

Hormone Replacement Strategies for 2016



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Royal College of Physicians London
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Hypothyroidism

Epidemiology (Whickham survey)

High TSH ($>5.0\text{mU/L}$) 7.5% female
2.5% males > 65 yrs

1.7% overt
13.7% subclinical hypothyroidism

Oxford Handbook of Endocrinology,
Eds, John Wass and Katharine Owen 2014



Hypothyroidism

Synthetic levothyroxine - on an empty stomach
- 1.6-1.8 mcg/kg/day

Young - commence 50-100 mcg Increase 25mcg
Elderly - commence 25 - 50mcg every 4 weeks

TSH checked after 4-6 weeks at each increment
aim TSH < 2.5 mU/L

For preference use the same brand



Persistent elevation of TSH on Thyroxine

Mostly poor compliance



The following do not interfere with the absorption of Thyroxine?

1. Atrophic gastritis
2. Phenytoin
3. Ferrous sulphate
4. Omeprazole
5. Aluminium hydroxide



Interference with absorption of thyroxine

Coeliac disease

Drugs ↓ absorption of thyroxine

Calcium salts
Ferrous sulphate
Aluminium hydroxide
Cholestyramine
Omeprazole

↑ clearance of thyroxine

Rifampicin
Phenytoin
Phenobarbitone
Carbamazepine
Imatinib

Atrophic gastritis with h pylori (↓ T4 by 30%)

A Thyroxine Absorption Test Followed by Weekly Thyroxine Administration: A Method to Assess Non-Adherence to Treatment

JN Walker, S Pallai, V Ibbotson, A. Vincent, N Karavitaki, AP
Weetman, JAH Wass , A Allahabadia

[Eur J Endocrinol.](#) 2013 May 10;168(6):913-7

Supervised 7 x 1.6 mcg/kg weekly - with monthly
TSH monitoring



“Allergy” to Thyroxine

Tablets contain:

- Lactose
- Starch
- Stearates
- Citrate
- Acacia

Use liquid thyroxine



Subclinical hypothyroidism

Raised TSH – normal thyroid hormone levels

Note past radioactive iodine

+ve thyroid antibodies (5% per year → overt)

8 x risk of hypothyroidism

with elevated TSH, 38 x increased risk

Thyroid antibodies increase the miscarriage rate

? Replace if attempting pregnancy

Vanderpump MP 2010, Clin End, 72, 436-40



Subclinical hypothyroidism

Give thyroxine if TSH > 10 mU/L

If TSH 4-10 mU/L + symptoms consider trial of thyroxine

In patients attempting pregnancy - treat mild TSH elevation

Biondi B 2008 End. Rev 29, 76-131

Pearce S et al 2013 2, 215-228



Hypothyroidism

Combine T4 & T3?

5% treated hypothyroid patients - symptomatic

Causes - other endocrine/non endocrine disease -
Coeliac disease
Vitamin D deficiency
B12 deficiency
Depression

Treatment - ensure TSH < 2.5 mU/L

Iatrogenic hyperthyroidism - arrhythmias
fractures

Conversion of T4 → T3 may not be normal in 10%

Trial of T3 5mcg thrice daily + reduce T4



Nygaard B 2009 Eur J Endocrinol 2009; 161, 895-902

Pituitary Hypothyroidism

Monitor fT4 in hypopituitary hypothyroidism
→ (upper normal)



Pregnancy & Hypothyroidism

Risks

Spontaneous miscarriage rate increased x 2
preeclampsia – 21% if sub optimally treated

Foetus dependant on maternal thyroxine until 12 weeks
Risk of impaired foetal intellectual & cognitive development
Increased perinatal death

Lazarus J 2011 Br. Med. Bull, 97 137-48



Pregnancy & hypothyroidism

Management

Diagnosed in pregnancy - start 100mcg & measure T4 and TSH in 4 weeks

If on T4 - increase dose by 25-50 mcg

- optimise (TSH <2.5 mU/L) prior to pregnancy

On confirmation of pregnancy

- aim TSH < 2.5 mU/L plus fT4 upper end of normal
- monitor thyroid function monthly in first trimester
- no contemporaneous iron

Aziz F 2011 Eur J. Endocrinol 164, 871-876

Alexander EH et al NEJM 351, 241-249



Progression of hypopituitarism

GH → LH/FSH → TSH and ACTH

Prolactin deficiency rare

Diabetes insipidus not seen with anterior pituitary tumours



Anterior pituitary hormone replacement

Drug	Dose	Monitor
Hydrocortisone	10mg on waking 5mg lunch	Urine cortisol
or Prednisolone	5mg early evening 3mg on waking 2mg early evening	HC levels
Thyroxine	100-150 mcg/day	fT4 (prior to morning dose)
GH	0.2-0.6 mcg/day	IGF1

NB. GH therapy can unmask undiagnosed hypothyroidism



Toogood A, End Metab Clin. North Am 2008 37, 235-261

Benefits of GH replacement

- ↑ QoL and psychological wellbeing
- Improved exercise capacity
- ↑ lean body mass – reduced fat mass
- ↑ bone mineral density
- ↓ cholesterol and other cardiovascular risk factors

No studies on cardiovascular mortality



Contraindication to GH therapy

Active malignancy

Benign intracranial hypertension

Pre-proliferative/proliferative retinopathy in D.M.



Adverse effects of GH replacement

Sodium and water retention

weight gain

carpal tunnel syndrome

Hyperinsulinaemia

Arthralgia

Myalgia

No risk of tumour development so far described

No colonoscopy study yet done



Treatment of Diabetes Insipidus

Diagnosis – 8 hour water deprivation test

- Desmopressin
- vasopressin analogue
 - acts on V2 receptors in the kidney
 - dose: 100-1000 mcg/d oral
 - 10-40 mcg/d intranasal
 - 0.1-2mcg/d s.c.
 - wide variation in dose

Monitor Na & osmolality

ORIGINAL ARTICLE

Current treatment protocols can offer a normal or near-normal quality of life in the majority of patients with non-functioning pituitary adenomas

Cristina Capatina*, Constantinos Christodoulides*, Alberto Fernandez*, Simon Cudlipt, Ashley B. Grossman*, John A. H. Wass* and Niki Karavitaki*

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Case History

C.C. Aged 23

Weight loss 65 to 45kg

Holiday in Borneo – pigmented

Vomiting Na 126 x 2

Not investigated



Case History

C.C. Aged 23

Weight loss 65 to 45kg

Holiday in Borneo – pigmented

Vomiting Na 126 x 2

Not investigated

Died – undiagnosed Addison's



Features of Addison's

Anorexia & weight loss	100%
Tiredness, weakness	100%
Skin pigmentation	94%
Postural hypotension	88-94%
Abdominal pain	
Arthralgia	
PUO	13%
Salt craving	16%



Secondary vs. Primary

No mineralocorticoid deficiency

No pigmentation



Investigation

Na ↓ (90%)

K ↑ (65%)

Cortisol ↓

ACTH ↑

Synacthen

Anaemia (normocytic)

Eosinophilia

Mild-hypercalcaemia

Adrenal suppression

Depot synacthen



Treatment of Acute Adrenal Suppression

BMJ 2012; 345 e6333

BMJ

BMJ 2012;345:e6333 doi: 10.1136/bmj.e6333 (Published 9 October 2012)

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EDITORIALS

How to avoid precipitating an acute adrenal crisis

Most importantly, heed patients' requests for hydrocortisone

John A H Wass *professor of endocrinology*¹, Wiebke Arlt *professor of medicine*²



Emergency Management - Life threatening!

Fluids – several litres first 24 hours

Hydrocortisone 100mg i.v.

+ 100mg i.m then 6 hourly

or

200mg i.v. by continuous
infusion/24 hours

Not mineralocorticoid because xs glucocorticoid steroids



Patients will die if inadequately treated

Intercurrent illness

Surgery

↑ dose

Intercurrent illness

Addison's Disease Self Help Group

<http://www.addisons.org.uk/>



The following statements on the need for consideration of steroid cover are incorrect:-

1. Patients on prednisolone 5mg per day or more
2. Patients on inhaled steroids
3. Patients undergoing colonoscopy
4. Patients with pituitary apoplexy
5. Patients undergoing tooth extraction



Patients on Steroids

Prednisolone more than 5mg/day
more than 1 month

NB. Inhaled steroids
dermatological steroids
joint injected steroids

All suppress the
synacthen test



Hydrocortisone

Minor - endoscopy 100mg i.m. before

Moderate - hernia repair - 100mg i.m. 6 hourly/24 hours

Major - open heart surgery - 100mg i.m 6 hourly/72 hours

Then resume normal medication

Major illness

Hydrocortisone 100mg i.m. 6 hourly until illness resolved



Pregnancy and Addison's Disease

Normal pregnancy

CBG ↑

Free cortisol increases last trimester

Renin ↑

In Addison's

↑ HC by 25-50% last trimester

Adjust mineralocorticoids by BP and K⁺

During labour

Parenteral steroids



Treatment of Primary Adrenal Insufficiency

Glucocorticoids

Mineralocorticoids

Fludro 100-150 daily

Monitor renin

DHEA 25-50 mg daily (May improve mood and wellbeing)



Alternatives to HRT at the menopause

Vasomotor symptoms

Venlafaxine 75mg

Paroxetine 20mg

Fluoxetine 70

Gabapentin 300 mg

Megestrol acetate 20mg

Citalopram 30mg



Risk & Benefits per 10,000 women treated with HRT per year (WHI 2002)

Benefits

No. of Patients

Hip fractures prevented

5

Colon cancer prevented

6

Adverse effects

Coronary heart disease exists

7

Cerebrovascular exists

8

Pulmonary embolism

5

Breast cancer (> 5years use)

8



Identification of Late-Onset Hypogonadism in Middle-Aged and Elderly Men

Frederick C.W. Wu, M.D., Abdelouahid Tajar, Ph.D., Jennifer M. Beynon, M.B.,
Stephen R. Pye, M.Phil., Alan J. Silman, M.D., Joseph D. Finn, B.Sc.,
Terence W. O'Neill, M.D., Gyorgy Bartfai, M.D., Felipe F. Casanueva, M.D., Ph.D.,
Gianni Forti, M.D., Aleksander Giwercman, M.D., Ph.D.,
Thang S. Han, M.D., Ph.D., Krzysztof Kula, M.D., Ph.D., Michael E.J. Lean, M.D.,
Neil Pendleton, M.D., Margus Punab, M.D., Ph.D., Steven Boonen, M.D., Ph.D.,
Dirk Vanderschueren, M.D., Ph.D., Fernand Labrie, M.D., Ph.D.,
and Ilpo T. Huhtaniemi, M.D., Ph.D., for the EMAS Group*

N Engl J Med 2010;363:123-35.

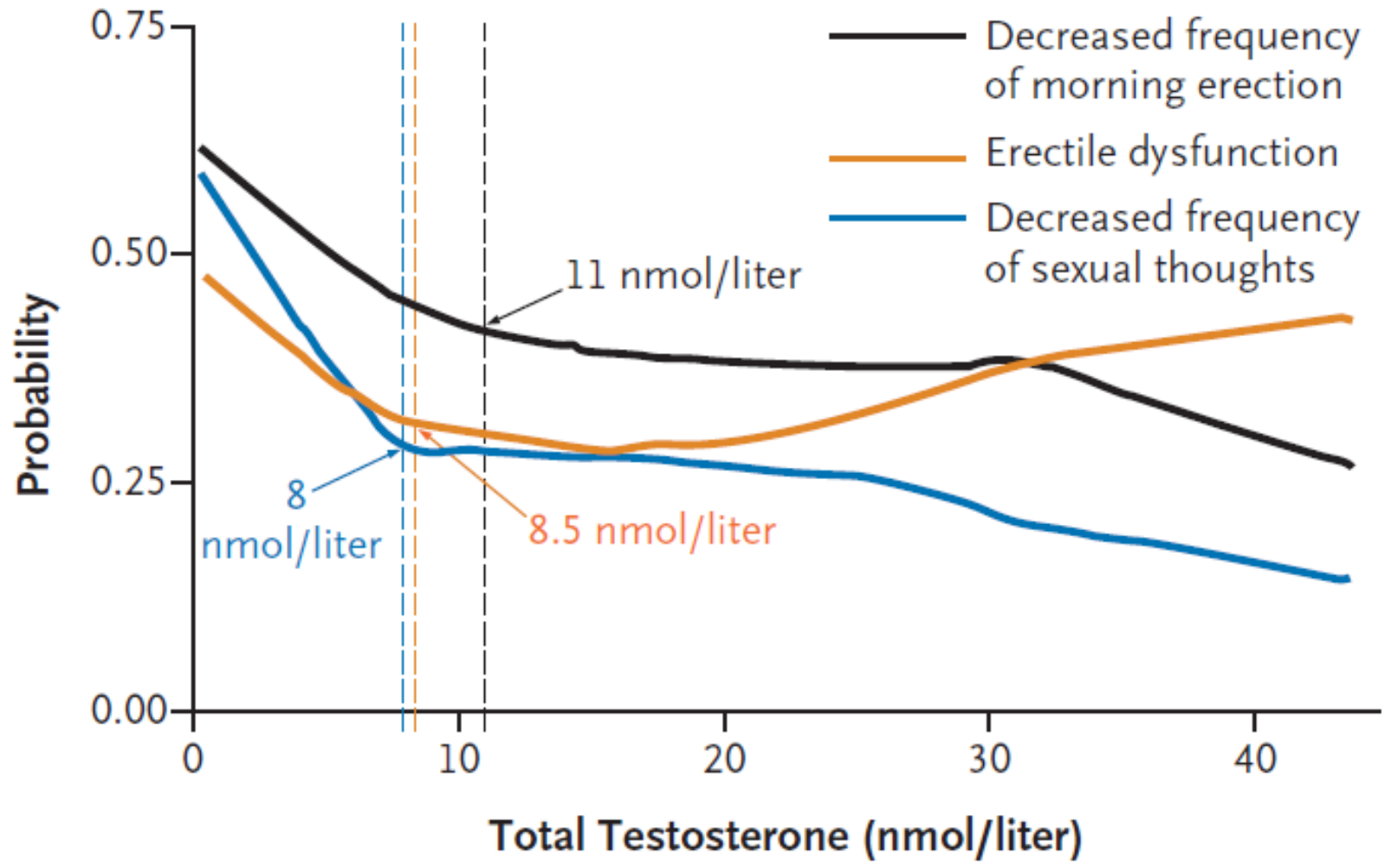


CONCLUSIONS

Late-onset hypogonadism can be defined by the presence of at least three sexual symptoms associated with a total testosterone level of less than 11 nmol per liter (3.2 ng per milliliter) and a free testosterone level of less than 220 pmol per liter (64 pg per milliliter).



A Sexual Symptoms and Total Testosterone



Testosterone Therapy Monitoring

3 months after start and then at least yearly

Clinical evaluation

Serum testosterone

Rectal examination

PSA (if > 45 years)

Haemoglobin

Lipids



Testosterone Preparation

Nebido	1g 3 monthly after loading	Convenient
Transdermal gel	5-10 daily	Convenient Occ. Skin reactions
Oral testosterone		
Buccal testosterone		
T. Implants		



Conclusions

Hormone replacement therapy has rapidly advanced in the last 5 years

Monitoring is essential if optimal quality of life is achieved

