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1   **TITLE PAGE**

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6   **Title**

7   Society for Endocrinology guidelines for the treatment of male hypogonadism

8

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49

75 **Summary**

76 Male hypogonadism (MH) is a common endocrine disorder. However, uncertainties and

77 variations in its diagnosis and management exist. There are several current guidelines on

78 testosterone replacement therapy (TRT) which have been driven predominantly by single

79 disciplines. The Society for Endocrinology commissioned this new guideline to provide all

80 care providers with a multidisciplinary approach to treating patients with MH. This guideline

81 has been compiled using expertise from endocrine (medical and nursing), primary care,

82 clinical biochemistry, urology & reproductive medicine practices. These guidelines also

83 provide a patient perspective to help clinicians best manage MH.

84

85 **Key Words**

86 Hypogonadism, testosterone, libido, erectile dysfunction, guideline

87

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MAIN TEXT

Key points

1. Testicular defects cause hypergonadotrophic hypogonadism or PH, identified by elevated serum gonadotrophin and low T concentrations. There is rarely a need for repeated venepuncture under optimal conditions to confirm the diagnosis.

2. The biochemical features of central hypogonadism may be indistinguishable from systemic disease (i.e. non-gonadal illness - NGI), sleep-deprivation, or even afternoon or post-prandial venepuncture. Contextual clinical ascertainment, appropriate conditions for blood sampling, and repeated measurements are required for diagnostic rigour.

3. Weight loss is a highly effective way for obese men with NGI to simultaneously reduce their cardio-metabolic risk and overall well-being, while increasing their testosterone levels.

4. Most patients with MH require long-term testosterone treatment. Effective self-management and optimising therapy is needed to achieve desired treatment outcomes, improve patient well-being and quality of life, and to minimise adverse effects of testosterone treatment over- or under- replacement. Clinicians should consider individual needs and preferences when discussing testosterone initiation. Clinicians should develop a tailored treatment plan in partnership with their patients considering the benefits and disadvantages of available testosterone treatment formulations individualised for each patient.

5. All patients should be provided with education about their condition and treatment aiming to improve adherence and optimisation of testosterone treatment. Clinicians should

111   consider individual needs and preferences when discussing testosterone treatment

112   initiation.

113   6. Regardless of the aetiology of hypogonadism, sexual dysfunction and infertility can

114   severely impact quality of life, including psychological, relationship and interpersonal

115   issues.

116

1. Introduction and Methods

118 Male Hypogonadism (MH) is defined by deficient testosterone production and impaired

119 spermatogenesis by the testes. MH can manifest at any point in life, from puberty, adult life

120 and through to old age, and is characterised biochemically by low circulating serum

121 testosterone levels and clinically by a wide range of signs and symptoms of T deficiency (Table

122 1) [1]. MH has consequences for health and well-being beyond sexual function and contributes

123 to male infertility. The actual prevalence of MH is uncertain, depending on whether estimates

124 are based upon the diagnosis of a hypogonadism-related disease (e.g. Klinefelter syndrome),

125 or based solely on a defined biochemical cut-off (e.g. serum testosterone <10 nmol/L), giving

126 rise to conflicting narratives. Cross-sectional and longitudinal epidemiologic data have

127 identified an age-related decline in serum testosterone, particularly the circulating free fraction,

128 and yet much of this results from accumulating co-morbidities, such as obesity, chronic disease,

129 medications and frailty, rather than from primary disorders of the hypothalamo-pituitary-

130 gonadal axis, or even from ageing *per se* [1,2]. Nevertheless, although hypogonadism-associated

131 conditions may be individually rare, the large number and diversity of these conditions results

132 in a cumulatively significant mass of patients. This is likely to increase with more cancer

133 survivors, gonadectomised female-to-male gender transitions, primary care opiate scripts, and

134 greater numbers of diagnosed Klinefelter cases. In the UK healthcare environment, these men

135 largely depend on Endocrinologists for an accurate diagnosis and long-term management plans.

136 The Society for Endocrinology (SfE) is a professional and scientific body dedicated to the

137 advancement of knowledge and promotion of good practice in the field. Although based in the

138 United Kingdom, it is not a narrowly national body and, indeed, a significant number of

139 committee members and officers practice in the Republic of Ireland. The SfE's Clinical

140 Committee commissioned this Guideline and appointed CNJ and RQ as co-chairs. The Clinical

141 Committee and co-chairs nominated a working-group to represent multiple disciplines relevant

142 to the guideline. A patient member was also nominated to attend all meetings, and approve

143 decisions with other working group members. Meetings (face-to-face and remote) were held

144 between 2019 and 2020 to assign specific areas of the guideline scope to members of the

145 working group to perform narrative reviews of the literature and provide reports on their topic.

146 Individual reports were peer-reviewed by other members of the working group. Where

147 consensus could not be reached on specific points, the co-chairs made decisions on content. An

148 advanced draft of this guideline was revised following peer review by the SfE Clinical

149 Committee, prior to submission for publication.

150

151 **2. Aetiology of male hypogonadism**

152 Making a clear distinction between Primary Hypogonadism (PH) and Central Hypogonadism

153 (CH) through measurement of serum LH and FSH levels, as opposed to making a non-specific

154 diagnosis of "testosterone deficiency" or "low testosterone", is a mandatory clinical

155 requirement under all circumstances, because the outcome of this analysis determines:

156 1. The available first-line options for inducing/restoring fertility, which differ fundamentally:

157   gonadotrophin therapy to induce spermatogenesis in CH *versus* mTESE, donor sperm or

158   adoption, as potential options to becoming a parent.

159   2. The palette of potential differential diagnoses, which can in turn signpost specific disease

160   management strategies beyond testosterone therapy, *e.g.* mitigation of the risks of

161   developing type 2 diabetes (T2DM), cancer, or venous thromboembolism in men with

162   Klinefelter syndrome; screening for the presence of hyperprolactinaemia, iron overload,

163   wider pituitary dysfunction, or parasellar mass lesion in CH.

164   3. The nature of any confirmatory or second line investigations required, such as pituitary

165   biochemical profiling and imaging in CH, *versus* karyotype/copy number variation in PH.

166   4. Confirmation of the diagnosis of MH through further contextual clinical ascertainment.

167   For instance, the diagnosis is invariably secure when basal biochemistry indicates PH, but

168   further contextual clinical ascertainment is required to properly distinguish CH (for which

169   testosterone treatment is first line therapy) from NGI, for which first-line interventions are

170   instead directed at lifestyle-coaching, disease-management, or addressing general health

171   needs.

172 It is crucial to identifying the aetiology of CH is ruling out potential causes and confounders,

173 which demands contextual clinical history, physical examination, medication review and

174 biochemical assessment under controlled conditions, usually on more than one occasion.

175

176 *2.1. Primary Hypogonadism*

177 Primary Hypogonadism (PH) is characterized by elevated serum gonadotrophin levels in the

178 setting of low testosterone levels due to Leydig cell dysfunction (whether impaired cellular

179 function, or reduced cell mass). It may be accompanied by impaired or absent spermatogenesis.

180 Some testicular disorders underlying hypogonadism are exceedingly rare, such as congenital

181 anorchia (*i.e.* vanishing testes), Leydig cell hypoplasia secondary to inactivating mutations of

182 the LH receptor [3], *dystrophia myotonica* and Kennedy syndrome, but much more common are

183 cryptorchidism, trauma, orchitis, Klinefelter syndrome, post radiotherapy or chemotherapy

184 damage, and male ageing. An under-reported feature of PH is a 3-fold greater prevalence of

185 MetS and T2DM, albeit the direction of causation is unclear [4-6].

186

187 *2.2. Cryptorchidism*

188 The lower temperature of the scrotum (compared to the abdomen) is critical for Sertoli and

189 germ cell function and survival. Approximately 1-2% of males are born with cryptorchidism

190 that persists beyond 3-4 months postnatal and 80-90% of cases are unilateral [7]. Testes that

191 remain in the inguinal canal (or abdomen) beyond the first year of life have significantly

192 reduced function and it is recommended that surgical correction of undescended testes is

193 performed in the first year of life, usually after six months when anaesthetic risks diminish [8].

194 Even in unilateral cryptorchidism, the contralateral testis is not completely normal suggesting

195 that cryptorchidism is a bilateral disease [9]. There are concerns that endocrine disruptors

196 (chemicals in the environment – air, soil, or water supply – food sources, personal care

197 products and manufactured products that interfere with the normal function of the endocrine

198 system) may be contributing to a rising incidence [10].

199

200 *2.3. Klinefelter syndrome*

201 Klinefelter syndrome (KS) with a 47XXY or 48XXXY karyotype is the most common

202 chromosomal aneuploidy and the most common form of PH in males, occurring in

203 approximately 1:660 males [11]. The gonadal phenotype comprises seminiferous tubule atrophy,

204 disrupted spermatogenesis and small testes, but with Leydig cell function preserved in the

205 initial life stages. Gynaecomastia is prominent, along with behavioural and neurocognitive

206 problems, and tall stature resulting from 3 copies of the SHOX gene. Only 10% of patients

207 with KS are diagnosed before puberty and approximately 25% are never diagnosed [11]. This

208 likely reflects a combination of poor medical training in reproductive medicine and mosaic

209 forms of KS having a milder clinical phenotype with non-specific symptomatology.

210 Serum LH, FSH and inhibin B (InB) levels are typically normal until puberty, at which point

211 seminiferous tubules degenerate, losing germ cell, then Sertoli cells and eventually hyalinise

212 and testicular function progressively declines, with testicular volume rarely exceeding 5-6 mL

213 [11]. Testosterone therapy becomes mandatory when serum T concentrations become

214 hypogonadal, or when clinical features develop. However, there is a view that testosterone

215 treatment should also be considered from the point at which serum gonadotrophins begin to

216 rise in early puberty, so as to ensure full development of secondary sexual characteristics and

217 optimise bone health [11].

218 Reports have identified increased risk for mediastinal tumours, autoimmune disorders, vascular

219 disease, thromboembolism and cancer in cohorts of patients with KS, some of which may relate

220 to poorer lifestyle. As with other forms of PH, there is an approximately tripled risk for

221 metabolic complications including obesity, MetS and T2DM. Accordingly, lifestyle coaching

222 should be part of regular consultations along with ongoing monitoring of bone health with

223 densitometry and regular assessment of adherence to testosterone therapy. In addition to these

224 health problems and the physical stigmata of KS, affected boys often have poor motor skills,

225 behavioural problems and may exhibit neurocognitive deficits [12]. While highly variable, many

226 patients with KS have problems with cognition and language acquisition such as dyslexia,

227 learning disabilities and difficulties with executive function. These difficulties often require

228 speech and language therapy, special education programmes and/or psychological counselling.

229 The combination of cognitive behavioural problems and hypogonadism can negatively affect

230 quality of life and prevent effective adaptation to living with KS [13]. Impulsivity and anger-

231 management issues may be inherent to the condition but are unlikely to be caused or

232 exacerbated by physiological testosterone therapy. A multi-disciplinary approach including

233   medical, nursing, psychological and social care can assure assessment of psychosocial

234   concerns, discussing these aspects with patients and families, identifying educational or

235   employment and social resources, and making appropriate inter-professional referrals as

236   needed. With increasing age, the diagnostic yield from screening for KS among men presenting

237   with PH progressively falls and its clinical utility becomes less apparent.

238

239   *2.4. Acquired primary hypogonadism*

240   Acquired PH in men may result from trauma, infection, or inflammation (*i.e.* mumps orchitis),

241   medical / surgical interventions, systemic disease, or chronological ageing (**Table 1**), albeit an

242   underlying cause frequently cannot be identified. Unlike in women, there does not appear to

243   be a syndrome of primary, autoimmune testicular insufficiency. Orchitis may occur secondary

244   to viral infection and develops in around 25% of mumps infections among post-pubertal men

245   [14]. Unilateral inflammation occurs in approximately two-thirds of patients and can lead to loss

246   of testicular volume, but fertility is maintained in 75% of cases. Bilateral orchitis is less

247   common, but spermatogenesis recovers in only a third of men [14] and an unknown proportion

248   develop PH. The European Male Ageing Study (EMAS) found that 1–2% of older men had PH

249   and another 10% had compensated primary hypogonadism (CPH), which were associated in

250   equal measure with burden of comorbidities and chronological age [15]; the SPECT-China study

251   showed similar findings were very similar [6]. Unlike the menopause in females, the majority of

252   older men in the general population maintain adequate gonadal function, while the small

253   minority of men who develop hypogonadism usually have poor health with multiple co-

254   morbidities and/or obesity.

255   **Insert Table 1 here**

256

257   *2.5. Hypothalamic and pituitary disorders – Central hypogonadism (CH)*

258 Testosterone secretion is contingent upon adequate LH stimulation of the Leydig cells.

259 Hypogonadism resulting from inadequate gonadotrophin stimulation is biochemically evident

260 in low (or inappropriately normal) serum gonadotrophin levels. CH can be congenital or

261 acquired (**Table 1**) and results from either defects at the level of the hypothalamus (*i.e.* isolated

262 GnRH deficiency), pituitary defects causing inadequate gonadotrophin release, genetic

263 mutations resulting in inadequate action of GnRH or gonadotrophins, or functional suppression

264 of the hypothalamo-pituitary-gonadal (HPG) axis [16]. However, certain conditions can lead to a

265 false-positive biochemical "diagnosis" of CH, which include venepuncture performed in the

266 non-fasted state, in the afternoon, during intercurrent illness, sleep-deprivation or from taking

267 undeclared medicinal or recreational drugs. This emphasises the importance of a

268 comprehensive history that accounts for contextual clinical correlation factors and

269 venepuncture under standardised conditions (8-10 am, fasted and well-rested).

270

271 *2.6. Congenital hypogonadotrophic hypogonadism*

272 Congenital hypogonadotrophic hypogonadism (CHH) is a rare disorder (1/4,000–10,000

273 males) caused by isolated GnRH deficiency and clinically characterized by absent or

274 incomplete puberty and infertility [16]. When CHH occurs with anosmia (lack of sense of smell),

275 it is termed Kallmann syndrome. While sense of smell and reproduction may appear to be

276 unrelated functions, the embryonic origins of GnRH neurons in the olfactory placode provide

277 the development link. More than 30 genes have been identified as underlying CHH and

278 Kallmann syndrome either alone or in combination [16-18]. Some gene mutations disrupt GnRH

279 neuron development and migration manifesting as Kallmann syndrome; others may disrupt

280 GnRH homeostasis and secretion and clinically present as cases of normosmic CHH [16]. In some

281 cases, mutations in the gene encoding the GnRH receptor (*GNRHR*) result in decreased GnRH

282 action and CHH ensues (described below). CHH may occur with other associated phenotypes

283 such as cryptorchidism with or without micropenis, renal agenesis, hearing loss, midline

284 defects (cleft lip/palate) and skeletal anomalies. CHH can be difficult to distinguish from other

285 causes of pubertal delay and, consequently, many patients are diagnosed late with significant

286 psychosocial impact [19]. These patients need of psychological support and may benefit from

287 peer-to-peer support. Effective treatments are available for inducing secondary sexual

288 characteristics and fertility in most men with CHH [16,20]. Spontaneous fertility has been

289 reported; on rare occasions associated with "fertile eunuch" or Pasqualini syndrome, but more

290 commonly with the hormonal reversal of CHH that is observed in about 10-15% of cases

291 following treatment, but may not be sustained and thus warrants ongoing monitoring [21].

292

293 *2.7. Other syndromic forms of congenital central hypogonadism*

294 Developmental defects can result in hypothalamic-pituitary dysfunction CH. Many problems

295 present with a constellation of features and thus are referred to as syndromic forms. These

296 cases are typically identified during childhood, as anterior hormone deficiency, adrenal failure,

297 obesity, or neurologic aspects command attention well before absent puberty manifests [22].

298 Given the complexity of these cases patients and families need purposeful planned transitional

299 care to ensure continuity and ongoing support.

300

301 *2.8. Combined pituitary hormone deficiency (CPHD) and septo-optic dysplasia (SOD)*

302 Patients with combined pituitary hormone deficiency (CPHD) are often diagnosed early in

303 childhood and treated for the respective pituitary hormone deficiencies, yet gonadotrophin

304 deficiency may not become apparent until the failure of puberty to commence spontaneously.

305 Importantly, these patients are responsive to treatment inducing secondary sexual

306 characteristics and fertility [23]. A number of genes have been identified to underlie this

307 condition yet the majority of cases remain without an identified genetic cause [24]. Septo-optic

308 dysplasia (SOD) is a developmental brain malformation that can present with pituitary

309 hormone deficiencies, severe visual impairment, neurocognitive disability and developmental

310 disorders on the autism spectrum [25]. Notably, genetic overlap has been reported between SOD,

311 CPHD, CHH and CHARGE syndrome [18,26].

312

313 *2.9. CHARGE, Bardet-Biedl and Prader Willi Syndromes*

314 The constellation of <u>c</u>oloboma (ocular malformation of the lens, iris, or retina), congenital <u>h</u>eart

315 defects, choanal <u>a</u>tresia (abnormal formation of the nasal cavity), <u>r</u>etardation of growth and

316 development, <u>g</u>enital hypoplasia, and <u>e</u>ar anomalies associated with deafness define CHARGE

317 syndrome [27]. In addition to immunologic problems, patients with CHARGE syndrome may

318 exhibit hypogonadotrophic hypogonadism necessitating treatment. Approximately two-thirds

319 of cases are explained by mutation Chromodomain-helicase-DNA-binding protein 7 (*CHD7*)

320 [27] a gene also involved in CHH and Kallmann syndrome [16]. Bardet-Biedl syndrome (BBS) is a

321 recessive genetic disorder of the cellular cilia that may present with a wide range of clinical

322 features (obesity, mental retardation, renal anomalies, polydactyly, retinal degeneration, as

323 well as cardiovascular, hepatic and metabolic problems[28]. In addition to being clinically

324 heterogeneous, BBS is genetically diverse with 19 identified loci and complex genetics (i.e.

325 digenicity, oligogenicity) [28] akin to CHH and Kallmann syndrome [16]. Although traditionally

326 associated with CH, a recent clinical study found no evidence for hypogonadism among males

327 with BBS when this was screened for systematically [29]. Prader Willi syndrome (PWS) is a rare

328 genetic disorder (1/10'000-25'000) on chromosome 15 that causes physical, mental and social

329 disability. During infancy, PWS is characterized by hypotonia and poor feeding (failure to

330 thrive). Subsequently, additional features such as developmental delays, cognitive disability,

331 short stature, hyperphagia, obesity, and behavioural problems (i.e. obsessive food seeking)

332   emerge [30]. Multiple endocrine deficiencies are common with patients typically needing growth

333   hormone and testosterone therapy [31].

334

335   *2.10. Adrenal hypoplasia congenita*

336   A rare form of hypogonadotrophic hypogonadism occurs in the setting of adrenal hypoplasia

337   congenital. Mutations in Nuclear receptor subfamily 0, group B, member 1 (*NR0B1*, formerly

338   *DAX1*) result in early adrenal failure, and subsequently absent/incomplete puberty is the initial

339   sign of CH [32].

340

341   *2.11. Acquired central hypogonadism (CH)*

342   In this situation, CH develops in adult life following prior full pubertal development and can

343   result from trauma (*e.g.* skull fracture, pituitary stalk dissection and, particularly, military blast

344   trauma), vascular events (*e.g.* pituitary apoplexy), infiltrative or metabolic disorders (*e.g.* iron

345   overload, or hypophysitis), parasellar tumours, surgery, radiotherapy, hyperprolactinaemia,

346   energy-deficit, or illicit drug use (*i.e.* marijuana, opiates or androgens) [14].

347   *Anabolic androgens:* Anabolic androgens are testosterone-like substances exerting powerful

348   effects on the muscle, bone, reproductive health, cardiovascular system, brain, and behaviour

349   [33]. Most men taking anabolic androgens, do so for cosmetic rather reasons rather than for

350   athletic performance. The supra-physiological androgen levels suppress the HPG axis,

351   resulting in testicular atrophy and infertility which can be reversible. In addition, affected men

352   may develop psychiatric disturbances including mania, depression and anxiety, together with

353   psychical and psychological dependency. However, as androgens are typically abused in very

354   high doses and as some products have an extended half-life, recovery of HPG axis function can

355   take from several months to a year or longer [33-34], with fertility taking up to 3 years to fully

356   recover [34]. Significantly, levels of Insulin-like Factor 3 (INSL3) remain low for at least 3 years

following cessation of androgen abuse, independently of testosterone, suggesting a persistent impairment of Leydig cell function [35].

In adult-onset isolated GnRH deficiency, men who previously completed puberty present in adulthood with CH secondary to profound HPG axis suppression and complete loss of LH pulsatility [36]. These men have no other apparent underlying cause of their hypogonadism and defect is identified as hypothalamic as they respond to physiologic pulsatile GnRH therapy. Long-term follow up studies suggest that the neuroendocrine defect is permanent as these men do not subsequently regain HPG axis function [37].

2.12. Parasellar tumours causing central hypogonadism

Craniopharyngiomas, Rathke's cleft cysts, pituitary adenomas, gliomas, germinomas, and meningiomas can cause CH. As space-occupying lesions, compression and destruction of the hypothalamic-pituitary region can impair GnRH-induced gonadotrophin secretion. In adults, prolactin-secreting pituitary adenomas (prolactinomas) are the most frequently encountered and can cause functional HPG axis suppression in addition to CH from mass-effect [14].

2.13. Iatrogenic central hypogonadism

Common causes include surgery, chemotherapy, radiation treatment, long-term high-dose glucocorticoid treatment, or opiates used for chronic pain management or narcotic addiction [38], along with androgen deprivation therapy (ADT) for prostate cancer, for which the achievement of CH is the goal of treatment. Finally, transgender males also require testosterone therapy, which is generally sufficient to suppress hypothalamo-pituitary-ovarian function pending oophorectomy, but in the interim may be combined with a GnRH analogue or progestogen (systemic or intrauterine) should amenorrhoea not be achieved by testosterone alone.

382   *2.14. Functional central hypogonadism*

383   CH can also result from physiological causes and this is better known in females, where

384   physical, emotional, or nutritional stressors can result in suppression of menses (functional

385   hypothalamic amenorrhea) [39], albeit there may also be a genetic propensity [40,41]. However,

386   males appear more resistant to hypothalamic suppression from either excessive exercise or

387   energy deficits, as only small series have been reported to date and, moreover, genetic

388   influences have not been identified [42]. Typically, such cases are restricted to patients with

389   eating disorders (*i.e.* anorexia nervosa) or endurance athletes on very low-fat diets. A much

390   more common form of functional hypogonadism results from hyperprolactinaemia suppressing

391   hypothalamic GnRH secretion. Elevated serum prolactin levels may result from physiologic

392   causes (*e.g.* stress, illness, sleep deprivation), pathophysiologic (*i.e.* prolactinoma) or

393   iatrogenic causes (*i.e.* dopamine antagonist drugs) [43]. Notably, dopamine negatively regulates

394   prolactin secretion while serotonin has a stimulatory role. Thus, both dopamine-antagonist

395   antipsychotic drugs and serotonergic anti-depressants can cause elevated prolactin levels and

396   may induce hypogonadism [43]. Opiates (see *2.13*) are another common cause of functional

397   central hypogonadism. Importantly, the HPG axis recovers once the underlying stimulus to

398   energy-deficit or hyperprolactinaemia (or the opiate drug itself) is removed, and the evidence

399   for benefit of testosterone treatment is patchy, particularly in respect of opiates, wherein many

400   adverse impacts on health arise independently of hypogonadism. Nevertheless, as the clinical

401   features of these forms of functional hypogonadism (sexual dysfunction, fatigue, anaemia,

402   osteoporosis, sarcopaenia, gynaecomastia and infertility) are so strikingly congruent with those

403   of permanent forms of MH, testosterone treatment should generally be prescribed unless

404   resolution or removal of the stimulus to MH is anticipated within a reasonable timeframe.

405

406   *2.15. Systemic disease – non-gonadal illness (NGI)*

407   Stress from acute illness, including surgery, burn injuries, myocardial infarction, stroke and

408   sepsis have all been noted to suppress the HPG axis [44] and, when stress becomes prolonged as

409   per any chronic illness, suppression of GnRH-induced gonadotrophin secretion becomes

410   entrenched [45]. NGI is also observed in relation to ageing and obesity (see below). Importantly,

411   this effect is reversible upon recovery from or remission of the underlying disease process. The

412   evidence basis for testosterone treatment of NGI arising from these conditions is slim.

413

414   *2.16. Ageing and central hypogonadism*

415   Four key epidemiologic studies, as summarised by Dean et al, examined testosterone

416   deficiency in ageing Western men: 1) the Massachusetts Men's Aging Study (n >1,600, aged

417   40-70 years), 2) Boston Area Community Health Survey (n >1,400, aged 30-79 years), 3)

418   Hypogonadism in men (n >2,100, aged >45 years), and 4) the European Male Ageing Study

419   (EMAS) (n>3,000, aged 40-79 years) [46]. These studies point to a progressive decline in serum

420   T with age and alterations in sex hormone binding globulin (SHBG). The Survey on Prevalence

421   in East China for Metabolic Diseases and Risk Factors (SPECT-China study) found a similar

422   fall in testosterone levels to EMAS up to and including middle age, whereas older men who

423   had maintained traditional non-Western diet and largely avoided weight-gain did not exhibit

424   lower testosterone levels than younger Chinese men [6]. Historically, several terms were used to

425   describe the age-related fall in serum testosterone, including male menopause, andropause, and

426   androgen deficiency syndrome of the aging male. The EMAS multicentre European cohort

427   study provided much-needed clarity and defined "late-onset hypogonadism" (LOH) as at least

428   three sexual symptoms (decreased sexual interest, morning erections and erectile dysfunction

429   [ED]) in the setting of a total serum testosterone level <11 nmol/L and calculated free

430   testosterone <220 pmol/L [47]. Importantly, low serum T levels combined with potentially

431   attributable sexual symptoms only occur in a small minority of ageing men (2-6%) and can be

432 largely attributed to comorbidities causing gonadotrophin suppression (*i.e.* NGI), and in

433 particular obesity. Therefore the priority is to address or treat comorbidities as far as possible,

434 with the evidence for benefit of testosterone treatment being slim. In contrast, as outlined in

435 section *2.4*, both EMAS and SPECT-China crucially identified a small subset of older men (1-

436 2%) having acquired *primary* hypogonadism that was equally associated with chronologic age

437 and comorbidities [46].

438

439 *2.17. Obesity and male hypogonadism*

440 There are consistent data showing a negative correlation between obesity and testosterone,

441 irrespective of age [15,48]. Obese men often exhibit low-normal serum gonadotropins with

442 slightly low testosterone, but this is reversible and studies of lifestyle modification (i.e. diet

443 and exercise) or bariatric surgery show that the rise in serum testosterone is proportional to the

444 amount of weight lost [48,49]. The relationship between testosterone and fat (obesity) appears to

445 be bi-directional, with several underlying mechanisms underpinning this. Lower serum

446 testosterone levels result in decreased lean muscle mass and increased fat mass, which in turn

447 promotes adipocyte-aromatase-mediated conversion of testosterone to oestradiol, thereby

448 directly decreasing circulating testosterone, as well as doing so indirectly via oestradiol-

449 mediated suppression of GnRH secretion, creating thus a vicious cycle. Other contributing

450 factors include the dysregulated signalling of leptin, adiponectin and gut hormones (ghrelin,

451 peptide YY), the effects of pro-inflammatory adipocytokines (*e.g.* tumour necrosis factor alpha,

452 interleukin [50] and physiologic stressors accompanying obesity (e.g. chronic diseases such

453 metabolic syndrome, sleep apnoea and arthritis), overall constituting non-gonadal illness (NGI)

454 [48]. However, due to the inhibitory effect of hyperinsulinaemia on hepatic SHBG secretion,

455 obese men tend to run low SHBG levels, such that measurement of total testosterone may at

456 first sight appear to indicate a CH (or NGI) biochemical picture, whereas in fact free T is likely

457 to be normal. These men are not usually anaemic, osteopaenic, or infertile and thus the

458 mainstays of management are lifestyle change, weight loss and the identification and treatment

459 of other obesity-associated comorbidities, such as sleep apnoea. Although testosterone

460 treatment may improve lean body mass and surrogate markers of cardio-metabolic metabolic

461 health in these men, the erythrocytosis that is frequently induced thereby makes the overall

462 balance of benefits versus risks far less clear.

463

464

465 **3. Diagnosing male hypogonadism**

466 The diagnosis of MH requires a combination of characteristic clinical features and

467 corroborative biochemistry. Lacking any relevant clinical features or risk factors on medical

468 history, there would usually be no justification for initiating a biochemical workup. The

469 diagnosis of MH may be obvious due to strong risk factors including pubertal delay [51] prior

470 cancer alkylating therapy, radiotherapy or orchidectomy, and known Klinefelter syndrome.

471 However, the diagnosis of MH may be challenging because some clinical features may be non-

472 specific. Clinical features suggestive of MH comprise the sexual (reduced libido and sexual

473 activity, erectile dysfunction and reduced spontaneous erections), skeletal (loss of height, low

474 trauma fractures and low bone density), reproductive (cryptorchidism, infertility or low sperm

475 count), vasomotor (hot flushes and sweats), haematological (reduced haemoglobin or

476 haematocrit in the absence of other identifiable cause) and tender glandular gynaecomastia. By

477 contrast, symptoms such as disturbances of mood, sleep, or neurocognitive function, reduced

478 muscle mass and strength and increased body fat appear to be less specific to MH [1] and, indeed,

479 are much less likely to improve with testosterone treatment [52]. A targeted medical history is

480 required identify confounding factors that might affect the interpretation of the biochemical

481 profile, such as non-gonadal illness, energy deficit or excess, and drugs particularly androgens,

482 opioids, glucocorticoids and cannabinoids. Examination should note if voice tone is pre- or

483 post-pubertal, male pattern hair development, gynaecomastia, testicular volume, and evidence

484 of cryptorchidism or orchidopexy.

485 A variety of criteria have been proposed for the diagnosis of MH as discussed in two recent

486 reviews comparing current guidelines [53,54]. A harmonised reference range for serum total

487 testosterone has been calculated in over 9,000 healthy non-obese young men from Europe and

488 North America using the Centers for Disease Control and Prevention (CDC) reference method;

489 the 2.5[th] and 97.5[th] percentile were reported as 9.2nmol/L and 31.8nmol/L, respectively [55,56].

490 However, the diagnosis of MH also needs to take into account the presence of clinical features

491 likely caused by low testosterone. The EMAS study observed that in approximately 3,400 men

492 aged 40-79 years, the odds of experiencing sexual symptoms increased with either a total

493 testosterone <8nmol/L (regardless of calculated free testosterone) or total testosterone

494 <11nmol/L (with cFT<220pmol/L) [47]; men with levels of testosterone above these threshold

495 were no more likely to experience symptoms related to hypogonadism than the background

496 population. The presence of specific risk factors described above and diagnostic features such

497 as anaemia and low bone mineral density can help make the diagnosis where results are

498 equivocal.

499 It is also important to consider the potential clinical benefits of testosterone treatment for men

500 with MH. Results from a systematic review and meta-analysis demonstrated that testosterone

501 treatment improves sexual symptoms in men with serum testosterone <8 nmol/L unrelated to

502 non-gonadal illness [57]. However, there is a paucity of published evidence investigating the

503 clinical effects of testosterone treatment in men whose baseline serum total testosterone is

504 >12nmol/L. Although the clinical effects of testosterone treatment in men *without*

505 hypogonadism represent an interesting area of research, there is currently insufficient evidence

506 to be able to translate this into clinical practice and testosterone treatment is not licenced in

men without MH [58]. In summary, a multi-method approach is necessary to establish the diagnosis of MH, though it is evident that the higher the serum testosterone threshold is set, the greater the risk of making an incorrect diagnosis of MH. This emphasises the importance of contextualising clinical and laboratory information when making a differential diagnosis.

4. Analytical performance of serum testosterone assays for men

The UK National External Quality Assurance Scheme (NEQAS) for Steroid Hormones monitors laboratory performance in the measurement of serum testosterone, SHBG and the derived analyte Free Testosterone. Most laboratories use either commercial diagnostic kits using an immunoassay principle or a Mass Spectrometry method. Overall, the performance of these tests is generally acceptable compared to other hormone analytes. The UK NEQAS for Steroid Hormones has trend data covering many years allowing to gauge the current state-of-the-art. Method bias, when compared to the reference value, does shift over time within any laboratory and an assay which is unbiased today could nevertheless drift into having a 5% bias over a period of years. Although mass spectrometry (MS) performance for testosterone levels in the female range is superior to that of immunoassays (many of which display a concentration-dependent bias with a negative bias at lower concentrations), the performance of some immunoassays outperforms MS methods in the male range. The between-laboratory agreement for some immunoassays can be as good as 4% CV, whereas MS users vary by up to ±10%, which could be considered a desirable performance limit. Therefore, MS is by no means the gold standard that was previously supposed and, at present, ±15% is used as the definition of out-of-consensus performance. The recovery of added testosterone for most methods is not quantitative and can be as high as 130% and as low as 90% for some of the major methods [59].

4.1. Free testosterone

532 Testosterone circulates bound to plasma proteins, predominantly albumin and, particularly, sex

533 hormone binding globulin (SHBG). However, levels of testosterone and its binding proteins

534 can vary considerably between and within individuals due to physiological and pathological

535 causes. Concentrations of SHBG can vary depending on variables such as diet, body mass

536 index (BMI), insulin, thyroid and sex steroid hormone concentrations, and age [60-69]. In these

537 situations, measurement or calculation of free testosterone should provide added confidence in

538 the differentiation between mild hypogonadism and eugonadism [70,71].

539 There are four approaches to estimating free testosterone, comprising direct measurements of

540 free testosterone by 1. equilibrium dialysis, 2. ultra-centrifugation, or 3. gel filtration, and 4.

541 calculation of the free testosterone fraction by mass action formula based on the binding

542 characteristics of SHBG and albumin. It is generally accepted that all three methods of direct

543 measurement are technically demanding, are not available to routine clinical laboratories and,

544 crucially, lack much in the way of clinical correlation to established measures of androgen

545 action, such as sexual function, bone mineral density and haemopoiesis. The commonly used

546 alternative is to calculate the free fraction, for which there are several available formulae,

547 though they all give different results possibly due to SHBG and albumin having inconstant

548 binding characteristics (Heinrich-Balard et al 2015; Goldman et 2017). CFT using the

549 Vermeulen formula has been increasingly used in clinical practice over the past 20 years and

550 the calculated free testosterone results have shown clinical validity in many studies [62,72-81]. The

551 original Vermeulen equation was validated using assays for testosterone and SHBG that are no

552 longer available but has recently been re-validated using current state-of-the-art methods [61].

553 Calculated free testosterone has been increasingly used in clinical practice over the past 20

554 years. However, the implementation is challenged by the variability of analytical methods for

555 testosterone and SHBG used in routine clinical laboratories. These variations as well as the

556 various equations to calculate free testosterone have a significant impact on the results reported

557 by clinical laboratories. The most recent data from UKNEQAS show that there are seven

558 methods for testosterone and six methods for SHBG in common use [59] which creates a myriad

559 of combinations and calculated free testosterone results [60,61,63,66-68]. It is essential, therefore,

560 that each combination of assays has its own specific reference ranges and decision limits for

561 free testosterone, and this requires close collaboration between clinical and laboratory

562 specialists. Clinicians and laboratories should avoid using generic or extraneous reference

563 ranges, in order to safeguard against misclassification of patients [1,82]. It is important to highlight

564 that the accuracy and clinical utility of free testosterone quantification is limited in the absence

565 of these precautions; future efforts to resolve these issues would reduce risks of misdiagnosing

566 men with symptoms suggestive of hypogonadism.

567 In summary, total testosterone is the unchallenged first-line investigation for suspected

568 hypogonadism. Calculated free testosterone is used only as a second-line test in conditions

569 associated with deranged SHBG concentrations, or when total testosterone is in the borderline

570 range for patients with clinical features suggestive of androgen deficiency. However, the use

571 of free testosterone is still controversial [64] and it is impossible to derive accurate free

572 testosterone estimations without tightly regulated testosterone and SHBG assay performance.

573

574 **5. Testosterone therapy**

575 MH is associated with several physical, psychological, and social symptoms and, with rare

576 exceptions, patients require long-term testosterone treatment and older age or disability should

577 be no barrier for initiating testosterone treatment. Current treatment formulations and

578 modalities for testosterone treatment, though not yet perfected, can offer an individualized

579 treatment regime if accompanied by appropriate patient education and shared decision making.

580 Given the complexity of testosterone treatment, it is crucial that patients understand and engage

581   with their treatment planning, and are supported to self-monitor testosterone treatment in order

582   to recognise and manage potential adverse effects [83].

583   Currently available testosterone formulations, dosage, administration and benefits and

584   disadvantages of each formulation are presented in **Table 2** [1,83,84]. The clinician should support

585   the patient to identify a suitable testosterone formulation through a structured needs assessment

586   and by providing patients with a rationale of benefits and disadvantages of each testosterone

587   treatment formulation [83]. The most used formulations in the UK are transdermal gels and

588   intramuscular injections.

589   **Insert Table 2 here**

590

591

592

593   *5.1. Testosterone transdermal gel*

594   This is a clear alcohol gel applied once a day, preferably in the morning, to dry, clean, unbroken

595   and healthy skin, excluding the genital area. The gel is absorbed rapidly through the skin within

596   5–10 min and testosterone level elevate to the reference range within 2–4 h after application.

597   Dose titration, aiming for mid-normal reference range for total testosterone, is based on blood

598   test taken approximately 2-6 hours post-gel application, avoiding the gel application site [85,86].

599   Full absorption of the gel may take up to six hours and, therefore, showering or swimming

600   within that time should be avoided. It is important to advise patients on the potential risk of

601   direct skin-to-skin transfer of testosterone. Transfer of testosterone gel to pregnant women may

602   cause abnormalities or harm to the unborn baby. To minimise risk of transfer, patients are

603   advised to: wash hands thoroughly immediately after applying the gel; cover the application

604   site (shoulders, upper arms, abdomen) with clothing once the gel has dried; shower before any

605   situation involving close skin-to-skin contact within 6 hours after applying the gel.

606   Testosterone gel is well tolerated; however, occasional irritation or dryness may occur which

607   patients can treat with unscented moisturising topical creams.

608

609   *5.2. Testosterone intramuscular injections*

610   These injections are administered intramuscularly (IM) into the gluteal muscle or upper thigh,

611   although improved pharmacokinetics and potentially greater tolerability have been reported

612   with off label subcutaneously (SC) injection [87]. They are oily preparations (such as castor oil)

613   which allow slow release over a long period after being injected. Most patients have their

614   injection given by their GP or practice nurse, which often causes restrictions in lifestyle.

615   Testosterone injections provide high levels of testosterone (peaks) shortly after the injection,

616   which tend to drop below the reference range (troughs) towards the end of the injection interval.

617   This results in some patients experiencing symptoms related to high and low testosterone levels

618   between the injections, such as mood swings, difference in energy levels and sexual drive

619   which can be more prominent with the short acting IM injections.

620   Testosterone injections (**Table 2**) may be either of the following:

621   1. *Short acting* administered IM every 2-4 weeks or SC once a week depending on formulation

622   and patient response. Administration of testosterone cypionate and enanthate by SC injection

623   at 50-100 mg once a week has comparable pharmacokinetics, safety and tolerability to IM

624   administration and a steady state concentration of serum testosterone between dose intervals

625   [87,88]. This can also support patient self-management as self-administration is more feasible than

626   IM injections. Education is important to consult patients and their families on how to monitor

627   improvement in well-being and response to treatment and any potential side effects as well as

628   peak and trough levels between injections [83].

629   2. *Long-acting* testosterone undecanoate 1 g/4 mL IM injections, typically every 10–14 weeks

630   although much longer intervals may be needed. This should be warmed and injected very

631 slowly deep into the gluteal muscle, to minimise injection-related pain and risk of micro-

632 embolism. The first and second injections are given 6–8 weeks apart as a loading dose, with

633 the third injection given 12 weeks later. However, for the graded induction of puberty in men

634 and older teenagers, the 6–8 week loading dose should be omitted [89,90]. A testosterone level

635 and full blood count measured just prior to the third injection will then determine the frequency

636 of future injection intervals. Other things being equal, the interval between injections is set to

637 achieve a trough testosterone at the lower end of the normal reference range [91,92], but other

638 factors such as adverse effects, haematocrit, bone density and clinical well-being also need to

639 be factored-in [54]. Once steady-state has been achieved, trough bloods should be measured every

640 3–5 injections or annually, depending on the final injection interval; it is not usually necessary

641 do draw blood with each injection.

642

643 *5.3. Benefits of testosterone treatment and side effects*

644 The objective of testosterone treatment is to reverse or prevent the symptoms and long-term

645 effects of MH and to maintain general well-being [1]. Optimised testosterone treatment can:

646 • Induce or complete secondary sexual development

647 • Improve sex drive, libido and sexual function

648 • Improve mood and well-being

649 • Improve muscle mass and strength

650 • Restore or maintain masculine characteristics such as facial and body hair

651 • Maintain bone strength and prevent osteoporosis

652 • Maintain red cell production and prevent anaemia.

653 testosterone treatment suppresses gonadotrophin secretion and is therefore unsuitable for men

654 during conception (see section on "fertility considerations"). It is important to consult the

655 patient on what to expect from testosterone treatment and the estimated time periods when he

656 will experience the benefits of testosterone treatment. Setting realistic expectations and

657 supporting the patient to recognise and manage potential testosterone treatment side effects

658 effectively has a significant impact on treatment adherence [83]. Effects of testosterone treatment

659 on sexual and quality of life parameters can appear within 3-6 weeks, such as improvement in

660 sexual interest, depressive symptoms and energy levels, but changes in physical parameters,

661 such as erythropoiesis, lipids, fat mass, lean body mass, glycaemic control, muscle strength

662 and bone density may require 6-12 months to become apparent [93].

663 The suitability of each treatment option and any formulations-specific side effect as outlined

664 in **Table 2** should be assessed and addressed at each consultation. Potential side effects

665 described with testosterone treatment include acne, headache, irritability, aggressiveness,

666 mood swings, depression, weight gain, oedema, prolonged painful or frequent erections,

667 gynaecomastia, increased haematocrit and male pattern baldness [1]. However, these side effects

668 can be significantly minimised with optimised testosterone treatment; noting also that

669 symptoms such as mood swings, depression, gynaecomastia and irritability are also prominent

670 in undertreated hypogonadism. The patient should be advised to monitor and discuss any of

671 these side effects with their endocrine team to review and adjust their treatment regime. A

672 symptoms diary is often very helpful which can be cross-checked against the biochemistry

673 results and testosterone treatment formulation.

674

675 **6. Post-finasteride syndrome and anabolic androgens**

676 Finasteride is a 5α-reductase enzyme inhibitor used in the treatment of benign prostatic

677 hypertrophy and male androgenetic alopecia (AGA). Patient self-reported studies show that

678 finasteride causes adverse drug-related reactions with sexual impairment (decreased libido,

679 erectile dysfunction, ejaculation problems), depression, anxiety, and physical symptoms that

680 persist after treatment discontinuation and can be permanent for some patients, though their

681 long-term impact and precise mechanism have not been clarified [94,95]. A recent study of 55 men

682 treated with finasteride for AGA found no significant difference in all sperm parameters,

683 serum, FSF, LH, testosterone, prolactin and oestradiol level at treatment initiation (T0), a year

684 after treatment (T12) and a year post-treatment discontinuation (T24) [96]. Current evidence does

685 not support indication of testosterone treatment in the treatment of post-finasteride syndrome

686 [97,98]. Men on finasteride should be counselled about the possibility of these adverse effects and

687 warned that unwanted symptoms can persist after treatment discontinuation, the origin of which

688 remains unclear. Patients should be referred to psychology services for relevant therapeutic

689 interventions [99].

690 Some retrospective series have explored the potential of hormone therapy including hCG and

691 selective oestrogen receptor modulators (SERM) to aid withdrawal from anabolic steroids[33].

692 However, there are currently no randomised control studies suggesting whether such treatment

693 can ameliorate symptoms of anabolic androgen withdrawal, or improve the prognosis of

694 successful withdrawal.

695

696 **7. Patient education to support self-management**

697 All patients should be provided with education about their condition and treatment aiming to

698 improve adherence and optimisation of testosterone treatment. Clinicians should consider the

699 patient's needs and individual preferences when discussing testosterone treatment initiation.

700 Except perhaps in the context of compensated PH, we do not subscribe to the concept of a time-

701 limited "individual therapeutic trial" of testosterone treatment and would expect and encourage

702 any man having a verified diagnosis of hypogonadism to continue treatment lifelong. Non-

703 adherence to testosterone treatment can compromise patients' quality of life, physical and

704 cognitive performance and bone density [19,100,101]. Nevertheless, treatment gaps of more than a

705 year and high discontinuation rates after six months post-testosterone treatment initiation were

706   reported by 37% [19,102] and 65% [103] of patients, respectively. Similar high discontinuation rates

707   post-testosterone treatment initiation were also reported by Donatucci et al; 52% of patients

708   on daily transdermal testosterone treatment discontinued treatment after 3 months compared to

709   31% of patients on short-acting testosterone treatment injections, though it should be noted that

710   the latter group did not include patients on long-acting testosterone undecanoate injections and

711   it is not clear if patients who discontinued testosterone treatment switched to another

712   testosterone treatment formulation [104]. The gap between stopping and restarting testosterone

713   treatment tended to decrease over time, suggesting that patients who experienced a benefit from

714   testosterone treatment remained on treatment [104]. Dissatisfaction with the information received

715   about treatment, perceived impaired communication with clinicians, and lack of continuity of

716   care were also reported by patients as significant barriers to treatment non-adherence.[19].

717   However, one should anticipate high drop-out rates among men without accurately verified

718   hypogonadism started empirical on testosterone treatment for non-specific symptoms and,

719   predictably, achieving little benefit.   Individual patient needs will often guide the treatment

720   option for testosterone treatment; factors that influence this are ease of use, ability to raise

721   testosterone levels, improvement in symptoms, convenience, cost, and the patient's preferred

722   route of administration such as topical versus injections [105,106]. Beyond the well-known effects

723   of testosterone treatment on sexual function (which may or may not be relevant to older men),

724   it is important to make them aware of the other long-term health benefits of testosterone

725   treatment, such as on bone and muscle strength [54,83].

726   Patient Advocacy Groups (PAG) play an important role in supporting patients with MH. The

727   patient member of The Guideline Committee leads a UK-based PAG and made a significant

728   contribution to these guidelines. His feedback which is summarised in **Box 1**, is based on the

729   shared experiences of PAG members which he is coordinating.

730   **Insert Box 1 here**

8. Cardiovascular and cerebrovascular risk during testosterone therapy

Androgens have an array of reported biological actions including systemic and coronary vasodilation [107], increase in haematocrit by stimulating erythropoiesis [108], promotion of platelet aggregation [109], positively inotrophic effects on cardiomyocytes [110] and shortened QT interval on electrocardiogram [111]. Androgens and testosterone treatment are therefore likely to have complex actions on cardiovascular and cerebrovascular risk.

Older men with untreated hypogonadism have increased mortality compared with eugonadal men, even after adjusting for age, study centre, body mass index (BMI), current smoking, and poor general health [112,113], There is ongoing controversy regarding the effects of testosterone treatment on cardiovascular risk. Indeed, a large multicentre randomised controlled trial (RCT) was stopped early due to an increased rate of adverse cardiovascular events in men aged >65 years taking testosterone treatment [114]; notably many subjects had significant co-morbidities and target serum testosterone levels were set in the top half of the reference range, which may have attributed to the risk of adverse events in this patient group. Other RCTs reported either no effect, or even a reduction in markers of cardiovascular disease [115,116]. testosterone treatment has been reported to increase noncalcified plaque volume and total plaque volume vs. placebo [117], and is associated with small reductions in LDL, HDL, VLDL cholesterol and fasting insulin [118]. Several systematic reviews have reported on different outcomes using several cardiovascular endpoints in varying patient subgroups [119-122]. Unsurprisingly, their varied conclusions underline the current lack of consensus regarding the clinical effectiveness and safety of testosterone treatment in symptomatic men with low testosterone. The NIH testosterone (T) trials provided the largest RCT data of testosterone treatment in men with MH [52]. A highly selected group of 790 men, 65 years of age or older, with a serum testosterone concentration ≤ 275 ng/dL (9.535 nmol/L), excluding men with PH, and symptoms suggesting

756   hypogonadism were randomly assigned to receive either testosterone gel or placebo gel for 1

757   year [52]. Though not powered to investigate the safety of testosterone treatment, the NIH T trials

758   reported that a total of 14 men had myocardial infarction, stroke, or death from cardiovascular

759   causes; 7/14 (50%) of these men received placebo [52]. The US Federal Drugs Administration

760   (FDA) recommends that men on testosterone treatment be advised of the potential

761   cardiovascular risks [123], whereas the European Medicines Agency (EMA) considers that there

762   is insufficient evidence to link testosterone treatment with increased cardiovascular risk [124].

763   Two ongoing projects may help to elucidate the safety of testosterone treatment. Firstly, the

764   NIHR Testosterone and Efficacy & Safety (TestES) consortium is an individual patient data

765   (IPD) meta-analysis pooling patient level adverse event data from individual RCTs [125].

766   Secondly, the US-led TRAVERSE trial is currently enrolling 6000 men aged 45–80 years with

767   serum testosterone levels<300ng/dL and high cardiovascular risk to random allocation of

768   testosterone gel or placebo for five years [126]. Additionally, published data from studies

769   involving transgender men and women clearly show an increased risk of cardiovascular disease

770   with oestrogen treatment in transwomen, but not from testosterone treatment in transmen,

771   although these individuals were young and therefore at low background risk [127,128].

772   A recent observational study suggested that in men with or without hypogonadism, testosterone

773   treatment was associated with increased risk of venous thrombo-embolism (VTE) (age-

774   adjusted odds ratios 2.32 and 2.02, respectively) when compared with men not taking

775   testosterone treatment [129]. Men with obesity, for whom lifestyle change likely represented a

776   better intervention anyway, were at higher risk of VTE in this study, and the highest overall

777   risk was observed during the first six months of treatment. Clinicians should therefore counsel

778   men that testosterone treatment can increase the risk of thrombosis, although the absolute risk

779   is low and can probably be mitigated by ensuring that haematocrit remains physiological. When

780   haematocrit is elevated >0.5, testosterone treatment should be adjusted according to the

781　treatment formulation, by either lowering the dose of the daily transdermal testosterone

782　treatment, by extending the interval periods between testosterone injections, or by switching to

783　transdermal testosterone treatment which may have a lower risk of erythrocytosis compared to

784　with injectable testosterone treatment [130]. Secondary causes of elevated haematocrit should also

785　be investigated and, when haematocrit remains markedly elevated, testosterone treatment

786　should be stopped and haematological advice urgently sought.

787　In summary, the available RCT and observational data fail to reveal any consistent association

788　(positive or negative) between testosterone treatment and cardiovascular and cerebrovascular

789　events. Therefore, we conclude that testosterone treatment has uncertain effects on

790　cardiovascular and cerebrovascular risk. However, further data are likely to become available

791　soon, which will provide a more secure evidence base in respect of cardiovascular risk or safety

792　for clinicians prescribing testosterone treatment to men with hypogonadism. Meanwhile,

793　clinicians are advised to consider cardiovascular risk in men before initiating testosterone

794　treatment; in men with high cardiovascular risk, we recommend counselling them that the

795　cardiovascular safety of testosterone therapy remains uncertain

796

797　**9. Effects on bone mineral density**

798　Hypogonadism causes reductions in bone mineral density (BMD), while testosterone treatment

799　increases both vertebral and femoral BMD [131]. Currently, there are no data from which to

800　determine whether testosterone treatment reduces fracture risk in men with hypogonadism,

801　although this is assumed to be likely. In men with hypogonadism and reduced BMD, consider

802　repeating BMD assessment at an appropriate interval after commencement of testosterone

803　therapy. testosterone treatment is not indicated for treatment of osteoporosis in the absence of

804　MH. For older men with MH having established osteoporosis and already at high risk of

805　fracture, bone-specific drugs should be considered in addition to testosterone treatment.

806　However, for younger men with MH, it is more logical to defer consideration of bone-specific

807　drugs until testosterone treatment-induced improvements in BMD have plateaued. At that

808　point, if osteoporosis is still present, then bone-specific drugs can be added to testosterone

809　treatment. However, hard data are lacking.

810

811　**10. Screening for prostate cancer in men during testosterone therapy**

812　Prostate cancer is the most common non-dermatological cancer and the second leading cause

813　of cancer death in men in Europe and North America [132]. Prostate cancer primarily affects older

814　men. It is therefore not surprising that many older men are at risk of both male hypogonadism

815　and prostate cancer. Androgen hormones are trophic to prostate tissue, and androgen

816　deprivation therapy is routinely used for the treatment of prostate cancer.

817

818　*10.1. Testosterone therapy in men without prostate cancer*

819　Circulating levels of testosterone are correlated with serum PSA in hypogonadism; however,

820　there is no statistical relationship with PSA in eugonadal men (*the saturation hypothesis*) [133].

821　A systematic review suggested that testosterone treatment does not increase the subsequent risk

822　of prostate cancer in men without prior disease [134]. Furthermore, a Canadian study on 12,779

823　men with new hypogonadism found that during 58,224 person-years of follow-up, use of

824　testosterone treatment was not associated with an overall increased risk of prostate cancer

825　(hazard ratio 0.97; 95%CI 0.71-1.32) [135]. For these reasons, it is generally accepted that

826　testosterone treatment does not increase the risk of developing new prostate cancer. However,

827　these is a physiological restoration of prostate size after initiation of testosterone treatment in

828　men with MH which may unmask *incidental* problems. It is important to ask men with MH

829　about the occurrence of urinary symptoms within the first few months following testosterone

830　treatment initiation; those symptoms should be investigated according to routine practice.

831   Historically, prostate cancer screening has been conducted during testosterone treatment, in the

832   form of serum PSA measurement and digital rectal examination (DRE) (since 1% of prostate

833   cancers are non-PSA-secreting). However, endocrinologists generally have no experience

834   recognising the features of prostate cancer during DRE, which makes this practice likely to be

835   ineffective and potentially harmful. Major risk factors for prostate cancer are increased age,

836   black ethnicity and family history, and all men (regardless of testosterone treatment) should

837   undergo screening according to local practice. Theoretically, prostate screening might exclude

838   a pre-existing tumour during testosterone treatment, but there is insufficient evidence to support

839   the efficacy or safety of such an approach. In the absence of robust evidence, we do not

840   recommend that mandatory screening for prostate cancer be performed during testosterone

841   treatment.

842

843   *10.2. Testosterone therapy in men with prostate cancer*

844   A recent systematic review of 36 studies including 2,459 testosterone-treated patients found

845   that testosterone treatment is not associated with increased risk of disease progression in

846   prostate cancer [136]. The quality of studies included was poor though, with no level 1 evidence.

847   Also, this review suggested that testosterone treatment might be harmful in men with metastatic

848   prostate cancer (progression rate: 38.5%-100.0%), those undergoing active surveillance for

849   low-risk localised prostate cancer (15.4-57.1%), and those with high-risk prostate cancer who

850   were successfully treated (0.0%-50.0%). Joint management with a urologist is mandatory in

851   men with known prostate cancer (treated or untreated), to monitor PSA and where necessary,

852   conduct imaging with MRI, PSMA-PET, or CT/bone scan based on PSA kinetics and the

853   clinical state of the patient. For those men with untreated prostate cancer (for example those

854   for conservative management / surveillance) monitoring will be more intense and a multi-

855   disciplinary decision between patient, urologist/uro-oncologist, and endocrinologist should be

856   made regarding risks *versus* benefit for testosterone treatment. Any changes on surveillance

857   MRI imaging, PSA kinetics, or development of prostate cancer-associated symptoms will

858   usually be an indication to cease testosterone treatment.

859   It is important to note that these recommendations are expert opinion based on the best

860   available evidence, and that there remains significant uncertainty about screening for prostate

861   cancer in the general population, albeit even more so in men on testosterone treatment. Our

862   recommendations thus offer a pragmatic solution to a problem whose precise dimensions are

863   unknown. It is hoped that these recommendations can be tailored in future based on RCTs

864   examining prostate cancer risk in men on testosterone treatment and especially those with risk

865   factors based on age, family history, and ethnicity.

866

867   **11. Fertility considerations for testosterone therapy**

868   *11.1. Fertility in men with MH*

869   Fertility is initiated at puberty, secondary to the rise in GnRH/gonadotrophin secretion and

870   increasing testosterone production by the testis. It is well established that optimal normal

871   spermatogenesis requires both FSH and testosterone, but there is a lack of a clear dose-

872   dependency for both these trophic factors. Testosterone concentrations in the testis are approx.

873   100-fold higher than in the circulation and this is essential for the paracrine action of

874   testosterone on Sertoli cells to support spermatogenesis. Thus, intratesticular or paracrine

875   testosterone deficiency sufficient to impact on spermatogenesis is not a consideration where

876   there is ongoing LH secretion and functional Leydig cells. However, classical hypogonadal

877   pathologies are important causes of infertility, e.g. Klinefelter syndrome, Kallmann syndrome,

878   hypopituitarism. Where the pathology is in the hypothalamus or pituitary causing CH, there is

879   the potential for successful endocrine treatment. Obesity is also associated with CH [137].

880   Although spermatogenesis is dependent on LH and FSH, there are no accurate cut-off levels

881   for either parameter in CHH that usefully predict male infertility or disordered

882   spermatogenesis, so a semen analysis should be obtained whenever fertility needs to be

883   assessed. Men with normal or elevated gonadotrophin levels (or an isolated elevation of FSH)

884   do not benefit from gonadotrophin therapy, or indeed any other medical therapy, to stimulate

885   spermatogenesis or improve fertility and assisted reproduction will often be required.

886

887   *11.2. Impact of testosterone therapy on fertility*

888   Exogenous testosterone will suppress gonadotrophin secretion and thus spermatogenesis, and

889   indeed this is the basis for the development of hormonal male contraception. Conversely it

890   cannot be assumed that testosterone treatment will cause infertility, and contraception should

891   always be discussed and advised where appropriate. Fertility intentions should be explicitly

892   discussed with the patient whenever testosterone treatment is being considered, and the likely

893   time needed for induction of spermatogenesis (see below). Patients with CH can, however, be

894   reassured that testosterone treatment does not negatively impact the chances of success from

895   subsequent gonadotrophin therapy [20].

896

897   *11.3. Treatment of subfertility in men with MH*

898   Subfertility should be investigated with physical examination for signs of hypogonadism,

899   semen analysis (with a second sample if the first is abnormal), complemented with

900   measurement of LH, FSH and testosterone prior to initiating testosterone treatment. Fertility

901   may benefit from lifestyle factors such as balanced diet and smoking cessation. In the situation

902   of a heterosexual relationship, it is always essential to consider the fertility status and age of

903   the female partner in order to establish the prospects for successful conception (whether natural

904   or assisted) and pregnancy prior to starting treatment for the male partner. In men with CH, the

905   considerations are starting human chorionic gonadotrophin (hCG), FSH, or both. Pulsatile

906   GnRH therapy might be used in men with normal pituitary function but is not widely available.

907   hCG can be considered an LH-mimetic, with very high potency and long half-life compared to

908   LH. Administration is with the aim of stimulating the Leydig cells of the testis and thus

909   stimulating endogenous testosterone production: it is therefore only of value when there is

910   clear-cut LH and testosterone deficiency. Very low doses of hCG (125 IU) will restore

911   intratesticular testosterone concentration [138], while higher doses are required to normalise

912   circulating testosterone concentrations. A conventional starting dose is 1000-1500 IU sc twice

913   a week, with a check of FBC, testosterone and oestradiol levels after 4 weeks. The dose can be

914   increased to 2,500 IU twice or thrice-weekly, with higher doses rarely required or being

915   effective; a high serum oestradiol level signposting risk of gynaecomastia may suggest

916   reduction of the hCG dose. Unfortunately, there are currently no hCG products with marketing

917   authorisation in the UK, so the choice lies between one having UK and European marketing

918   authorisation for women only, or one that has marketing authorisation for use in males in

919   certain European countries, but not yet in the UK. One possibility is to use Ovitrelle®, which

920   is a prefilled pen-type injector containing 10,000 IU recombinant hCG marketed for IVF in

921   women. The dose is adjustable according to the number of 'clicks' on twisting the barrel, but

922   there are no marked gradations. **Table 3** indicates the dose according to the number of clicks,

923   but it is important to recognise that this is empirical. We do not endorse combination therapy

924   with both hCG and testosterone in men with MH

925   **Insert Table 3 here**

926

927   hCG alone may be enough to restore spermatogenesis in men with CH of post-pubertal onset,

928   e.g. after pituitary surgery [139]. This may reflect some remaining FSH secretion, albeit at low

929   levels. Post-pubertal stimulation of spermatogenesis can be successfully achieved more often

930   than where there has not been pubertal development (84% vs 68%), and with higher sperm

931 concentrations achieved [20]. Similarly, a second course of gonadotrophin therapy will stimulate

932 spermatogenesis faster than the first course. Regarding FSH administration, the issues are

933 whether it is required, and when to initiate it. As described above, men with adult-onset CH

934 may not require it. It is however almost invariably required in men with congenital/prepubertal

935 CH, in whom both FSH and hCG therapy should be initiated simultaneously at the outset. The

936 historic approach was to add FSH after 6 months treatment with hCG if the man remained

937 azoospermic, but in fact men with congenital/prepubertal hypogonadotrophism hardly ever

938 achieve meaningful spermatogenesis with hCG monotherapy, even when prolonged for up to

939 10 years [140] and so this hCG-first regimen is logically reserved for men with CH acquired post-

940 pubertally. A dose of 75-300 IU sc three times per week is used, thus the patient also receiving

941 hCG will require to self-inject 5 times per week, potentially for many months. FSH levels can

942 be measured on treatment and a physiological target range 4 to 8 IU/L is advisable [141]. The

943 long-acting FSH analogue corifollitrophin alpha requires administration every 2 weeks, and

944 while there is evidence of efficacy in this indication [142], it is not widely used.

945 It has been postulated that in men with the most severe form of congenital CH (testicular

946 volume < 4 ml), pre-treatment with FSH for several months before adding hCG may improve

947 subsequent spermatogenesis, but the evidence is limited albeit the scientific basis appears

948 sound [141]. Moreover, FSH monotherapy necessarily prolongs untreated hypogonadism unless

949 exogenous testosterone is also given. Prior administration of androgens has been shown in a

950 meta-analysis and subsequent RCT not to result in a slower response to gonadotrophin therapy

951 [20,143].

952 Repeat semen analysis should be performed 3 months after initiating treatment, and at 3-month

953 intervals thereafter. Baseline testicular volume, pubertal status and a history of cryptorchidism

954 are indicators of time to respond, but fertility may be achieved even with a history of bilateral

955 testicular maldescent [144-146]. Patients should be clearly counselled at the start about the likely

956   prolonged duration of treatment; however, it is important to recognise that fertility may be

957   achieved with very low sperm concentrations, and conventionally normal sperm concentrations

958   will not be achieved in many men. A meta-analysis indicated that a mean sperm concentration

959   of 5.2 million/ml (95%CI 4.7-7.1) was achieved by gonadotrophin therapy [20], with a median

960   time to achieve sperm in the ejaculate of 7.1 months (95% CI 6.3-10.1) and to conception of

961   28.2 months (21.6-38.5) [145]. The need for protracted treatment and the anticipated production

962   of low numbers of sperm (but seemingly of high quality) should be carefully considered to

963   prevent premature recourse to assisted reproduction, but conversely the age of the female

964   partner may also be a factor in when that becomes appropriate. *i.e.* when the female partner is

965   in her late 30s, prompt recourse to assisted reproductive technology (ART) would be wise from

966   the moment that sperm appear in the ejaculate.

967   Once pregnancy is established, there are the following options:

968   • Revert to or initiate testosterone therapy;

969   • If the couple are considering a second child, it is possible to stop FSH and continue

970   with hCG alone. This will maintain testosterone production and continue to support

971   some degree of spermatogenesis: at the time a further pregnancy is desired, FSH may

972   be restarted if indicated by repeat semen analysis;

973   • If there is concern over testicular function (e.g. if only a very low sperm concentration

974   has been achieved, and ICSI was required) embryo (where available) and sperm

975   cryopreservation should be considered.

976

977 **Box 1:** Patient feedback on testosterone treatment and self-management support

- In the UK, patients generally have good access to testosterone treatment

- A wide variation exists in the follow-up testing of patients, including the availability of bone densitometry

- Improved awareness of the different needs of various patients on testosterone treatment is required

- For some patients, blood testing is not done in a timely manner, *e.g.* at the end of a long acting testosterone IM injection, which can result in weeks of low testosterone before the patient received their next injection.

Patients on long term therapy have symptomatic awareness of abnormalities in their testosterone levels, which can be very useful to monitor and can be used as a guide even in the absence of blood test results. Active communication between the patient and health care provider is crucial to optimising testosterone treatment and avoid over- or under-replacement. Engaging with the patient is particularly important in the rarer forms of male hypogonadism where different treatment protocols may be more appropriate.

Some patients may be hesitant about starting or continuing testosterone treatment as they are unaware of all the treatment benefits and may be concerned about side effects, which can have a negative impact on adherence to treatment. Clinicians are advised to make patients aware of all possible testosterone treatments and differences in approach regarding monitoring and to support them to select the most suitable treatment for their needs.

978

Table 1: Aetiology of male hypogonadism

Congenital disorders	Acquired diseases
Primary Gonadal Insufficiency	
Klinefelter syndrome	Gonadectomy - bilateral
uncorrected bilateral Cryptorchidism	Trauma or Torsion - bilateral
Testicular regression (vanishing testes)	Orchitis - bilateral
Partial Androgen Insensitivity syndrome	Chemotherapy - alkylating
inactivating LHCG receptor mutations	Radiotherapy - pelvic
Congenital adrenal hyperplasia	Ageing and age-associated co-morbidities
	Heavy Tobacco smoking
	Chronic alcohol abuse
	Systemic diseases:
	- HIV infection
	- Sickle cell disease
	- Coeliac disease
	- Uraemia
Central Hypogonadism	
Isolated GnRH deficiency	Parasellar tumours, especially prolactinoma
- Kallmann syndrome	
- normosmic Congenital HH	Inflammatory/Infiltrative diseases
	- sarcoidosis
Syndromic forms of GnRH deficiency :	- histiocytosis
- Combined Pituitary Hormone deficiency	- Iron overload, *e.g.* genetic Haemochromatosis
- Septo-Optic Dysplasia	
- CHARGE syndrome	
- Bardet-Biedl syndrome?	Trauma / Vascular / Radiation
- Prader-Willli syndrome	- military blast trauma
- *Adrenohypoplasia Congenita* (*NROB1*)	- pituitary Apoplexy or Stalk transection
- leptin deficiency / leptin resistance	- cranial Surgery & Irradiation
	Drug-induced
	- Opioids & Narcotics
	- high-dose Glucocorticoids
	- Androgen Deprivation Therapy
	- Anti-dopaminergic Antipsychotics
	- Cannabinoids
	- Androgenic anabolic steroids
	- Estrogens
	-

Table 2: Testosterone therapy formulations and their characteristics. T – Testosterone.

Formulation and *dose*	Administration & monitoring	Advantages	Disadvantages
Transdermal topical T gels and axillary solution *50–100 mg of 1% Testogel®, 40–70 mg of 2% Tostran®, 23-46 mg of Testavan® or 20.25–81 mg of 16.2mg/g (Testogel® pump) transdermal gel once daily* *60 mg of T solution applied in the axillae once daily (not available in the UK)*	Clear alcohol gel available in sachets, tubes and pumps containing, applied dry, clean skin on shoulders, abdomen, upper arms or thighs (avoid genital area). Monitor total T 2-6 hours post-gel application, 2-3 weeks post-treatment initiation or dose adjustment, aiming for mid-normal reference range total T.	Convenient, flexible and easy application; good skin tolerability. Effective, provides T levels within normal range for 24 h. Steady physiological levels of serum T with no "peak & troughs" between applications. Dose easily adjustable to individual needs. No pain of injections.	May cause skin dryness and irritation for some patients. Takes time to apply. Potential of transfer to a female partner or child by direct skin-to-skin contact. Fear of transfer may inhibit intimacy; patient education minimises potential of transfer. Increased DHT levels due to presence of 5α-reductase in the skin. Considerable inter- and intra-individual T levels require close dose titration.
Long-acting T undecanoate IM injections *1000 mg in 4 mL (Nebido®) ampoule of oily preparation every 10-14 weeks*	Injected slowly deep into the gluteal muscle. The second injection (loading dose) is given at 6 weeks, and the third dose 12-weeks after the second. Injection interval is adjusted based on trough total T level just before the third injection, aiming for lower end of normal reference range level. Monitor trough total T and FBC every 3–5 injections or annually.	Effective, maintains physiological serum T levels for 3 months or longer. Smoother serum T profile compared to short-acting T injections, with less noticeable "peak and trough" symptoms. Convenient, 3-monthly administration without the side effects seen with T implants.	Pain, discomfort and adverse reaction at injection site. Requires large muscle bulk for injection. Lifestyle restrictions as it cannot be self-administered. Not recommended as first-line treatment option due to inability of withdrawal in case of adverse events (AE). Rare AE of pulmonary micro-embolism presenting with severe coughing episode during injection.
Short-acting T injections 1. *Combination of testosterone esters 250 mg/mL (Sustanon®) IM every 3–4 weeks (propionate 30 mg, phenylpropionate 60 mg, isocaproate 60 mg, decanoate 100 mg);* 2. *Testosterone enanthate or cypionate 150–200 mg IM every 2 weeks or 50–100 mg IM or SC once a week*	Oily preparation (1 mL) injected slowly into the gluteal muscle or upper thigh. Adjust injection interval based on trough total T level at the end of the injection aiming for lower end of normal reference range. Monitor trough total T and FBC every 6-12 months.	Dose flexibility and convenient administration, relatively inexpensive. Improves symptoms of androgen deficiency; mostly noticeable in the first days after the injection. SC injection has comparable pharmacokinetics, safety and tolerability to IM injection and can be self-injected.	Potentially unpleasant "peak & trough" symptoms due to supraphysiological T levels post-injection which decline to hypogonadal range by the next injection. Risk of polycythaemia due to supraphysiological T levels. Pain, discomfort at injection site. Lifestyle restrictions for patients not self-injecting.

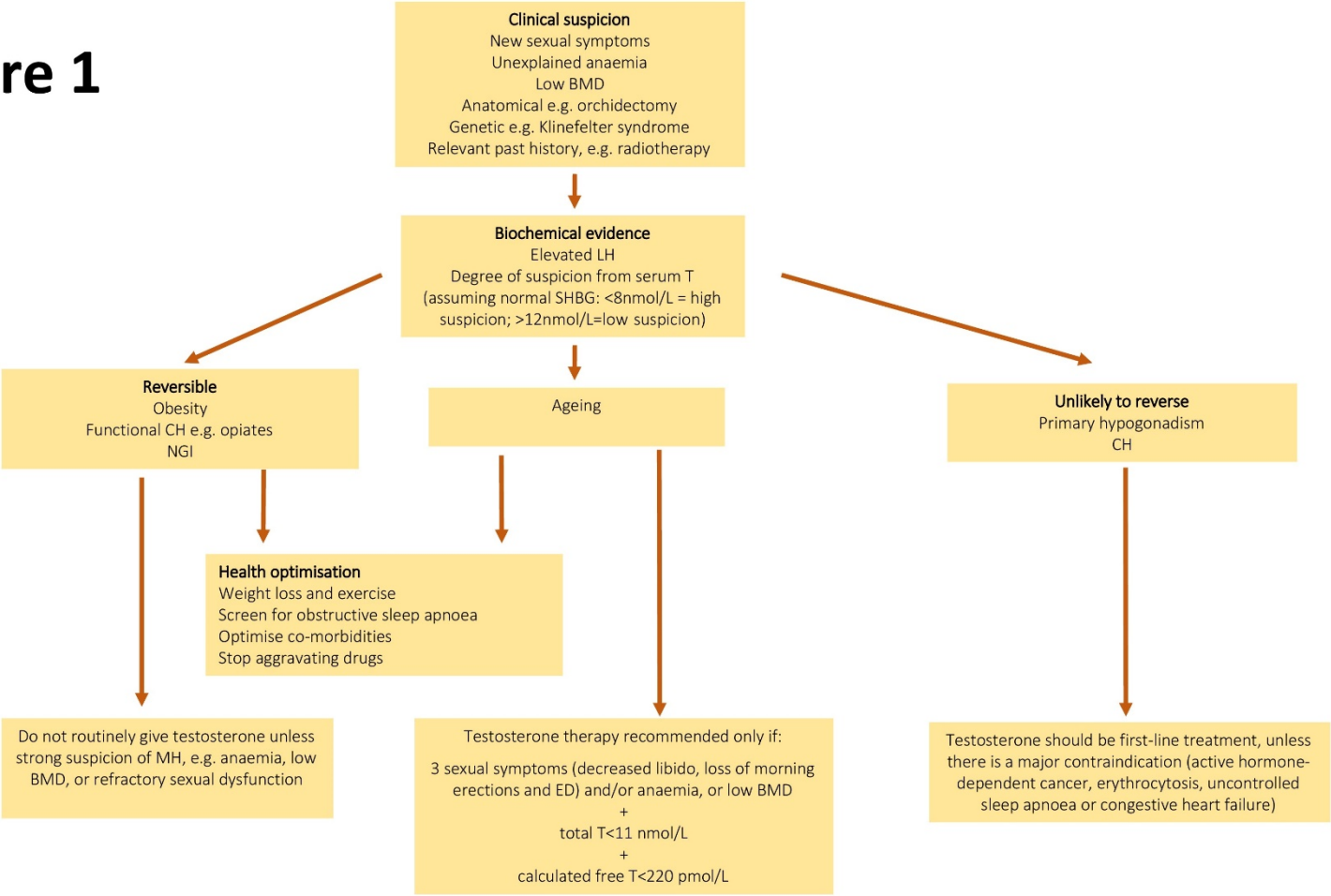|			
Bio-adhesive Buccal T tablet *30 mg controlled-release tablets applied to the upper gum twice daily (not available in the UK)*	T is absorbed gradually from the buccal mucosa over 12 h. Applied on healthy, clean gum; the solid tablet softens and moulds to the shape of the gum. Monitor T 2-6 hours post-tablet application, 2-3 weeks post-treatment initiation, aiming for mid-normal reference range total T.	Easy and fast to apply; Effective; serum T levels remain within physiological range with twice daily application without significant peaks and troughs; "easy to remember" administration with teeth brushing daily routine.	Risk of gum-related adverse events reported by 16% of treated men. May detach when eating shortly after application. Takes time to get used to; patient education is vital for medication adherence.
Subcutaneous T implants *Testosterone pellets 100 or 200 mg to a total of 600–1200 mg T per dose (rarely administered)*	3–6 pellets every 4–6 months. Pellets implanted in the subcutaneous adipose tissue with surgical incision under local anaesthetic.	Serum T peaks at 1 month and is sustained in normal range for up to 6 months. Convenience—twice or thrice a year application.	Painful procedure with high risk of infection at the insertion point and scar tissue. Risk of spontaneous extrusion after implantation.
Oral T undecanoate capsules 40 mg *1–3 capsules (40–120 mg) twice or thrice daily with meals*	Taken orally; absorption is improved when taken with fatty meal. Swallow without chewing.	Easy and convenient administration. Suitable for patients who cannot tolerate other forms of treatment and those who require low levels of T, not a preferred treatment option.	Low bioavailability and very high inter- and intra-individual variability in absorption resulting in insufficient serum T levels. Normal serum T level attained for only up to 3–5 h.

982

983 **Table 3:**

984 **Dosing using prefilled Ovitrelle® (human chorionic gonadotrophin, hCG) 6,500 IU pen**

985

Ovitrelle® dose (IU)	No of clicks (calculated dose, IU)
1500	6 (1560)
2000	8 (2080)
2500	10 (2600)
3000	12 (3120)
4000	15 (3900)
5000	19 (4950)

986

Figure 1: Flowchart for male hypogonadism management

MH, male hypogonadism; TT, total testosterone; LH, luteinising hormone; SHBG, sex hormone binding globulin; CH, central hypogonadism; NGI, non-

gonadal illness; BMD, bone mineral density; ED, erectile dysfunction

Figure 1

Clinical suspicion
New sexual symptoms
Unexplained anaemia
Low BMD
Anatomical e.g. orchidectomy
Genetic e.g. Klinefelter syndrome
Relevant past history, e.g. radiotherapy

Biochemical evidence
Elevated LH
Degree of suspicion from serum T
(assuming normal SHBG: <8nmol/L = high
suspicion; >12nmol/L=low suspicion)

Reversible
Obesity
Functional CH e.g. opiates
NGI

Ageing

Unlikely to reverse
Primary hypogonadism
CH

Health optimisation
Weight loss and exercise
Screen for obstructive sleep apnoea
Optimise co-morbidities
Stop aggravating drugs

Do not routinely give testosterone unless
strong suspicion of MH, e.g. anaemia, low
BMD, or refractory sexual dysfunction

Testosterone therapy recommended only if:

3 sexual symptoms (decreased libido, loss of morning
erections and ED) and/or anaemia, or low BMD
+
total T<11 nmol/L
+
calculated free T<220 pmol/L

Testosterone should be first-line treatment, unless
there is a major contraindication (active hormone-
dependent cancer, erythrocytosis, uncontrolled
sleep apnoea or congestive heart failure)

References

1. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2018;103(5):1715-1744.

2. Khera M, Broderick GA, Carson CC, 3rd, et al. Adult-Onset Hypogonadism. *Mayo Clin Proc.* 2016;91(7):908-926.

3. Salvi R, Pralong FP. Molecular characterization and phenotypic expression of mutations in genes for gonadotropins and their receptors in humans. *Front Horm Res.* 2010;39:1-12.

4. Bojesen A, Kristensen K, Birkebaek NH, et al. The metabolic syndrome is frequent in Klinefelter's syndrome and is associated with abdominal obesity and hypogonadism. *Diabetes Care.* 2006;29(7):1591-1598.

5. Dahlqvist JR, Vissing J. Diabetes in myotonic dystrophy. In: *Diabetes Associated with Single Gene Defects and Chromosomal Abnormalities.* Vol 25. Karger Publishers; 2017:182-187.

6. Cheng J, Han B, Li Q, et al. Testosterone: Relationships with Metabolic Disorders in Men-An Observational Study from SPECT-China. *International journal of endocrinology.* 2017;2017:4547658-4547658.

7. Lee PA, Houk CP. Cryptorchidism. *Curr Opin Endocrinol Diabetes Obes.* 2013;20(3):210-216.

8. Ritzen EM, Bergh A, Bjerknes R, et al. Nordic consensus on treatment of undescended testes. *Acta Paediatr.* 2007;96(5):638-643.

9. Chan E, Wayne C, Nasr A, Resource FfCAoPSE-B. Ideal timing of orchiopexy: a systematic review. *Pediatr Surg Int.* 2014;30(1):87-97.

10. Juul A, Almstrup K, Andersson AM, et al. Possible fetal determinants of male infertility. *Nature reviews Endocrinology.* 2014;10(9):553-562.

11. Groth KA, Skakkebæk A, Høst C, Gravholt CH, Bojesen A. Clinical review: Klinefelter syndrome--a clinical update. *J Clin Endocrinol Metab.* 2013;98(1):20-30.

12. Skakkebaek A, Wallentin M, Gravholt CH. Neuropsychology and socioeconomic aspects of Klinefelter syndrome: new developments. *Curr Opin Endocrinol Diabetes Obes.* 2015;22(3):209-216.

13. Turriff A, Levy HP, Biesecker B. Factors associated with adaptation to Klinefelter syndrome: the experience of adolescents and adults. *Patient education and counseling.* 2015;98(1):90-95.

14. Ross A, Bhasin S. Hypogonadism: Its Prevalence and Diagnosis. *The Urologic clinics of North America.* 2016;43(2):163-176.

1021 15. Tajar A, Forti G, O'Neill TW, et al. Characteristics of secondary, primary, and compensated
1022   hypogonadism in aging men: evidence from the European Male Ageing Study. *J Clin Endocrinol*
1023   *Metab.* 2010;95(4):1810-1818.

1024 16. Boehm U, Bouloux PM, Dattani MT, et al. Expert consensus document: European Consensus
1025   Statement on congenital hypogonadotropic hypogonadism-pathogenesis, diagnosis and treatment.
1026   *Nature reviews Endocrinology.* 2015;11(9):547-564.

1027 17. Stamou MI, Cox KH, Crowley WF, Jr. Discovering Genes Essential to the Hypothalamic Regulation of
1028   Human Reproduction Using a Human Disease Model: Adjusting to Life in the "-Omics" Era.
1029   *Endocrine reviews.* 2015;36(6):603-621.

1030 18. Cangiano B, Swee DS, Quinton R, Bonomi M. Genetics of congenital hypogonadotropic
1031   hypogonadism: peculiarities and phenotype of an oligogenic disease. *Hum Genet.* 2021;140(1):77-
1032   111.

1033 19. Dwyer A, Quinton R, Morin D, Pitteloud N. Identifying the unmet health needs of patients with
1034   congenital hypogonadotropic hypogonadism using a web-based needs assessment: implications for
1035   online interventions and peer-to-peer support. *Orphanet journal of rare diseases.* 2014;9:83.

1036 20. Rastrelli G, Corona G, Mannucci E, Maggi M. Factors affecting spermatogenesis upon gonadotropin-
1037   replacement therapy: a meta-analytic study. *Andrology.* 2014;2(6):794-808.

1038 21. Dwyer AA, Raivio T, Pitteloud N. MANAGEMENT OF ENDOCRINE DISEASE: Reversible
1039   hypogonadotropic hypogonadism. *European journal of endocrinology / European Federation of*
1040   *Endocrine Societies.* 2016;174(6):R267-274.

1041 22. Brioude F, Bouligand J, Trabado S, et al. Non-syndromic congenital hypogonadotropic
1042   hypogonadism: clinical presentation and genotype-phenotype relationships. *European journal of*
1043   *endocrinology / European Federation of Endocrine Societies.* 2010;162(5):835-851.

1044 23. Mao J, Xu H, Wang X, et al. Congenital combined pituitary hormone deficiency patients have better
1045   responses to gonadotrophin-induced spermatogenesis than idiopathic hypogonadotropic
1046   hypogonadism patients. *Hum Reprod.* 2015;30(9):2031-2037.

1047 24. Castinetti F, Reynaud R, Saveanu A, et al. MECHANISMS IN ENDOCRINOLOGY: An update in the
1048   genetic aetiologies of combined pituitary hormone deficiency. *European journal of endocrinology /*
1049   *European Federation of Endocrine Societies.* 2016;174(6):R239-247.

1050 25. Ryabets-Lienhard A, Stewart C, Borchert M, Geffner ME. The Optic Nerve Hypoplasia Spectrum:
1051   Review of the Literature and Clinical Guidelines. *Advances in pediatrics.* 2016;63(1):127-146.

1052 26. Raivio T, Avbelj M, McCabe MJ, et al. Genetic overlap in Kallmann syndrome, combined pituitary
1053 hormone deficiency, and septo-optic dysplasia. *J Clin Endocrinol Metab.* 2012;97(4):E694-699.

1054 27. Bergman JE, Janssen N, Hoefsloot LH, Jongmans MC, Hofstra RM, van Ravenswaaij-Arts CM. CHD7
1055 mutations and CHARGE syndrome: the clinical implications of an expanding phenotype. *J Med
1056 Genet.* 2011;48(5):334-342.

1057 28. Khan SA, Muhammad N, Khan MA, Kamal A, Rehman ZU, Khan S. Genetics of human Bardet-Biedl
1058 syndrome, an updates. *Clin Genet.* 2016;90(1):3-15.

1059 29. Koscinski I, Mark M, Messaddeq N, et al. Reproduction Function in Male Patients With Bardet Biedl
1060 Syndrome. *The Journal of Clinical Endocrinology & Metabolism.* 2020;105(12):e4417-e4429.

1061 30. Angulo MA, Butler MG, Cataletto ME. Prader-Willi syndrome: a review of clinical, genetic, and
1062 endocrine findings. *Journal of endocrinological investigation.* 2015;38(12):1249-1263.

1063 31. Deal CL, Tony M, Hoybye C, et al. GrowthHormone Research Society workshop summary:
1064 consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. *J
1065 Clin Endocrinol Metab.* 2013;98(6):E1072-1087.

1066 32. Jadhav U, Harris RM, Jameson JL. Hypogonadotropic hypogonadism in subjects with DAX1
1067 mutations. *Mol Cell Endocrinol.* 2011;346(1-2):65-73.

1068 33. Rahnema CD, Lipshultz LI, Crosnoe LE, Kovac JR, Kim ED. Anabolic steroid-induced hypogonadism:
1069 diagnosis and treatment. Fertil Steril. 2014;101(5):1271-9.

1070 34. Christou MA, Tigas S. Recovery of reproductive function following androgen abuse. *Curr Opin
1071 Endocrinol Diabetes Obes.* 2018;25(3):195-200.

1072 35. Rasmussen JJ, Albrethsen J, Frandsen MN, Jørgensen N, Juul A, Kistorp C. Serum Insulin-like Factor
1073 3 Levels Are Reduced in Former Androgen Users, Suggesting Impaired Leydig Cell Capacity. *The
1074 Journal of Clinical Endocrinology & Metabolism.* 2021;106(7):e2664-e2672.

1075 36. Nachtigall LB, Boepple PA, Pralong FP, Crowley WF, Jr. Adult-onset idiopathic hypogonadotropic
1076 hypogonadism--a treatable form of male infertility. *The New England journal of medicine.*
1077 1997;336(6):410-415.

1078 37. Dwyer AA, Hayes FJ, Plummer L, Pitteloud N, Crowley WF, Jr. The long-term clinical follow-up and
1079 natural history of men with adult-onset idiopathic hypogonadotropic hypogonadism. *J Clin
1080 Endocrinol Metab.* 2010;95(9):4235-4243.

1081 38. De Maddalena C, Bellini M, Berra M, Meriggiola MC, Aloisi AM. Opioid-induced hypogonadism: why
1082 and how to treat it. *Pain physician.* 2012;15(3 Suppl):ES111-118.

1083   39.   Fourman LT, Fazeli PK. Neuroendocrine causes of amenorrhea--an update. *J Clin Endocrinol Metab.*
1084   2015;100(3):812-824.

1085   40.   Caronia LM, Martin C, Welt CK, et al. A genetic basis for functional hypothalamic amenorrhea. *The*
1086   *New England journal of medicine.* 2011;364(3):215-225.

1087   41.   Delaney A, Burkholder AB, Lavender CA, et al. Increased Burden of Rare Sequence Variants in
1088   GnRH-Associated Genes in Women With Hypothalamic Amenorrhea. *J Clin Endocrinol Metab.*
1089   2021;106(3):e1441-e1452.

1090   42.   Chavan N, Dwyer A, KW. K, et al. Male functional hypogonadotropic hypogonadism: A distinct
1091   clinical entity? Abstract presented at 92nd Annual Meeting of the Endocrine Society; 2010; San
1092   Diego, USA.

1093   43.   Ajmal A, Joffe H, Nachtigall LB. Psychotropic-induced hyperprolactinemia: a clinical review.
1094   *Psychosomatics.* 2014;55(1):29-36.

1095   44.   Kalyani RR, Gavini S, Dobs AS. Male hypogonadism in systemic disease. *Endocrinology and*
1096   *metabolism clinics of North America.* 2007;36(2):333-348.

1097   45.   Turner HE, Wass JA. Gonadal function in men with chronic illness. *Clinical endocrinology.*
1098   1997;47(4):379-403.

1099   46.   Dean JD, McMahon CG, Guay AT, et al. The International Society for Sexual Medicine's Process of
1100   Care for the Assessment and Management of Testosterone Deficiency in Adult Men. *J Sex Med.*
1101   2015;12(8):1660-1686.

1102   47.   Wu FC, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and
1103   elderly men. *The New England journal of medicine.* 2010;363(2):123-135.

1104   48.   Kelly DM, Jones TH. Testosterone and obesity. *Obesity reviews : an official journal of the*
1105   *International Association for the Study of Obesity.* 2015;16(7):581-606.

1106   49.   Camacho EM, Huhtaniemi IT, O'Neill TW, et al. Age-associated changes in hypothalamic-pituitary-
1107   testicular function in middle-aged and older men are modified by weight change and lifestyle
1108   factors: longitudinal results from the European Male Ageing Study. *European journal of*
1109   *endocrinology / European Federation of Endocrine Societies.* 2013;168(3):445-455.

1110   50.   Lotti F, Marchiani S, Corona G, Maggi M. Metabolic Syndrome and Reproduction. *International*
1111   *Journal of Molecular Sciences.* 2021;22(4):1988.

1112   51.   Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Archives of disease*
1113   *in childhood.* 1970;45(239):13-23.

1114 52. Snyder PJ, Bhasin S, Cunningham GR, et al. Effects of Testosterone Treatment in Older Men. *The*
1115 *New England journal of medicine.* 2016;374(7):611-624.

1116 53. Kwong JCC, Krakowsky Y, Grober E. Testosterone Deficiency: A Review and Comparison of Current
1117 Guidelines. *J Sex Med.* 2019;16(6):812-820.

1118 54. Al-Sharefi A, Wilkes S, Jayasena CN, Quinton R. How to manage low testosterone level in men: a
1119 guide for primary care. *Br J Gen Pract.* 2020;70(696):364-365.

1120 55. Travison TG, Vesper HW, Orwoll E, et al. Harmonized Reference Ranges for Circulating Testosterone
1121 Levels in Men of Four Cohort Studies in the United States and Europe. *J Clin Endocrinol Metab.*
1122 2017;102(4):1161-1173.

1123 56. Brambilla DJ, Matsumoto AM, Araujo AB, McKinlay JB. The effect of diurnal variation on clinical
1124 measurement of serum testosterone and other sex hormone levels in men. *J Clin Endocrinol Metab.*
1125 2009;94(3):907-913.

1126 57. Ponce OJ, Spencer-Bonilla G, Alvarez-Villalobos N, et al. The efficacy and adverse events of
1127 testosterone replacement therapy in hypogonadal men: A systematic review and meta-analysis of
1128 randomized, placebo-controlled trials. *J Clin Endocrinol Metab.* 2018.

1129 58. Wittert G, Atlantis E, Allan C, et al. Testosterone therapy to prevent type 2 diabetes mellitus in at-
1130 risk men (T4DM): Design and implementation of a double-blind randomized controlled trial.
1131 *Diabetes Obes Metab.* 2019;21(4):772-780.

1132 59. UKNEQAS. Unpublished data from the United Kingdom National External Quality Assessment
1133 Service (UKNEQAS). Available via: https://ukneqas.org.uk/. [Accessed on 19th May 2021].

1134 60. Adaway J, Keevil B, Miller A, Monaghan PJ, Merrett N, Owen L. Ramifications of variability in sex
1135 hormone-binding globulin measurement by different immunoassays on the calculation of free
1136 testosterone. *Ann Clin Biochem.* 2020;57(1):88-94.

1137 61. Fiers T, Wu F, Moghetti P, Vanderschueren D, Lapauw B, Kaufman JM. Reassessing Free-
1138 Testosterone Calculation by Liquid Chromatography-Tandem Mass Spectrometry Direct Equilibrium
1139 Dialysis. *J Clin Endocrinol Metab.* 2018;103(6):2167-2174.

1140 62. Goldman AL, Bhasin S, Wu FCW, Krishna M, Matsumoto AM, Jasuja R. A Reappraisal of
1141 Testosterone's Binding in Circulation: Physiological and Clinical Implications. *Endocrine reviews.*
1142 2017;38(4):302-324.

1143 63. Hackbarth JS, Hoyne JB, Grebe SK, Singh RJ. Accuracy of calculated free testosterone differs
1144 between equations and depends on gender and SHBG concentration. *Steroids.* 2011;76(1-2):48-55.

1145 64.   Handelsman DJ. Free Testosterone: Pumping up the Tires or Ending the Free Ride? *Endocrine*
1146   *reviews.* 2017;38(4):297-301.

1147 65.   Heinrich-Balard L, Zeinyeh W, Déchaud H, et al. Inverse relationship between hSHBG affinity for
1148   testosterone and hSHBG concentration revealed by surface plasmon resonance. *Mol Cell*
1149   *Endocrinol.* 2015;399:201-207.

1150 66.   Ho CK, Stoddart M, Walton M, Anderson RA, Beckett GJ. Calculated free testosterone in men:
1151   comparison of four equations and with free androgen index. *Ann Clin Biochem.* 2006;43(Pt 5):389-
1152   397.

1153 67.   Ly LP, Sartorius G, Hull L, et al. Accuracy of calculated free testosterone formulae in men. *Clinical*
1154   *endocrinology.* 2010;73(3):382-388.

1155 68.   Sartorius G, Ly LP, Sikaris K, McLachlan R, Handelsman DJ. Predictive accuracy and sources of
1156   variability in calculated free testosterone estimates. *Ann Clin Biochem.* 2009;46(Pt 2):137-143.

1157 69.   Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation
1158   of free testosterone in serum. *J Clin Endocrinol Metab.* 1999;84(10):3666-3672.

1159 70.   Antonio L, Wu FC, O'Neill TW, et al. Low Free Testosterone Is Associated with Hypogonadal Signs
1160   and Symptoms in Men with Normal Total Testosterone. *J Clin Endocrinol Metab.* 2016;101(7):2647-
1161   2657.

1162 71.   Rastrelli G, O'Neill TW, Ahern T, et al. Symptomatic androgen deficiency develops only when both
1163   total and free testosterone decline in obese men who may have incident biochemical secondary
1164   hypogonadism: Prospective results from the EMAS. *Clinical endocrinology.* 2018;89(4):459-469.

1165 72.   O'Connor DB, Lee DM, Corona G, et al. The relationships between sex hormones and sexual
1166   function in middle-aged and older European men. *J Clin Endocrinol Metab.* 2011;96(10):E1577-
1167   1587.

1168 73.   Cawthon PM, Ensrud KE, Laughlin GA, et al. Sex hormones and frailty in older men: the
1169   osteoporotic fractures in men (MrOS) study. *J Clin Endocrinol Metab.* 2009;94(10):3806-3815.

1170 74.   Krasnoff JB, Basaria S, Pencina MJ, et al. Free testosterone levels are associated with mobility
1171   limitation and physical performance in community-dwelling men: the Framingham Offspring Study.
1172   *J Clin Endocrinol Metab.* 2010;95(6):2790-2799.

1173 75.   Hyde Z, Flicker L, Almeida OP, et al. Low free testosterone predicts frailty in older men: the health
1174   in men study. *J Clin Endocrinol Metab.* 2010;95(7):3165-3172.

1175   76.   Swiecicka A, Eendebak R, Lunt M, et al. Reproductive Hormone Levels Predict Changes in Frailty
1176   Status in Community-Dwelling Older Men: European Male Ageing Study Prospective Data. *J Clin*
1177   *Endocrinol Metab.* 2018;103(2):701-709.

1178   77.   Yeap BB, Almeida OP, Hyde Z, et al. Higher serum free testosterone is associated with better
1179   cognitive function in older men, while total testosterone is not. The Health In Men Study. *Clinical*
1180   *endocrinology.* 2008;68(3):404-412.

1181   78.   Almeida OP, Yeap BB, Hankey GJ, Jamrozik K, Flicker L. Low free testosterone concentration as a
1182   potentially treatable cause of depressive symptoms in older men. *Arch Gen Psychiatry.*
1183   2008;65(3):283-289.

1184   79.   Mellström D, Johnell O, Ljunggren O, et al. Free testosterone is an independent predictor of BMD
1185   and prevalent fractures in elderly men: MrOS Sweden. *J Bone Miner Res.* 2006;21(4):529-535.

1186   80.   LeBlanc ES, Nielson CM, Marshall LM, et al. The effects of serum testosterone, estradiol, and sex
1187   hormone binding globulin levels on fracture risk in older men. *J Clin Endocrinol Metab.*
1188   2009;94(9):3337-3346.

1189   81.   Woods DR, Hill NE, Neely RDG, Talks KL, Heggie A, Quinton R. Hematopoiesis Shows Closer
1190   Correlation with Calculated Free Testosterone in Men than Total Testosterone. *J Appl Lab Med.*
1191   2017;1(4):441-444.

1192   82.   Corona G, Torres LO, Maggi M. Testosterone Therapy: What We Have Learned From Trials. *J Sex*
1193   *Med.* 2020;17(3):447-460.

1194   83.   Llahana S. Testosterone Therapy in Adult Men with Hypogonadism. In: Llahana S, Follin C, Yedinak
1195   C, Grossman A, eds. *Advanced Practice in Endocrinology Nursing.* Cham: Springer International
1196   Publishing; 2019:885-902.

1197   84.   Bhasin S, Jameson JL. Disorders of the testes and male reproductive system In: Jameson JL, ed.
1198   *Harrison's Endocrinology* 4th Edition ed. New York: McGraw Hill Education; 2017:159 - 185.

1199   85.   Wang C, Berman N, Longstreth JA, et al. Pharmacokinetics of transdermal testosterone gel in
1200   hypogonadal men: application of gel at one site versus four sites: a General Clinical Research Center
1201   Study. *J Clin Endocrinol Metab.* 2000;85(3):964-969.

1202   86.   Cunningham G, Belkoff L, Brock G, et al. Efficacy and safety of a new topical testosterone
1203   replacement gel therapy for the treatment of male hypogonadism. *Endocrine practice : official*
1204   *journal of the American College of Endocrinology and the American Association of Clinical*
1205   *Endocrinologists.* 2017;23(5):557-565.

1206   87.   Spratt DI, Stewart II, Savage C, et al. Subcutaneous Injection of Testosterone Is an Effective and
1207   Preferred Alternative to Intramuscular Injection: Demonstration in Female-to-Male Transgender
1208   Patients. *The Journal of Clinical Endocrinology & Metabolism.* 2017;102(7):2349-2355.

1209   88.   Kaminetsky J, Jaffe JS, Swerdloff RS. Pharmacokinetic Profile of Subcutaneous Testosterone
1210   Enanthate Delivered via a Novel, Prefilled Single-Use Autoinjector: A Phase II Study. *Sex Med.*
1211   2015;3(4):269-279.

1212   89.   Santhakumar A, Miller M, Quinton R. Pubertal induction in adult males with isolated
1213   hypogonadotropic hypogonadism using long-acting intramuscular testosterone undecanoate 1-g
1214   depot (Nebido). *Clinical endocrinology.* 2014;80(1):155-157.

1215   90.   Pazderska A, Mamoojee Y, Artham S, et al. Safety and tolerability of one-year intramuscular
1216   testosterone regime to induce puberty in older men with CHH. *Endocrine connections.*
1217   2018;7(1):133-138.

1218   91.   Schubert M, Minnemann T, Hübler D, et al. Intramuscular testosterone undecanoate:
1219   pharmacokinetic aspects of a novel testosterone formulation during long-term treatment of men
1220   with hypogonadism. *J Clin Endocrinol Metab.* 2004;89(11):5429-5434.

1221   92.   Minnemann T, Schubert M, Freude S, et al. Comparison of a new long-acting testosterone
1222   undecanoate formulation vs testosterone enanthate for intramuscular androgen therapy in male
1223   hypogonadism. *Journal of endocrinological investigation.* 2008;31(8):718-723.

1224   93.   Saad F, Aversa A, Isidori AM, Zafalon L, Zitzmann M, Gooren L. Onset of effects of testosterone
1225   treatment and time span until maximum effects are achieved. *European journal of endocrinology /*
1226   *European Federation of Endocrine Societies.* 2011;165(5):675-685.

1227   94.   Coskuner ER, Ozkan B, Culha MG. Sexual Problems of Men With Androgenic Alopecia Treated With
1228   5-Alpha Reductase Inhibitors. *Sexual Medicine Reviews.* 2019;7(2):277-282.

1229   95.   Shin YS, Karna KK, Choi BR, Park JK. Finasteride and Erectile Dysfunction in Patients with Benign
1230   Prostatic Hyperplasia or Male Androgenetic Alopecia. *World J Mens Health.* 2019;37(2):157-165.

1231   96.   Pallotti F, Senofonte G, Pelloni M, et al. Androgenetic alopecia: effects of oral finasteride on
1232   hormone profile, reproduction and sexual function. *Endocrine.* 2020;68(3):688-694.

1233   97.   Diviccaro S, Melcangi RC, Giatti S. Post-finasteride syndrome: An emerging clinical problem.
1234   *Neurobiology of Stress.* 2020;12:100209.

1235   98.   Pereira AFJR, Coelho TOdA. Post-finasteride syndrome. *Anais Brasileiros de Dermatologia.*
1236   2020;95(3):271-277.

1237   99.   Gray SL, Semla TP. Post-finasteride syndrome. *BMJ (Clinical research ed).* 2019;366:l5047.

1238 100. Zitzmann M. Effects of testosterone replacement and its pharmacogenetics on physical
1239   performance and metabolism. *Asian J Androl.* 2008;10(3):364-372.

1240 101. Beauchet O. Testosterone and cognitive function: current clinical evidence of a relationship.
1241   *European journal of endocrinology / European Federation of Endocrine Societies.* 2006;155(6):773-
1242   781.

1243 102. Dwyer AA, Tiemensma J, Quinton R, Pitteloud N, Morin D. Adherence to treatment in men with
1244   hypogonadotrophic hypogonadism. *Clinical endocrinology.* 2017;86(3):377-383.

1245 103. Schoenfeld MJ, Shortridge E, Cui Z, Muram D. Medication adherence and treatment patterns for
1246   hypogonadal patients treated with topical testosterone therapy: a retrospective medical claims
1247   analysis. *The journal of sexual medicine.* 2013;10(5):1401.

1248 104. Donatucci C, Cui Z, Fang Y, Muram D. Long-term treatment patterns of testosterone replacement
1249   medications. *The journal of sexual medicine.* 2014;11(8):2092.

1250 105. Kovac JR, Rajanahally S, Smith RP, Coward RM, Lamb DJ, Lipshultz LI. Patient satisfaction with
1251   testosterone replacement therapies: the reasons behind the choices. *The journal of sexual*
1252   *medicine.* 2014;11(2):553-562.

1253 106. Szeinbach SL, Seoane-Vazquez E, Summers KH. Development of a men's Preference for
1254   Testosterone Replacement Therapy (P-TRT) instrument. *Patient preference and adherence.*
1255   2012;6:631-641.

1256 107. Kelly DM, Jones TH. Testosterone: a vascular hormone in health and disease. *J Endocrinol.*
1257   2013;217(3):R47-71.

1258 108. Coviello AD, Kaplan B, Lakshman KM, Chen T, Singh AB, Bhasin S. Effects of graded doses of
1259   testosterone on erythropoiesis in healthy young and older men. *J Clin Endocrinol Metab.*
1260   2008;93(3):914-919.

1261 109. Ajayi AA, Mathur R, Halushka PV. Testosterone increases human platelet thromboxane A2 receptor
1262   density and aggregation responses. *Circulation.* 1995;91(11):2742-2747.

1263 110. Tsang S, Wong SS, Wu S, Kravtsov GM, Wong TM. Testosterone-augmented contractile responses
1264   to alpha1- and beta1-adrenoceptor stimulation are associated with increased activities of RyR,
1265   SERCA, and NCX in the heart. *Am J Physiol Cell Physiol.* 2009;296(4):C766-782.

1266 111. Schwartz JB, Volterrani M, Caminiti G, et al. Effects of testosterone on the Q-T interval in older men
1267   and older women with chronic heart failure. *International journal of andrology.* 2011;34(5 Pt
1268   2):e415-421.

1269   112.   Pye SR, Huhtaniemi IT, Finn JD, et al. Late-onset hypogonadism and mortality in aging men. *J Clin*
1270   *Endocrinol Metab.* 2014;99(4):1357-1366.

1271   113.   Corona G, Rastrelli G, Di Pasquale G, Sforza A, Mannucci E, Maggi M. Endogenous Testosterone
1272   Levels and Cardiovascular Risk: Meta-Analysis of Observational Studies. *J Sex Med.*
1273   2018;15(9):1260-1271.

1274   114.   Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone
1275   administration. *The New England journal of medicine.* 2010;363(2):109-122.

1276   115.   Aversa A, Bruzziches R, Francomano D, et al. Effects of testosterone undecanoate on cardiovascular
1277   risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic
1278   syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. *J Sex*
1279   *Med.* 2010;7(10):3495-3503.

1280   116.   Brock G, Heiselman D, Maggi M, et al. Effect of Testosterone Solution 2% on Testosterone
1281   Concentration, Sex Drive and Energy in Hypogonadal Men: Results of a Placebo Controlled Study. *J*
1282   *Urol.* 2016;195(3):699-705.

1283   117.   Budoff MJ, Ellenberg SS, Lewis CE, et al. Testosterone Treatment and Coronary Artery Plaque
1284   Volume in Older Men With Low Testosterone. *Jama.* 2017;317(7):708-716.

1285   118.   Mohler ER, 3rd, Ellenberg SS, Lewis CE, et al. The Effect of Testosterone on Cardiovascular
1286   Biomarkers in the Testosterone Trials. *J Clin Endocrinol Metab.* 2018;103(2):681-688.

1287   119.   Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among
1288   men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med.*
1289   2013;11:108.

1290   120.   Corona G, Maseroli E, Rastrelli G, et al. Cardiovascular risk associated with testosterone-boosting
1291   medications: a systematic review and meta-analysis. *Expert Opin Drug Saf.* 2014;13(10):1327-1351.

1292   121.   Borst SE, Shuster JJ, Zou B, et al. Cardiovascular risks and elevation of serum DHT vary by route of
1293   testosterone administration: a systematic review and meta-analysis. *BMC Med.* 2014;12:211.

1294   122.   Seftel AD, Kathrins M, Niederberger C. Critical Update of the 2010 Endocrine Society Clinical
1295   Practice Guidelines for Male Hypogonadism: A Systematic Analysis. *Mayo Clin Proc.*
1296   2015;90(8):1104-1115.

1297   123.   FDA. FDA Drug Safety Communication: FDA cautions about using testosterone products for low
1298   testosterone due to aging; requires labeling change to inform of possible increased risk of heart
1299   attack and stroke with use. A US Federal Drugs Administration (FDA) drug safety communications

1300 announcement on 31st January 2014. Available on-line via:

1301 https://www.fda.gov/media/91048/download [Accessed 8th May 2021].

1302 124. EMA. European Medicines Agency EMA/706140/2014: No consistent evidence of an increased risk

1303 of heart problems with testosterone medicines. An EMA drug safety communications

1304 announcement on 21st November 2014. Available on-line via:

1305 https://www.ema.europa.eu/en/documents/referral/testosterone-article-31-referral-no-

1306 consistent-evidence-increased-risk-heart-problems-testosterone_en.pdf [Accessed 8th May 2021].

1307 125. Jayasena CN. NIHR HTA Testosterone Efficacy & Safety (TestES) Consortium: Investigating the

1308 effects of androgen replacement therapy. Multisite study funded by the National Institute of

1309 Healthcare Research Health Technology Assessment (NIHR HTA). On-line:

1310 https://www.imperial.ac.uk/metabolism-digestion-reproduction/research/diabetes-endocrinology-

1311 metabolism/endocrinology-and-investigative-medicine/nihr-testosterone/ [Accessed 8th May

1312 2021]. In:Ongoing unpublished work.

1313 126. AbbVie. A Study to Evaluate the Effect of Testosterone Replacement Therapy (TRT) on the

1314 Incidence of Major Adverse Cardiovascular Events (MACE) and Efficacy Measures in Hypogonadal

1315 Men (TRAVERSE). Ongoing unpublished clinical trial. On-line:

1316 https://www.clinicaltrials.gov/ct2/show/NCT03518034 [Accessed 8th May 2021].

1317 127. Getahun D, Nash R, Flanders WD, et al. Cross-sex Hormones and Acute Cardiovascular Events in

1318 Transgender Persons: A Cohort Study. *Ann Intern Med.* 2018;169(4):205-213.

1319 128. Nota NM, Wiepjes CM, de Blok CJM, Gooren LJG, Kreukels BPC, den Heijer M. Occurrence of Acute

1320 Cardiovascular Events in Transgender Individuals Receiving Hormone Therapy. *Circulation.*

1321 2019;139(11):1461-1462.

1322 129. Walker RF, Zakai NA, MacLehose RF, et al. Association of Testosterone Therapy With Risk of Venous

1323 Thromboembolism Among Men With and Without Hypogonadism. *JAMA Intern Med.*

1324 2020;180(2):190-197.

1325 130. Jick SS, Hagberg KW. The risk of adverse outcomes in association with use of testosterone products:

1326 a cohort study using the UK-based general practice research database. *Br J Clin Pharmacol.*

1327 2013;75(1):260-270.

1328 131. Snyder PJ, Kopperdahl DL, Stephens-Shields AJ, et al. Effect of Testosterone Treatment on

1329 Volumetric Bone Density and Strength in Older Men With Low Testosterone: A Controlled Clinical

1330 Trial. *JAMA Intern Med.* 2017;177(4):471-479.

1331 132. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7-30.

1332   133.   Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: the
1333   saturation model and the limits of androgen-dependent growth. *Eur Urol.* 2009;55(2):310-320.

1334   134.   Lenfant L, Leon P, Cancel-Tassin G, et al. Testosterone replacement therapy (TRT) and prostate
1335   cancer: An updated systematic review with a focus on previous or active localized prostate cancer.
1336   *Urol Oncol.* 2020;38(8):661-670.

1337   135.   Santella C, Renoux C, Yin H, Yu OHY, Azoulay L. Testosterone Replacement Therapy and the Risk of
1338   Prostate Cancer in Men With Late-Onset Hypogonadism. *Am J Epidemiol.* 2019;188(9):1666-1673.

1339   136.   Kim M, Byun SS, Hong SK. Testosterone Replacement Therapy in Men with Untreated or Treated
1340   Prostate Cancer: Do We Have Enough Evidences? *World J Mens Health.* 2020.

1341   137.   Chambers TJ, Anderson RA. The impact of obesity on male fertility. *Hormones.* 2015;14(4):563-568.

1342   138.   Roth MY, Page ST, Lin K, et al. Dose-dependent increase in intratesticular testosterone by very low-
1343   dose human chorionic gonadotropin in normal men with experimental gonadotropin deficiency. *J*
1344   *Clin Endocrinol Metab.* 2010;95(8):3806-3813.

1345   139.   Depenbusch M, von Eckardstein S, Simoni M, Nieschlag E. Maintenance of spermatogenesis in
1346   hypogonadotropic hypogonadal men with human chorionic gonadotropin alone. *European journal*
1347   *of endocrinology / European Federation of Endocrine Societies.* 2002;147(5):617-624.

1348   140.   Vicari E, Mongioì A, Calogero AE, et al. Therapy with human chorionic gonadotrophin alone induces
1349   spermatogenesis in men with isolated hypogonadotrophic hypogonadism--long-term follow-up.
1350   *International journal of andrology.* 1992;15(4):320-329.

1351   141.   Dwyer AA, Sykiotis GP, Hayes FJ, et al. Trial of recombinant follicle-stimulating hormone
1352   pretreatment for GnRH-induced fertility in patients with congenital hypogonadotropic
1353   hypogonadism. *J Clin Endocrinol Metab.* 2013;98(11):E1790-1795.

1354   142.   Nieschlag E, Bouloux PG, Stegmann BJ, et al. An open-label clinical trial to investigate the efficacy
1355   and safety of corifollitropin alfa combined with hCG in adult men with hypogonadotropic
1356   hypogonadism. *Reprod Biol Endocrinol.* 2017;15(1):17.

1357   143.   Rohayem J, Hauffa BP, Zacharin M, Kliesch S, Zitzmann M. Testicular growth and spermatogenesis:
1358   new goals for pubertal hormone replacement in boys with hypogonadotropic hypogonadism? -a
1359   multicentre prospective study of hCG/rFSH treatment outcomes during adolescence. *Clinical*
1360   *endocrinology.* 2017;86(1):75-87.

1361   144.   Büchter D, Behre HM, Kliesch S, Nieschlag E. Pulsatile GnRH or human chorionic
1362   gonadotropin/human menopausal gonadotropin as effective treatment for men with

1363   hypogonadotropic hypogonadism: a review of 42 cases. *European journal of endocrinology /*
1364   *European Federation of Endocrine Societies.* 1998;139(3):298-303.

1365 145.   Liu PY, Baker HW, Jayadev V, Zacharin M, Conway AJ, Handelsman DJ. Induction of spermatogenesis
1366   and fertility during gonadotropin treatment of gonadotropin-deficient infertile men: predictors of
1367   fertility outcome. *J Clin Endocrinol Metab.* 2009;94(3):801-808.

1368 146.   Warne DW, Decosterd G, Okada H, Yano Y, Koide N, Howles CM. A combined analysis of data to
1369   identify predictive factors for spermatogenesis in men with hypogonadotropic hypogonadism
1370   treated with recombinant human follicle-stimulating hormone and human chorionic gonadotropin.
1371   *Fertil Steril.* 2009;92(2):594-604.