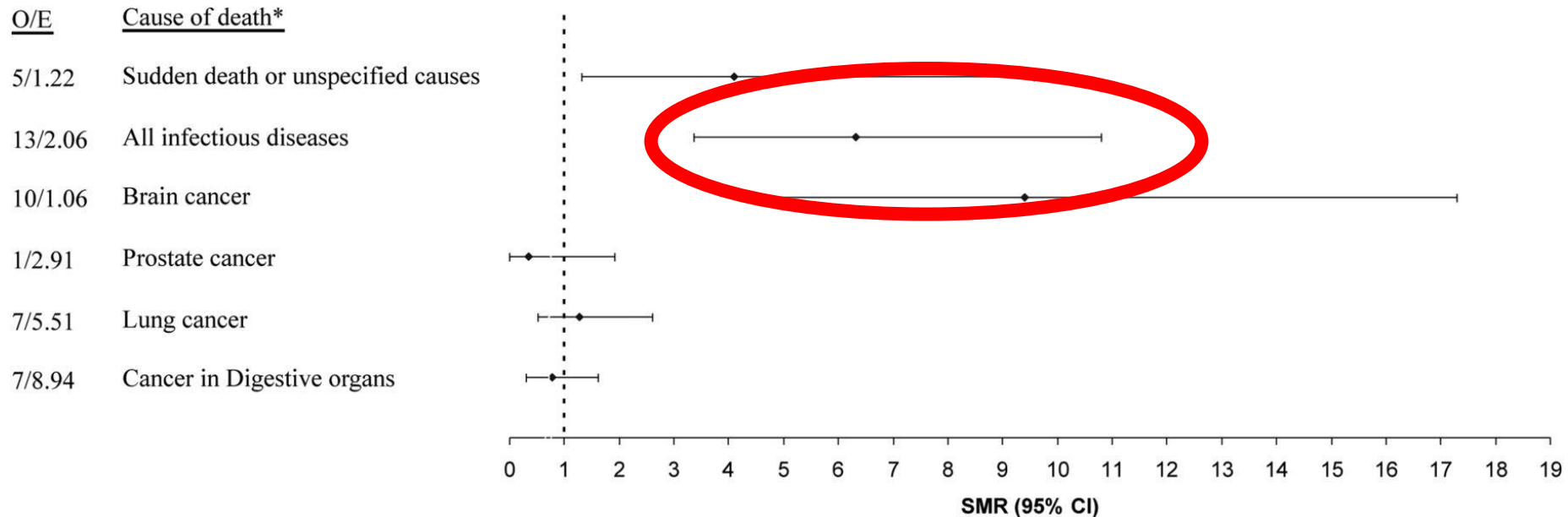
Zueger T *et al*, J Clin Endocrinol Metab 2012

**Therefore, minimizing
glucocorticoid doses is
important.**

**However, so is appropriate
supplementation.**

**Question: When should we
supplement?**

What is the Increased Death Rate in Hypopituitarism Due To?



Most deaths coded as “infectious disease” in origin were GI infections complicated by shock

Therefore, Although Minimizing Daily Glucocorticoid Doses is Important

- **It is also very important prepare patients for emergency stress-dosing**
 - **Especially for GI illnesses (fever, surgeries, hospitalizations, accidents also)**
 - **Prescribe 100 mg hydrocortisone for self-administration if severe GI illness**
 - **Instructions to page MD and go to emergency room**
 - **Medic Alert bracelet to be worn at all times**

Apoplexy Case: Adrenal Insufficiency

- **Serum cortisol while hypotensive: 1.8 mcg/dl (50 nmol/L), diagnostic of adrenal insufficiency**
- **Receives prednisone 3 mg daily (a decrease from the 5 mg daily I prescribed when he experienced apoplexy >20 years ago)**
 - **Mineralocorticoid replacement not necessary, as adrenal insufficiency is of central origin**
- **Monitored regularly for signs/symptoms of adrenal insufficiency or iatrogenic Cushing's syndrome**

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- **Central Hypogonadism**
- Growth Hormone Deficiency

Central Hypogonadism:

Treatment

- Gonadotropin therapy if fertility desired
- Testosterone replacement for most men
 - IM testosterone esters for men, less expensive option
 - Peak serum T supraphysiologic →
↑ HCT, prostate stimulation
 - Testosterone patches and gels
 - Study suggests that IM testosterone may be associated with a greater risk of cardiovascular events and deaths compared with gels (Layton JB et al., JAMA Intern Med 2015)

Other Treatment Options

- Testosterone pellets inserted every 4-6 months
- Testosterone undecanoate injected every 10 weeks (after an initial 4-week injection)
 - Black box warning for pulmonary-oil microembolism (POME) (0.2%) and anaphylaxis (0.05%)
- Testosterone nasal gel
 - Three times daily administration

FDA-Approved March, 2019: Long-Acting Testosterone Undecanoate Preparation

- Oral twice-daily, fatty meal not required
- 87% of patients achieved normal testosterone levels
- Black box warning: drug can cause blood pressure to rise, increasing the risk of heart attack, stroke and cardiovascular death
- Increase in PSA and Hct, and decrease in HDL observed
- Approved for men with hypopituitarism or genetic causes of hypogonadism, not age-related declines in testosterone levels

Is Testosterone Therapy Safe?

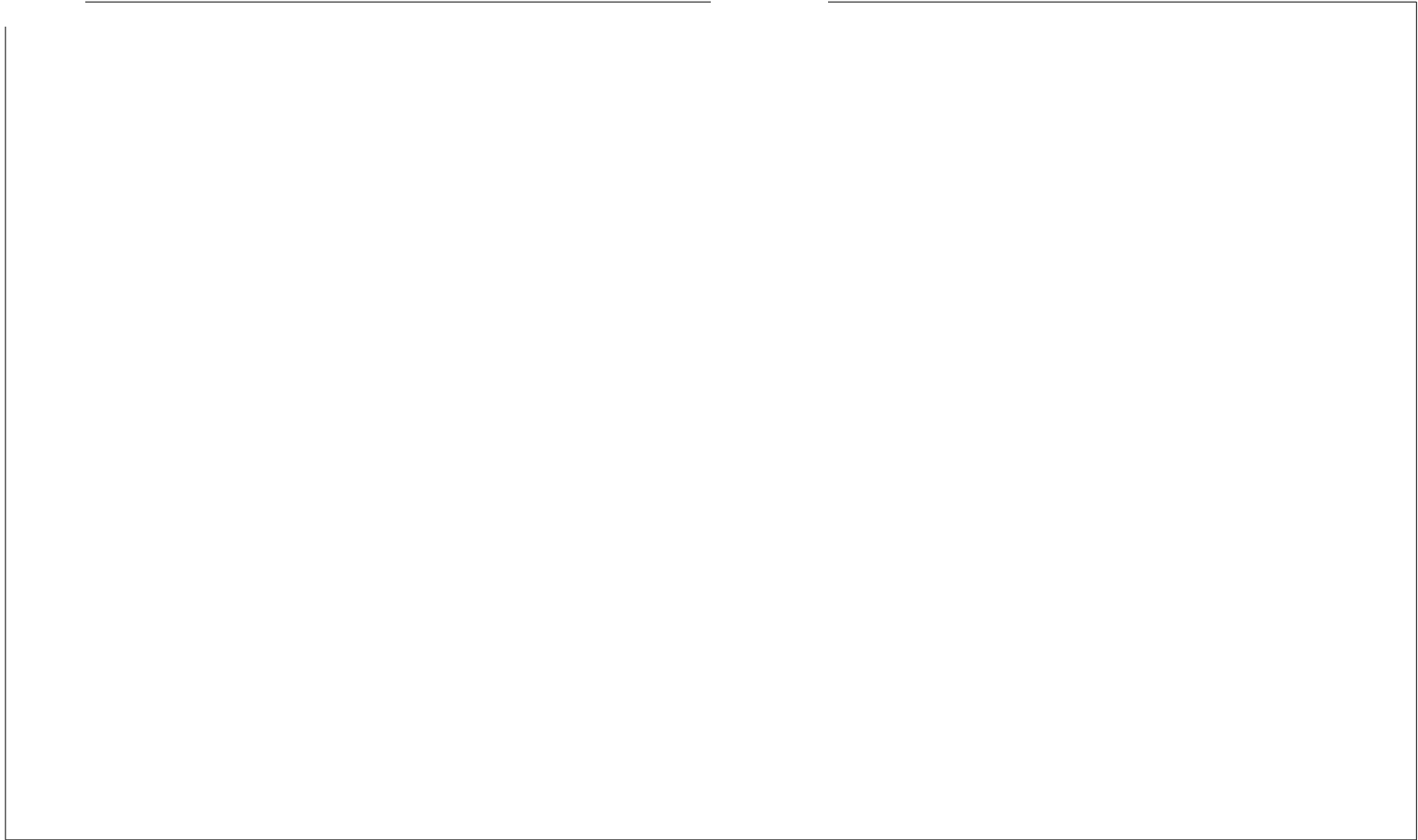
- A retrospective study showed that normalization of testosterone levels was associated with a reduction in mortality, MI and stroke in veterans with frankly low T levels
- Prospective trials in elderly men and those with preexisting cv disease who were treated for declines in testosterone levels due to aging have shown that higher T levels associated with markers of CV disease and increased CV events

Sharma R et al, *Eur Heart J* 2015, Ruige JB et al, *J Clin Endocrinol Metab*, 2013; Yeap BB et al, *J Clin Endocrinol Metab*, 2013; Basaria S et al, *NEJM*, 2010; Vigen R et al, *JAMA* 2013; Finkle WD et al, *PLOS ONE* 2014

New Studies Published in 2019

- **Testosterone therapy is associated with increased risk of venous thromboembolism among men with (OR 2.32) and without (OR 2.02) hypogonadism**
 - **Case-crossover study in 39,622 men (claims data)**
- **Testosterone therapy prevents progression from prediabetes to diabetes over 8 years in men with hypogonadism**
 - **8-year observational study in which 229 men received testosterone undecanoate**
 - **None progressed to overt diabetes; 90% normalized hgbA1c < 5.7%**
 - **87 untreated control subjects**
 - **40% progressed to diabetes (hgbA1c >6.5%)**

Testosterone Therapy Prevents Progression to Diabetes in Observational Study



Testosterone: Replace? Optimal Window?

- **Few studies in patients with hypopituitarism, many of whom have profound hypogonadism and prepubertal levels**
 - **Severe hypogonadism is associated with increased cv risk, increased visceral adiposity, reduced muscle mass, osteoporosis, fatigue, anemia, depression, sexual dysfunction**
- **Recommend replacing testosterone, esp in those with very low levels who do not have contraindications**
- **Conservative serum testosterone level targets, especially in elderly patients and those with cv disease or history of venous thromboembolism, is warranted**

Central Hypogonadism: Treatment

- **Estrogen/progestin replacement for women of reproductive age**
 - No data
 - WHI results cannot be extrapolated to hypopituitary women of reproductive age
 - Goal: restoration of “normal” hormonal milieu
 - Gonadotropin therapy if fertility desired

Central Hypogonadism: Treatment

- **Women of postmenopausal age**
 - **Decision re: HRT similar as for eupituitary women, but hot flashes rare and some intracranial tumors have estrogen receptors**

Apoplexy Case: Central Hypogonadism

- **Testosterone 135 ng/dl (normal range 267-916 ng/dl) (468 nmol/L, with a normal range of 926-3176 nmol/L)**
- **“Normal” LH, FSH and prolactin**
- **Doing well on physiologic testosterone therapy using a topical preparation**
 - **Hct and PSA measured annually**

Androgen Deficiency In Women

- **Effects of androgen replacement in men**
 - **Bone: ↑ bone density**
 - **Body composition: ↓ visceral fat, ↑ muscle mass and strength**
 - **Quality of life: ↑ libido and mood**

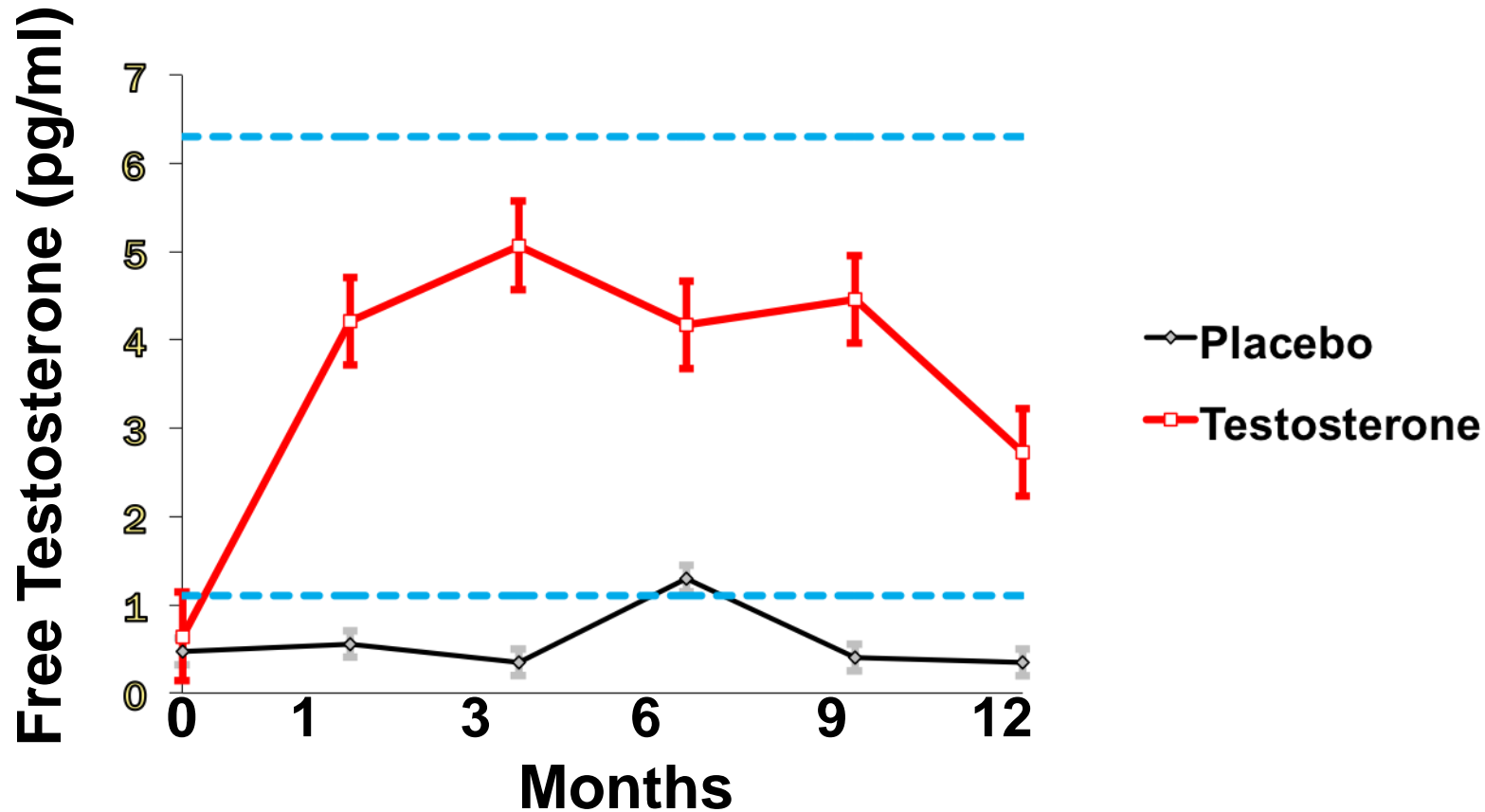
Androgens in Women

- **Testosterone levels:**
 - **1/10 to 1/20th male levels**
- **Important for libido and quality of life, body composition, bone density at the low concentrations present in women?**
- **Or are androgen levels too low to play an important biologic role in women?**

Androgen Deficiency In Women In Hypopituitarism

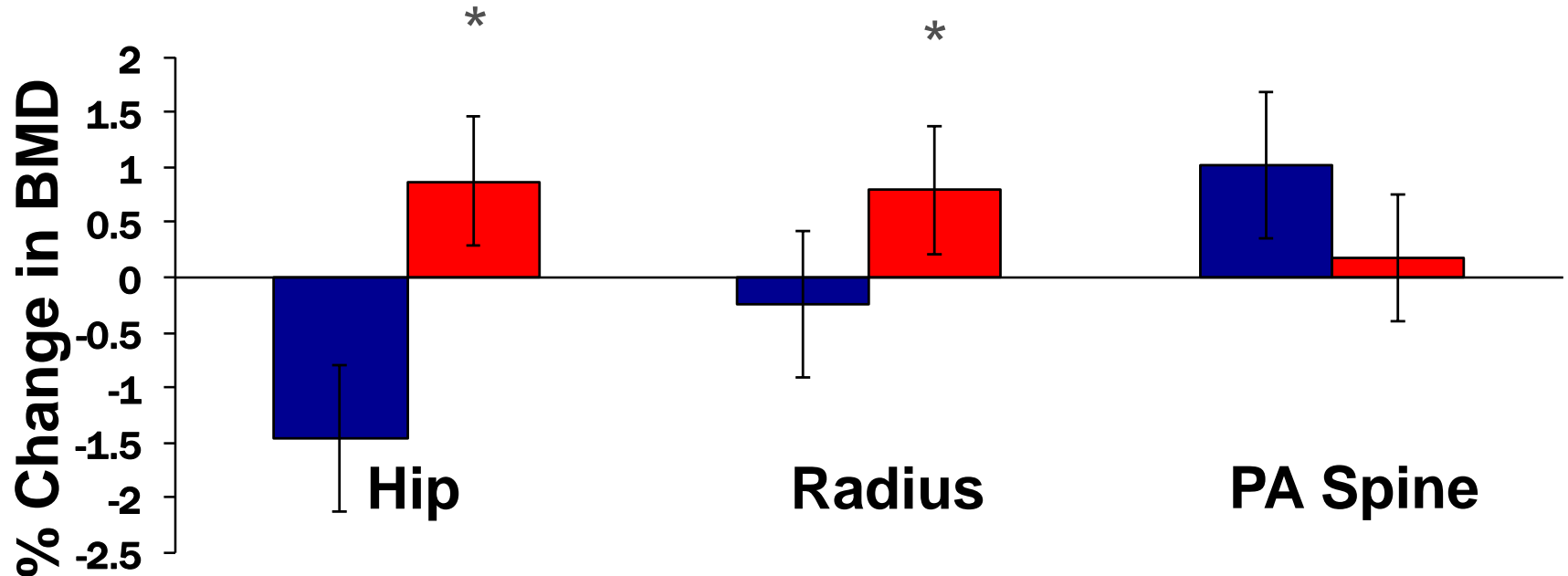
- **Hypopituitarism is characterized by hypogonadism and/or hypoadrenalism, which affects critical sources of androgen production in women**
 - **Testosterone and DHEAS are both low in women with hypopituitarism**

Randomized Trial: Free Testosterone Levels Increased Increased to Normal Female Range



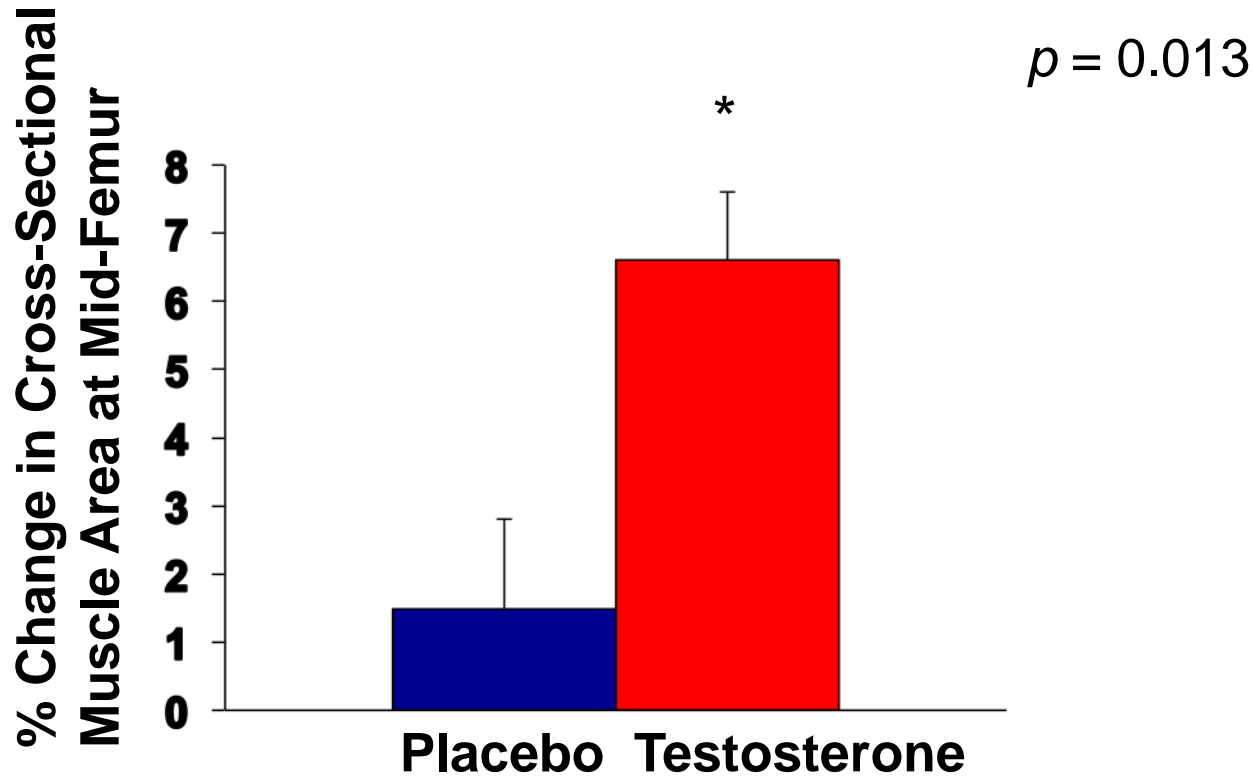
BMD (Hip and Radius) Increased with Testosterone Replacement

■ Placebo ■ Testosterone



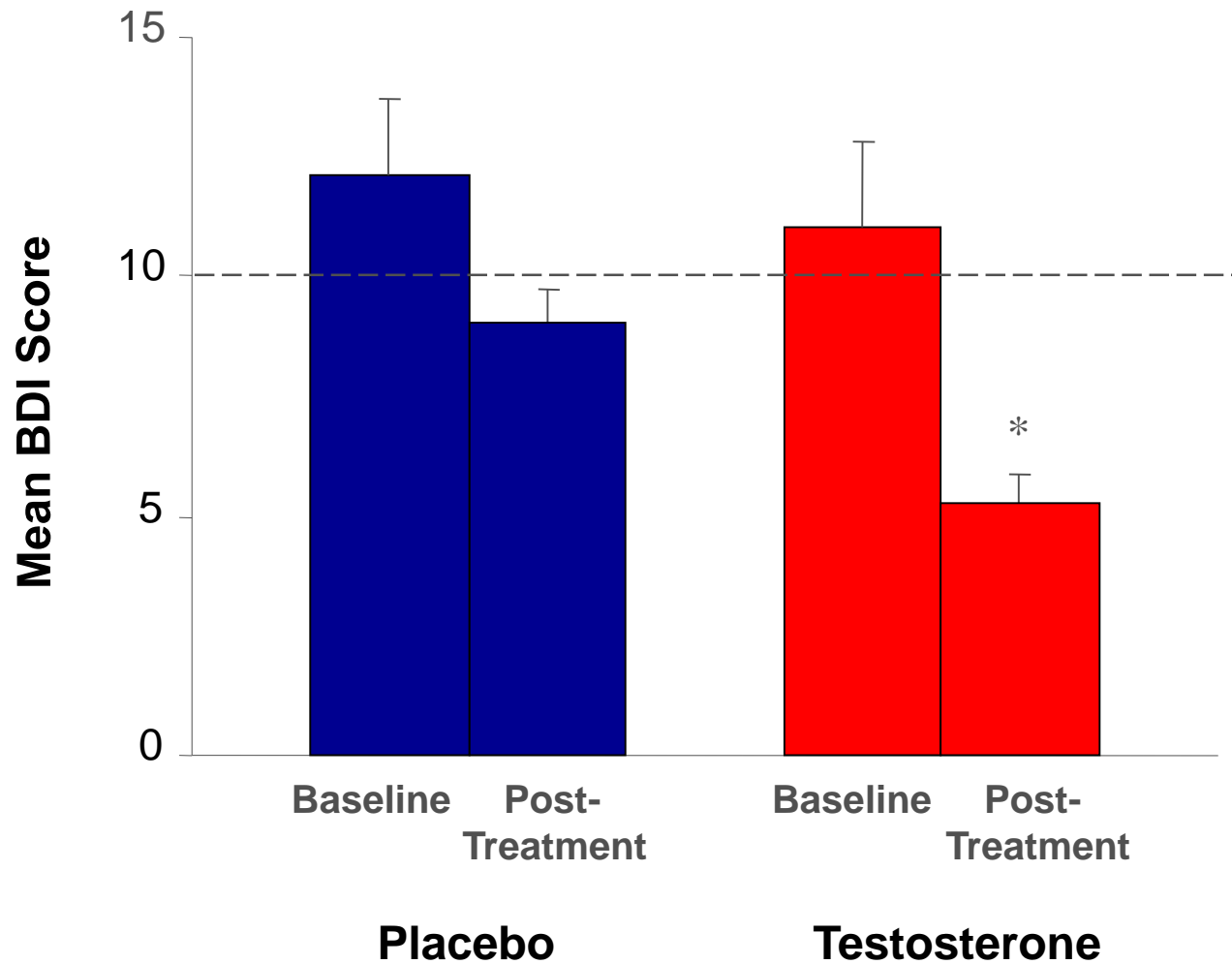
* $p < 0.02$

Thigh Muscle Area Increased with Testosterone Replacement



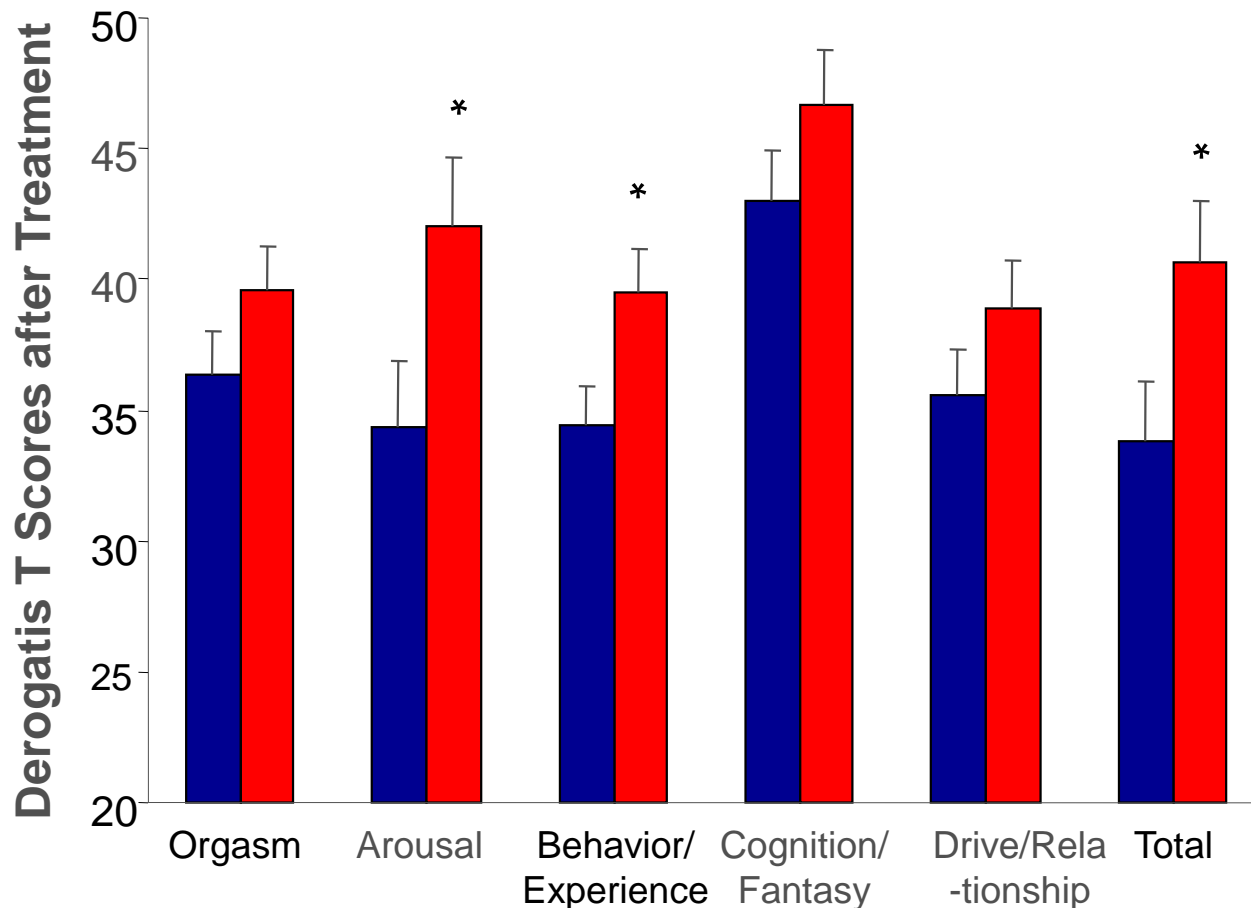
Mood Improved with Testosterone Replacement

Miller, KK et al, *J Clin Endocrinol Metab* 2006



Sexual Function Improved with Testosterone Replacement

Miller, KK et al, *J Clin Endocrinol Metab* 2006



2019 Systematic Review and Meta-analysis

- **46 reports of 36 RCT, including 8480 postmenopausal participants**
- **Testosterone improved sexual function**
- **Oral testosterone increased LDL and decreased TC, HDL and triglycerides**
- **No significant effects on muscle mass or cognitive endpoints (limited by small N)**
- **Increase in acne and hair growth but no serious adverse events**

DHEA Replacement Therapy in Women with Adrenal Insufficiency

- **Meta-analysis (10 studies total)**
 - **“DHEA may improve, in a small and perhaps trivial manner, health-related quality of life and depression....”**
 - **No significant effect on anxiety or sexual well-being**
 - **“The evidence appears insufficient to support the routine use of DHEA in women with adrenal insufficiency.”**

Possible Explanations for Lack of Stronger Effect

- **Effect is weak, nonexistent or only present for an uncharacterized subset**
- **Methodologic issues with some of the DHEA studies**
 - **Some studies used very low DHEA doses**
 - **Some studies combined data from men and women**
 - **Multiple different instruments used**
 - **Questionnaires not disease-specific**

Clinical Issues: Androgen Administration in Women

- **Risks**
 - **Hyperandrogenism**
 - **Low incidence in short-term studies**
 - **Long-term effects (greater than 24 months) of androgen use in women are not known**

No Government-Agency Approved Testosterone Preparation for Women in the U.S. or Europe

- **Pharmacokinetics of gels that are designed for men cannot be reliably dosed for women**
- **Compounding pharmacy preparations may result in variable levels and not FDA-monitored**

Global Consensus Position Statement 2019

- **The only evidence-based indication for the use of testosterone in women is for the treatment of postmenopausal women who have been diagnosed as having Hypoactive Sexual Desire Disorder**

Global Consensus Position Statement 2019

- **Prescribing of an approved male formulation is reasonable, provided hormone concentrations are maintained in the physiologic female range**
- **Compounded “bioidentical” testosterone therapy cannot be recommended**
 - **If used, the pharmacy should be compliant with purity of Active Pharmaceutical Ingredients and Good Manufacturing Practice**
- **Use of any testosterone preparation that results in supraphysiologic concentrations of testosterone, including pellets and injections, is not recommended**

Global Consensus Position Statement 2019

- **A baseline total testosterone concentration should be measured before commencement, with a repeat level 3–6 weeks**
- **Patients should be monitored for their clinical response to treatment and signs of androgen excess with a serum testosterone level every 6 months**
- **If no benefit is experienced by 6 months, treatment should be ceased**

DHEA is a Dietary Supplement in U.S., with Little FDA Oversight

- **Contain 0 to >100% of declared amount**
- **Oral → ↓ in HDL (risk of oral androgens and pre-androgens)**
- **Converted to androgens and estrogens**

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- **Growth Hormone Deficiency**

GHD Update: Diagnosis in Adults (AACE 2019 Guidelines)

- **GHRH not available in the U.S.**
- **If glucagon is used, important to use BMI-appropriate GH cut-points:**
 - **3 $\mu\text{g}/\text{L}$ for normal-weight**
 - **1 $\mu\text{g}/\text{L}$ for obese (BMI $>30 \text{ kg}/\text{m}^2$)**
 - **AACE Guidelines recommend choosing cut-off based on pre-test probability for overweight patients**
- **In patients with glucose intolerance, the diagnostic accuracy of the GST remains unclear**

Macimorelin: Orally Active GH Secretagogue

- **FDA approved this test for use as a diagnostic test for adult GHD in December, 2017**
- **Oral, very well tolerated, 90-minute test**
- **Expensive and variably covered by insurance**
- **Cut-point is 2.8 mg/L**
- **BMI-adjusted peak GH cut-points for this test are needed for overweight and obese patients**

Long-Acting GH

- The frequency of daily injections is one of the major factors contributing to nonadherence with rhGH therapy
- Weekly long-acting GH (LAGH) preparations are currently under development
- Not currently available in the U.S. market
 - Several preparations in later phase trials

Hypopituitarism: Future

Directions

- Perfect hormone replacement regimens
- Androgen replacement in women and GH deficiency and replacement
 - To whom should we prescribe?
 - Effects on cardiovascular and cancer risk?
- Other hormone deficiencies?
 - Low plasma oxytocin levels and increased psychopathology in hypopituitary men with diabetes insipidus demonstrated
 - Obesity, ↓quality of life largely unexplained