

## RESEARCH

# Safety and tolerability of one-year intramuscular testosterone regime to induce puberty in older men with CHH

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## Abstract

We present herein our 20-year experience of pubertal induction in apubertal older (median age 56 years; range 38.4–69.5) men with congenital hypogonadotrophic hypogonadism ( $n=7$ ) using a simple fixed-dose and fixed-interval intramuscular testosterone that we originally pioneered in relation to achieving virilisation of natal female transgender men. This regime was effective and well tolerated, resulting in complete virilisation by around 1 year after treatment initiation. No physical or psychological adverse effects were encountered in this group of potentially vulnerable individuals. There were no abnormal excursions of laboratory parameters and extended follow-up beyond the first year of treatment revealed remarkable improvements in bone density. We highlight advantages to both patients and physicians of this regime in testosterone-naïve older men with congenital hypogonadism and discourage the over-rigid application to such patients of treatment algorithms derived from paediatric practice in relation to the evaluation and management in younger teenagers with delayed puberty of uncertain cause.

## Key Words

- ▶ absent puberty
- ▶ intramuscular testosterone
- ▶ congenital hypogonadotrophic hypogonadism
- ▶ older men
- ▶ Kallmann's syndrome

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## Introduction

Delayed puberty is defined by the absence of testicular development 2.5 s.d. later than the population mean – typically 14 years of age in males (1). Although the majority of cases at age 14 have constitutional delay (CDP), the proportion of males with congenital hypogonadotrophic hypogonadism (CHH) rises steeply thereafter, eventually comprising the universality of cases by the third decade of life (2). Whereas both primary and secondary (CHH) ovarian insufficiencies can present with absent puberty in females, male hypogonadism in the context of absent puberty is almost invariably secondary (CHH) (1).

Although sharing a common clinical presentation and biochemistry with CDP, most CHH cases should be identifiable at baseline evaluation due to the presence of one or more red flags (e.g. congenital non-reproductive defects, particularly anosmia; history of testicular maldescent or neonatal micropenis, indicating likely absent minipuberty) (3), with the remainder being identifiable later during the process of pubertal induction through failure to normalise testicular volume with testosterone therapy (1).

Given the aforementioned factors, the diagnostic evaluation and management of pubertal delay should

be completed during the adolescent years, and yet this remains patently not the case. In line with the shared experiences of CHH men posted on online forums, two large CHH studies (one a traditional UK case notes-based series and another an international online patient survey), whose data collection was separated by over 20 years, found the median age of initiation of any meaningful treatment to be 18–19 years (4, 5). The predominant reasons for treatment delay emerging from these studies are listed in Table 1, with almost all these coming into play for certain unfortunate individuals (6). In practice, the significance of CHH red flags is usually missed, both perinatally and in adolescence, leading to unnecessary delays in diagnosis and treatment (3).

CHH men with absent (around two-thirds of the cases) or arrested partial puberty (one-third) can thus present via a variety of routes in later life, e.g. during investigation of anaemia, muscle weakness, osteoporosis, infertility or sexual dysfunction, as a result of patients having finally summoned the courage to seek medical attention, or just serendipitously. Physicians facing an older man exhibiting congenital absence of puberty – possibly for the first time in their careers – notably lack published guidance on how best to initiate treatment (which product, how much and how quickly?). They understandably turn for guidance to their paediatrician colleagues, who encounter disorders of puberty far more commonly.

Paediatric practice and guidance are universally based upon the ‘delayed puberty – query cause’ (DPQC) pathway, which understandably emphasises the importance of reassurance and the avoidance of over-medicalisation, recommending low-dose, low-frequency pulses of testosterone if/when treatment is required (7). For adolescent boys, in whom delay is usually constitutional, testosterone treatment is typically initiated as low-dose intramuscular (IM) pulses, with the dose and/or frequency tailored to allow clinical (testicular volume) and biochemical windows of opportunity for identifying endogenous gonadotrophin secretion. In teenagers with CHH or other organic hypogonadism, the aims are to

recapitulate the normal tempo of male puberty over 2–3 years, whilst optimising linear growth potential and not masking evidence for endogenous gonadotrophin-dependent puberty should it emerge (1).

However, for those with ‘totally obvious CHH’ (TOCHH – e.g. teenager with congenital anosmia or history of bilateral cryptorchidism, or any apubertal man in his third decade or beyond), feeding them into the DPQC pathway merely imposes unnecessary delays. Regimes envisaged and designed for teenagers with suspected CDP offer frustratingly slow progress for older CHH men, who have already attained near-final height, often exhibit segmental disproportion and, having experienced years of medical procrastination, express a reasonable desire to complete puberty without undue delay (6). Moreover, any opportunity for age-appropriate recapitulation of the normal tempo of puberty is long past.

Overvalued concerns that testosterone therapy might precipitate acute behaviour change – aggression, hypersexuality or priapism – in older apubertal men are surprisingly common among physicians, potentially further contributing to excessive caution with testosterone dosing in older men. Moreover, older men are more likely to harbour non-gonadal comorbidities for which there also seem to be lingering physician misconceptions in relation to the ‘risks’ of testosterone initiation. In addition, older men lacking capacity may no longer have a living relative for discussions of best interests. That CHH which is itself frequently associated with profound psychosocial issues adds another layer of complexity (8). Nevertheless, expert guidance is unequivocal, stating that age or disability *per se* should not constitute barriers to initiation of testosterone therapy in CHH (9).

The rarity of CHH (around 1 in 4000 males) (10) limits the accrual of experience even in the most specialist centres such as our own. The questions remain: what should the TOCHH pathway look like for a testosterone-naïve older man? And are there useful, and potentially more appropriate, experiences to be drawn from medical specialties other than paediatrics? Herein, we present our experience of a

**Table 1** Factors underlying delayed initiation of age-appropriate treatment for CHH males.

Patient/parent factors	Delayed presentation Failure to attend follow-up visits Failure to adhere to prescribed treatment
Physician factors/errors	Belief that ‘simple reassurance’ is the only required first-line management for case of absent puberty beyond age 14 Belief that partial puberty (testicular volume $\geq 4$ mL) means that progression of puberty to completion is inevitable, so that patients can thus be safely discharged from follow-up Failure to identify or recognise the significance of ‘red flag’ features pointing to CHH over CDP Failure to prescribe clinically-meaningful doses of testosterone to adult men with confirmed CHH

simple 1-year (fixed-dose; fixed-interval) completion-of-puberty regime with IM testosterone in older CHH men, presenting with untreated (or minimally treated) puberty. This regime has been significantly informed by our parallel clinical experience in achieving virilisation of testosterone-naïve (natal female) transgender males.

## Patients and methods

Case records were reviewed for all CHH men ( $n=7$ ) who have been undergoing pubertal induction with testosterone at our centre since 1998 – aged 35 years or older. The diagnoses comprised Kallmann's syndrome ( $n=5$ ), normosmic CHH ( $n=1$ ) and CHARGE syndrome ( $n=1$ ). Their clinical 'vignettes' are detailed in [supplementary data](#) (see section on [supplementary data](#) given at the end of this article), and offer some insights into the reasons for their extreme delay in presentation, but it was notable that one had major physical and learning impairments and another presented with life-changing injuries resulting from major self-harm episode influenced by low self-esteem.

Median age at treatment initiation was 56 years (range 38.4–69.5). Treatment over the first year was with IM Sustanon 250mg administered monthly ( $n=1$ ), or testosterone undecanoate 1g (Nebido/Reandron-TU) administered around four months apart ( $n=6$ ) – omitting the usual loading dose recommended at 6 weeks. All patients additionally received daily supplementation with calcium and cholecalciferol.

The data presented in this manuscript originated not from a registered clinical trial, but from an internal audit of our established clinical practice. Therefore, formal institutional ethical approval was not required, because non-identifiable data are used with all subjects or guardians consenting to the inclusion of the data being presented.

Statistical analysis was performed using SPSS for Windows version 22 (IBM SPSS Statistics 22). Data presented are expressed as medians with interquartile ranges. Pre- and post-treatment parameters were compared using the Mann–Whitney *U*-test.

## Results

Longitudinal data detailing pubertal staging, laboratory parameters and bone mineral density are shown in [Table 2](#). All patients completed puberty within a year of treatment initiation. Of those who were able to express an opinion ( $n=6$ ) were very satisfied with the pace of change

and final outcome, with similar views being expressed by the carers of patient 5. As expected for a group of men with CHH, rather than DPQC, none developed any features of endogenous puberty, such as an increase in trough LH concentration greater than 2.0IU/L, or testicular enlargement greater than 4mL.

During testosterone treatment, there were no adverse effects recorded, except for rapidly progressive male-pattern baldness ( $n=1$ ). Despite the presence of major cognitive or psychological issues in three out of seven men prior to initiation of testosterone therapy, there were neither adverse psychological events recorded nor any worsening in mood or behaviour noted during treatment. In the CHARGE patient-lacking capacity, DISDAT (Disability Distress Assessment Tool ([http://prc.coh.org/PainNOA/Dis%20DAT\\_Tool.pdf](http://prc.coh.org/PainNOA/Dis%20DAT_Tool.pdf)) scores regularly calculated by experienced disability care staff remained stable.

Trough serum testosterone concentrations during treatment did not show any wide excursions and, as expected, therapy resulted in significantly increased haemoglobin concentration ( $122\pm 29$ – $157\pm 8$ g/L) and haematocrit ( $37\%\pm 9$ – $45\%\pm 5$ ) – ( $P<0.05$ ), but without any suprphysiological rise. Patient numbers were necessarily insufficient in respect of detecting significant changes in lipid profile, PSA or HbA1c, but the raw data appeared very reassuring. Follow-up beyond the initial year of treatment revealed a median increase of 49% in lumbar spine bone mineral density: median *t*-score rising from minus  $3.5\pm 1.0$  at baseline to minus  $1.8\pm 1.2$  after a median 6 years of testosterone therapy ( $P<0.05$ ).

## Discussion

Aside from isolated reports and conference abstracts, this is the first systematic evaluation of pubertal induction (methods and outcomes) in testosterone-naïve older men with congenital hypogonadism. Subject to necessarily limited patient numbers accruing to a less common presentation of a rare disease, we have demonstrated that completion of puberty over 1 year with IM testosterone can be achieved with patients' satisfaction and without significant adverse events in older apubertal men with CHH; thereafter, there are sustained major improvements in bone mineral density, even as far as the sixth and seventh decades of life. Pubertal induction in this context can be achieved using either short- or long-acting IM testosterone injections, but depot-TU conveniently minimises outpatient visits.

Although baseline osteopaenia or osteoporosis is entirely expected in these patients, as a result of congenital

**Table 2** Baseline patient characteristics and responses to testosterone therapy.

	1	2	3	4	5	6	7
<b>Case</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
Diagnosis	KS	KS	KS	KS	CHARGE	nCHH	KS
Cryptorchidism?	No	Bilateral	Unilateral	Bilateral	No	No	Bilateral
Other congenital anomalies	–	–	Synkinesia and right renal agenesis	–	Multiple (supplementary data)	Asymptomatic aqueduct stenosis	–
Age at treatment initiation (years)	50.8	38.4	69.5	57.8	64	56.6	51.6
Height (cm)	170	182	160	172	160	187	155
BMI (kg/m <sup>2</sup> )	30	25	19	22	26	28	21
Tanner stage (G.P.A)	3.3.1	3.3.3	3.2.2	2.2.2	2.1.1	2.2.2	4.4.2
Baseline	5.5.3	5.5.3	5.5.3	5.5.3	5.5.3	5.5.3	5.5.3
1 year							
Mean testis (vol. mL)	1	2	1	3	1.0	2	3
Baseline	1	3–4	2.5	3	1.0	3	3
1 year							
Testosterone (nmol/L)	1.0	<1.0	<1.0	<1.0	1.0	<1.0	1.6
Baseline	16.5±3.3	15.1±0.4	16.4±0.14	13.4±6.5	15.6±2.8	11±3.5	8.1±1.4
1 year trough							
LH (U/L)	<1.0	<0.5	<1.0	<1.9	<0.5	<0.5	<1.0
Baseline	<0.5	<0.5	<1.0	<1.0	<0.5	1.5	<1.0
1 year trough							
FSH (U/L)	1.1	0.5	<1.0	<1.0	1.2	<0.5	<1.0
Baseline	<0.5	1.3	<1.0	<1.0	<0.5	1.4	<1.0
1 year trough							
Hb (g/L)	13.8	14.1	9.6	12.0	12.2	9.1	15.0
Baseline	15.7	15.6	13.2	18.7	15.3	16.0	16.1
1 year trough							
HbA1c (mmol/mol)	41	32	–	37	40	–	41
Baseline	41	35	39	36	34	–	38
1 year							
Chol (mmol/L)	5.1	3.9	5.9	4.9	6.1	–	6.0
Baseline	5.2	4.1	5.2	3.9	5.7	5.0	5.5
1 year							
HDL-C (mmol/L)	1.4	0.9	–	1.6	1.4	–	1.7
Baseline	1.5	0.9	0.7	1.7	1.3	0.8	1.8
1 year							
TGs (mmol/L)	1.1	1.1	3.7	1.5	1.3	–	1.0
Baseline	0.9	1.2	2.2	0.6	1.2	2.3	1.0
1 year							
PSA (µg/L)	0.28	–	–	0.25	–	0.31	0.40
Baseline	0.40	0.77	–	0.49	0.2	0.57	0.87
1 year							
Calcium (mmol/L) (2.2–2.6)	2.28	2.10	2.52	2.31	2.42	2.29	2.31
Baseline	2.37	2.39	2.52	2.38	2.41	2.33	2.30
1 year							

Phos (mmol/L) (0.8–1.5)	1.10	0.92	1.32	1.38	1.32	1.19	0.85
Baseline	0.86	0.94	0.74	1.16	1.50	0.95	0.91
1 year							
Alk P (U/L) (30–130)	86	115	175	73	99	83	62
Baseline	65	79	79	78	94	75	64
1 year							
PTH (pmol/L) (1.1–6.4)	–	7.3	–	–	7.0	4.3	–
Baseline	1.3	2.7	–	2.4	2.7	–	2.1
1 year							
25OHD (nmol/L) (50–175)	–	<10	–	–	<13	27	–
Baseline	58	70	–	76	64	86	78
1 year							
L1–4 t-score	–3.4	–	–2.5	–3.0	–3.9	–3.5	–3.8
Baseline	–1.8 (10)	–0.9 (6)	–2.3 (4)	–1.6 (7)	–3.3 (2.5)	–1.7 (4)	–2.8 (10)
Latest							
Hip t-score	–1.5	–	–1.5	–2.5	–2.9	–1.7	–3.2
Baseline	–0.9 (10)	–1.0 (6)	–1.5 (4)	–1.5 (7)	–2.3 (2.5)	–1.4 (4)	–2.9 (10)
Latest (years)							
NoF t-score	–1.8	–	–1.4	–2.8	–3.0	–1.8	–3.4
Baseline	–1.1 (10)	–0.8 (6)	–2.0 (4)	–1.9 (7)	–3.0 (2.5)	–1.8 (4)	–3.4 (10)
Latest (years)							
Gene mutations	Het. <i>FGFR1</i> c.854C>G [p.P285R]	Het. <i>PROK2</i> c.217C>T [p.R73C]	Hem. <i>ANOS1</i> [W334X]	Hem. <i>ANOS1</i> c1759G>T [V587L] Het. <i>CHD7</i> c.8950C>T [p.L2984F]	Not tested, but presumed <i>CHD7</i> deletion	Negative 14-gene screen	Hem. <i>ANOS1</i> c1756C>T [Q586X]
MRI	Normal	Normal	Normal	Not tolerated	Not tolerated	Normal	Normal
Pituitary	Absent	Not imaged	Not imaged	Not imaged	Not imaged	Normal	Not imaged
Olfact. bulbs							

Preliminary data on patients 1, 4 and 6 were presented in: Santhakumar, A., Miller, M., Quinton, R. Pubertal induction in adult males with isolated hypogonadotropic hypogonadism using long-acting intramuscular testosterone undecanoate 1 g depot (Nebido). *Clinical Endocrinology*. 2013; 80, 155–157.

androgen deficiency, our protocol is to defer adjuvant antiresorptive therapy until anabolic (testosterone-driven) improvements in bone mineral density have plateaued. We would, of course, revisit this strategy in the event of intercurrent spinal fracture for which parenteral antiresorptives may also be beneficial for pain control and bone remodelling, but have not yet faced this scenario in this group of patients.

Despite widespread physician concerns about potential behaviour disturbance in testosterone-naïve adult men undergoing physiological normalisation of serum testosterone, literature review failed to uncover any evidence to underpin these concerns. This reflects our experience reported herein, which is in line with that of clinicians treating much larger numbers of older testosterone-naïve transgender males with cross-hormone regimes. Transgender men have a particularly high baseline prevalence of psychological/psychiatric disease and are likewise virilised fairly rapidly, and yet significant testosterone-related behaviour disturbance has not been observed in this population (11, 12).

However, we emphasise that the regime described herein delivers just 2g of TU over the first 32 weeks of therapy and, in testosterone-naïve men, would strongly caution against using standard TU initiation regimes as per the product datasheet comprising two injections spaced 6 weeks apart followed by 12-weekly maintenance injections (i.e. cumulative 4g of TE over the first 30 weeks of therapy).

## Conclusions

We suggest that clinicians avoid reflexly applying DPQC management algorithms to older testosterone-naïve men (or younger ones with 'red flags' for CHH). We instead commend to them this simple and well-tolerated pubertal induction regime using fixed-dose and fixed-interval IM testosterone. In respect of potential psychological issues experienced by older testosterone-naïve men during pubertal induction, we believe that the more transferrable lessons emerge from the transgender – rather than the adolescent – literature.

### Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-17-0241>.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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