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Testosterone replacement therapy in men with type 2 diabetes mellitus and functional hypogonadism —an Integrated Diabetes and Endocrine Academy (IDEA) consensus guideline

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ABSTRACT

Background: Though testosterone replacement therapy in men with organic hypogonadism is established, its role in men with type 2 diabetes mellitus (T2DM) and functional hypogonadism is unclear.
Methods: Thirteen experts addressed ten topic-specific questions after an in-depth review of literature, where all relevant issues were critically evaluated.
Results: Ten recommendations concerning diagnosis and management of men with T2DM and functional hypogonadism have been put forward.
Conclusion: Routine measurement of serum testosterone in all, and inappropriate replacement of testosterone in asymptomatic T2DM men with functional hypogonadism and borderline low serum testosterone values, is not recommended.

1. Introduction

Epidemiological studies reveal an increased prevalence of sexual dysfunction in men with Type 2 diabetes mellitus (T2DM) [1–3]. Sexual dysfunction leads to poor quality of life and is the core symptom of functional hypogonadism in men with T2DM [4]. However, although exogenous testosterone replacement therapy has been shown to reduce fat mass and increase muscle mass, its effects on symptoms of sexual dysfunction [4,5] and metabolic parameters [6–8] are not uniform. Moreover, the long-term risks of testosterone replacement therapy in men with T2DM and functional hypogonadism are unclear. The objective of this task force was to prepare a set of easy-to-follow, evidence-based recommendations for testosterone replacement therapy in men with T2DM and functional hypogonadism.

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2. Methods

2.1. Constitution of the consensus task force, gathering, and appraisal of evidence

Thirteen expert physicians, diabetologists, and endocrinologists from different regions of India and the United Kingdom were invited by the Integrated Diabetes and Endocrine Academy (IDEA), a not-for-profit academic organization in the field of endocrinology, diabetes and metabolic diseases from Kolkata, India to constitute the task force. Literature search was performed using online database search of Pub Med and the Cochrane Library, from inception till date of meeting. Published articles from peer reviewed journals, fulfilling the inclusion criteria, were selected. Ten topic-specific questions were formulated. The selected articles and questions were circulated for in-depth reading and analysis among all the panelists of the task force six weeks prior to the face-to-face meeting. A closed room meeting was held in Kolkata, India with all members of the task force in attendance, where each one of the ten questions was discussed in great detail. After the initial discussion, a primary draft consensus report was prepared, which was circulated twice amongst all panelists. The final consensus recommendations were prepared after incorporating the inputs of the members of the task force.

The Ten Key Questions Discussed

1. What are the types of hypogonadism?
2. Is testosterone deficiency common among men with type 2 diabetes mellitus?
3. What is the pathogenesis of hypogonadism in men with type 2 diabetes mellitus?
4. When to test for hypogonadism in men with type 2 diabetes mellitus?
5. How to establish the diagnosis of testosterone deficiency in men with type 2 diabetes mellitus?
6. Does lifestyle modification have an impact on men with type 2 diabetes mellitus and functional hypogonadism?
7. Does testosterone replacement therapy have an impact on anthropometric and metabolic parameters in men with type 2 diabetes mellitus and functional hypogonadism?
8. What are the effects of testosterone replacement therapy on sexual dysfunction, constitutional symptoms, and mood in men with type 2 diabetes mellitus and functional hypogonadism?
9. Which testosterone formulation to choose for replacement therapy in men with type 2 diabetes mellitus and functional hypogonadism?
10. What are the adverse effects of, and contraindications for, testosterone replacement therapy in men with type 2 diabetes mellitus and functional hypogonadism?

2.2. What are the types of hypogonadism (Table 1)?

Hypogonadism is a clinical syndrome, resulting from the inability of the testes to produce physiological levels of testosterone and/or normal number of spermatozoa, due to defect at one or multiple levels of the hypothalamic-pituitary-gonadal axis [9]. Primary hypogonadism is a result of a pathological defect at the testicular level, characterized by low serum testosterone, elevated gonadotropins, and defective spermatogenesis. The defect in secondary hypogonadism is in the hypothalamic-pituitary axis, which is characterized by low serum testosterone, low or inappropriately normal gonadotropin, and defective spermatogenesis. The causes of hypogonadism can either be organic or functional. Organic hypogonadism is a result of a pathological lesion anywhere in the hypothalamic-pituitary-gonadal axis; it can be primary or secondary, and is mostly irreversible. On the other hand, in functional hypogonadism, there is suppression of gonadotropins, leading to subnormal testosterone, not due to an organic lesion in the hypothalamic-pituitary region but because of reversible conditions like drug ingestion, alcohol, and chronic disease conditions like obesity, type 2 diabetes, heart, liver and kidney failure [9].

This task force has limited itself to reviewing the evidence, and constructing consensus recommendations for men with T2DM and functional hypogonadism, who do not desire fertility. These consensus recommendations do not address men with T2DM and primary hypogonadism, secondary hypogonadism due to structural lesions in the hypothalamic-pituitary region, functional hypogonadism who desire fertility, or disorders of spermatogenesis.

2.3. Is testosterone deficiency common among men with type 2 diabetes mellitus?

Functional hypogonadism is common in men with type 2 diabetes mellitus (T2DM). Barrett-Connor et al., in 1990 reported that serum total testosterone and sex-hormone binding globulin (SHBG) were significantly lower in 110 men with diabetes aged between 40 and 79 years when compared to 875 men without diabetes; 21% men with diabetes had serum testosterone below 3.5 ng/ml (12 nmol/l) as compared to only 13% without diabetes [10]. Dhindsa et al., in 2004 reported low serum free testosterone with inappropriately low gonadotropins in 33% of 103 obese men [mean body mass index (BMI):33.4 kg/m^2] with T2DM aged 31–75 years, and poor glycemic control (mean HbA1c: 8.4%); hypogonadotropic hypogonadism in the affected men was independent of the duration of diabetes or degree of hyperglycemia but inversely correlated with BMI [11]. Grossman et al. reported reduced total serum testosterone in 43%, and reduced calculated free testosterone in 57%, of 580 men with T2DM [12]. Kumar et al. in a study among Indian men with T2DM and erectile dysfunction (ED), noted that low serum testosterone was prevalent in 0%, 70% and 97% of men with mild, moderate or severe ED respectively [13]. Ganesh et al. studied 100 Indian men with T2DM and found 11 patients (11%) with hypogonadotropic hypogonadism [14]. In a cross-sectional study of 355 men with T2DM aged >30 years, Kapoor et al. found 17% men with a serum testosterone <2.3 ng/ml (8 nmol/L), and further 25% with a serum testosterone between 2.3 and 3.5 ng/ml (8–12 nmol/L); these low values had a significant negative correlation with BMI [15].

Consensus Statement 1a: Functional hypogonadism, defined as subnormal testosterone value with low/inappropriately normal gonadotropins and no organic defect in the hypothalamic-pituitary region, is common in men with type 2 diabetes mellitus.

Consensus Statement 1b: All men with type 2 diabetes mellitus and organic hypogonadism (primary and secondary hypogonadism due to structural lesions in the hypothalamic-pituitary region, or disorders of spermatogenesis) and men with type 2 diabetes mellitus and functional hypogonadism who desire fertility, must be referred to an endocrinologist for proper evaluation and management.

Table 1
Classification of hypogonadism
a) Organic hypogonadism.

Primary	Secondary
Congenital/Genetic	**Congenital**
Klinefelter's syndrome	Primary empty sella syndrome
Myotonic dystrophy	**Traumatic/Surgical**
Cryptorchidism/Absent testis (anorchia)	-Traumatic brain injury
Acquired	-Pituitary stalk section/pituitary surgery
Infection	**Neoplastic**
	Hypothalamic/pituitary tumors
-Viral orchitis (Mumps)	**Infiltrative disorders**
-Bacterial	-Sarcoidosis
Sexually transmitted disease gonorrhea/chlamydia	- Granulomatous and lymphocytic hypophysitis
-Pyogenic bacteria: E Coli; Pseudomonas; Streptococcus; Staphylococcus; Klebsiella	
Trauma/Surgical	**Iron overload states**
-Torsion testis/blunt trauma to the testis	-Hemochromatosis
- Orchidectomy	-Repeated blood transfusion in thalassemia
Iatrogenic	**Iatrogenic**
-Testicular irradiation	-Cranial irradiation
-Post chemotherapy	- Iatrogenic immunomodulatory hypophysitis (following treatment with immunomodulators like ipilimumab)
Late onset hypogonadism	**Idiopathic hypogonadotropic hypogonadism**

b) Functional hypogonadism.

Primary	Secondary
Drugs	**Systemic**
-Ketoconazole	- Old age
- Bicalutamide	- Wasting due to chronic illness/excessive exercise
-Enobosarm	-Multiorgan failure (heart/kidney/lungs)
- Enzalutamide	- Sepsis
Systemic	**Metabolic/Endocrine**
-Chronic illness with wasting	- Obesity
-Old age	- Type 2 Diabetes
	- Cushing's syndrome/iatrogenic glucocorticoid excess
	-Hyperprolactinemia
End stage renal disease	**Drugs**
	-Alcohol
	-Opioids
	-Marijuana
	-Anabolic steroid abuse
	-Gonadotropin release hormone agonists

2.4. Pathogenesis of hypogonadism in men with type 2 diabetes mellitus (Fig. 1)

2.4.1. Role of obesity, insulin resistance, and sex hormone binding globulin (SHBG) (Table 2)

T2DM causes functional hypogonadism through a complex interplay of multiple mechanisms. In most, but not all studies, it was noted that serum testosterone in men with T2DM and functional hypogonadism was inversely correlated with age and BMI. The prevalence of hypogonadotropic hypogonadism is higher in men with T2DM when compared to those with type 1 diabetes (T1DM) (26% vs. 6%), unless they are obese; obesity negated the low prevalence in men with T1DM, suggesting that insulin resistance is probably the common mediator of low serum testosterone in men with T1DM and T2DM [3].

Longitudinal data from the European Male Aging Study (EMAS) that included 2966 community-dwelling men aged 40–79 years from eight European countries, showed that weight gain was progressively associated with a decline in serum testosterone, whereas weight loss was proportionately associated with increase in serum testosterone [16]. Zheng et al. evaluated 213 men with T2DM for risk factors for development of hypogonadism; serum total testosterone negatively correlated with body mass index (BMI), waist circumference and HOMA-insulin resistance index [17]. This correlation between T2DM, functional hypogonadism, and obesity is summarized in Table 2 [18].

Some researchers have postulated that low serum SHBG, an index of increased insulin resistance, could explain the low serum total testosterone seen in men with T2DM. Indeed, a euglycemic–hyper insulinemic clamp study in non-diabetic men found a closer relationship between insulin sensitivity and SHBG than between insulin sensitivity and total testosterone, suggesting that insulin sensitivity primarily influences serum SHBG [19]. Similarly, in a study of 350 Finnish men, low serum SHBG was associated with insulin resistance independent of total testosterone, whereas the inverse relationship between insulin resistance and testosterone was lost after adjustment for SHBG [20]. To further examine the confounding effects of SHBG on the association between insulin resistance and testosterone, Tsai et al. in a study of 221 middle-aged non-diabetic men, found that the inverse relationship between bioavailable and free testosterone with insulin resistance was lost when adjustments were made for total body fat, suggesting that the relationship between bioavailable or free testosterone and insulin resistance was not independent of adiposity [21].

2.4.2. Role of adipocytokines and estrogen

It is postulated that in obese men, augmented P450 aromatase activity in the mesenchymal cells and preadipocytes leads to increased conversion of androstenedione and testosterone to estrogen [22]. This relative excess of estrogen suppresses the secretion of gonadotropin releasing hormone (GnRH) and luteinizing

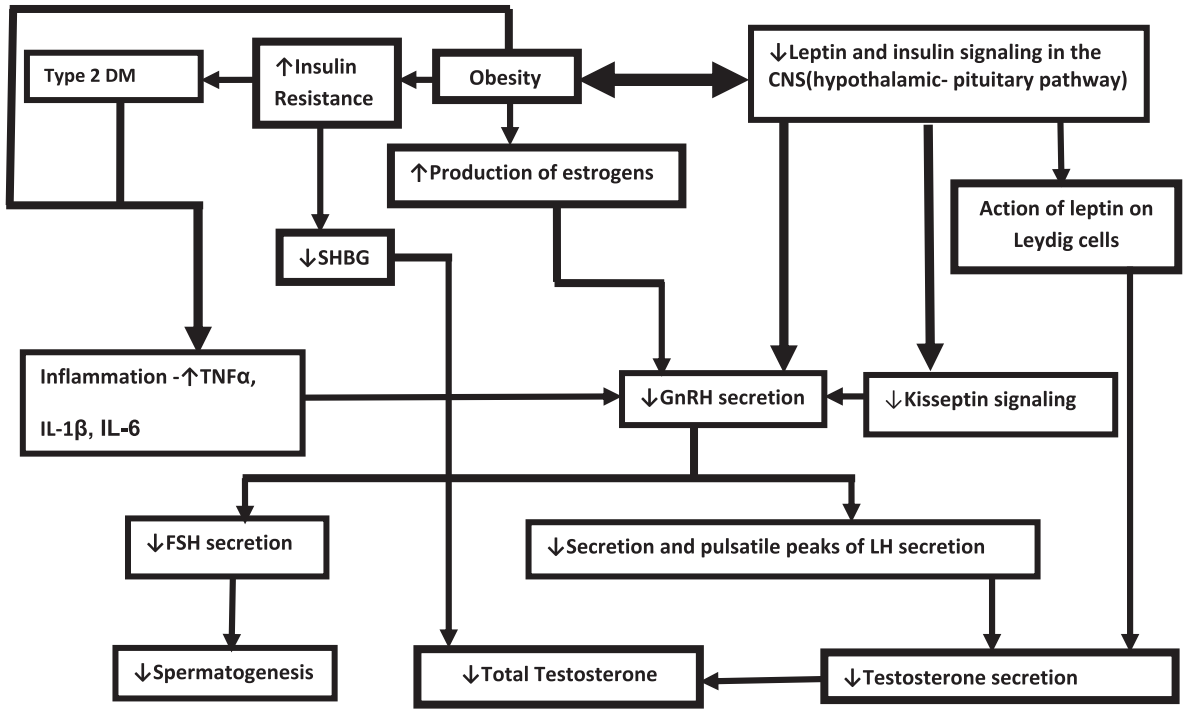

Fig. 1. Pathogenesis of functional hypogonadism in men with type 2 diabetes mellitus.

Table 2
Prevalence of functional hypogonadism in obese men with or without type 2 diabetes mellitus [18].

Author Year	n	Age (in years) ± SD	BMI (kg/m^2)	% with T2DM	%hypogonadal (based on total testosterone value)[a]	%hypogonadal (based on free testosterone value)
2008 **Hofstra et al**[b]	**149**	**43.3 ± 0.8**	**42.7 ± 0.7**	**37**	**57.7**	**35.6**
2010 **Dhindsa et al**[c]	**489**	**57.9 ± 7.1**	**34.6 ± 3.2**	**21.5**	**NA**	**40**
2014 **Calderon et al**[b]	**35**	**39.5 ± 9.5**	**42.7 ± 0.7**	**NS**[d]	**68.5**	**45.7**
2016 **Calderon et al**[b]	**100**	**40.5 ± 9.5**	**47.2 ± 7.2**[e]	**NS**[f]	**44**	**34**

NA = Data not available; NS= Not specified.
[a] Total Testosterone < 3 ng/ml.
[b] Free Testosterone <65 ng/ml.
[c] Free Testosterone <50 ng/ml.
[d] Exact prevalence of DM not specified but mean fasting plasma glucose (FPG) was 115.6 ± 47.7 mg/dl.
[e] Mean BMI in the hypogonadal cohort; in the remaining 56% non-hypogonadal cohort BMI was 46.2 ± 6.6 kg/m.^{2}.
[f] Exact prevalence of DM not specified but mean FPG was 129.7 ± 55.8 mg/dl.

hormone (LH), which contributes to testosterone deficiency [23]. The hypogonadal-obesity-adipocytokine hypothesis attempts to explain the inability of the body to augment testosterone production in response to low serum testosterone. Leptin, the best known adipocytokine, normally stimulates GnRH secretion by acting on the leptin receptors expressed on kisspeptin neurons. However, in obesity, despite an increase in leptin, GnRH secretion is not augmented since the hypothalamic pituitary axis becomes resistant to the action of leptin. Moreover, leptin also directly suppresses the stimulatory action of gonadotropins on the Leydig cells [24–26]. [Fig. 1].

2.4.3. Role of inflammatory markers

Inflammatory markers, such as tumor necrosis factor-α (TNF-α), interleukin-6 and interleukin-1β, are increased in men with T2DM and obesity. In animal studies, these inflammatory markers, in conjunction with raised estrogen, suppress hypothalamic GnRH secretion, resulting in reduced release of LH and follicle stimulating hormone (FSH), leading to hypogonadotropic hypogonadism [14,27]. In some studies, hypogonadal obese men have been shown to have lower pulsatile peaks of LH, presumably due to a combination of the above factors [3].

Consensus Statement 2: Functional hypogonadism in men with type 2 diabetes mellitus is a result of a complex interaction between multiple factors including age, visceral obesity, insulin resistance, serum SHBG, serum leptin and various inflammatory cytokines.

2.7. When to test for hypogonadism in men with type 2 diabetes mellitus (Table 3)?

Symptoms and signs suggestive of hypogonadism in men with T2DM are often non-specific. The secondary symptoms of hypogonadism, like fatigability, lethargy, tiredness, and reduced exercise capacity could also be due to poor metabolic control, underlying coronary artery disease, peripheral vascular disease, chronic kidney disease or anemia. Among the core symptoms of functional hypogonadism, erectile dysfunction (ED) is the commonest; it is reported in some studies by up to one-third of men with T2DM and functional hypogonadism [11]. However, ED in men with T2DM is often not due to testosterone deficiency, but is a result of poor metabolic control, arteriopathy and autonomic neuropathy [28]. Reduced frequency of sexual thoughts, low sexual desire, and reduced early morning erections should alert one towards the possibility of hypogonadism. As obesity, T2DM and functional hypogonadism are interrelated, American Association of Clinical Endocrinology (AACE) and American Diabetes Association (ADA) recommend measuring serum Testosterone in all T2DM patients with BMI>30 kg/m^2. However, this is difficult to implement as many men with T2DM are unwilling to discuss their sexual problems unless specifically asked for.

The EMAS Group reported that in men aged 40–79 years, only three sexual symptoms, namely low sexual desire, poor early morning erection, and erectile dysfunction had an association with low serum testosterone; there was an inverse relationship between increasing number of sexual symptoms and decreasing serum testosterone [29]. Kumar et al. also reported that among Indian men with T2DM, the proportion of men with low serum testosterone increased with increasing severity of ED [13,30].

Consensus Statement 3a. The task force recommends measuring serum testosterone in men with type 2 diabetes mellitus with one or more 'core symptoms' of low serum testosterone, including reduced sexual thoughts, reduced sexual drive, reduced early morning penile tumescence and erectile dysfunction.

Consensus Statement 3b. The task force recommends against measuring serum testosterone in men with type 2 diabetes mellitus with 'non-specific' symptoms in the absence of a core symptom of low serum testosterone.

Consensus Statement 3c. The task force recommends against measuring serum testosterone routinely in all asymptomatic men with type 2 diabetes mellitus.

2.8. How to establish the diagnosis of testosterone deficiency in men with type 2 diabetes mellitus (Table 4; Fig. 2)?

Testosterone is mostly bound to sex hormone binding globulin (SHBG) (45%) and albumin (50%); less than 5% circulates as free testosterone [31]. Testosterone bound to SHBG is biologically inactive; however, testosterone bound to albumin can weakly dissociate. Bioavailable testosterone is the combined pool of free testosterone and albumin-bound testosterone. SHBG concentration is low in men with T2DM and obesity, primary hypothyroidism, acromegaly, nephrotic syndrome and on concurrent anabolic steroids. Low SHBG may result in a subnormal total testosterone in eugonadal men. In contrast, factors that increase SHBG, including aging, hyperthyroidism, estrogens, HIV disease, hepatitis C, alcoholic cirrhosis and anticonvulsants, may lead to falsely normal serum total testosterone in a man with hypogonadism [32].

Total testosterone can be measured in the serum using immunometric assays, radioimmunoassay (RIA) or liquid chromatography–tandem mass spectrometry (LC-TM/MS). The LC-TM/MS method provides the highest sensitivity and specificity, particularly at lower values. There is considerable inter-assay and inter-laboratory variability in serum total testosterone measurements; it is therefore recommended that the same laboratory standards are followed for repeat testosterone assays [9]. Measurement of total testosterone should be the investigation of choice for assessing suspected hypogonadism.

Free testosterone is best measured by equilibrium dialysis, a technology not readily available in most laboratories; the alternative method is to calculate the value by using total testosterone, SHBG, and albumin concentrations. Free testosterone assessment is specifically indicated where there is a discrepancy between measured serum total testosterone and the clinical picture, or in states with altered SHBG. Direct analog based free testosterone assays are inaccurate and should be avoided [9].

There is considerable controversy concerning the lower normal limit of serum total testosterone to define hypogonadism; values between 2.3ng/ml-3.5 ng/ml (8–12 nmol/l) have been suggested. After reviewing the guidelines issued by various associations and organizations [9,16,29,33–35], the task force settled on a lower normal limit of serum total testosterone of 2.3 ng/ml (8 nmol/l) to diagnose hypogonadism. In situations where free testosterone is measured, a value of 46 pg/ml was adjudged as the lower normal limit to define hypogonadism [35].

Keeping in mind the diurnal variation in serum testosterone, the ideal time of the day to collect blood sample for testosterone assay is at 9 a.m. [36]; samples collected between 7:00–11:00 a.m. or within 3 hours of waking is acceptable [34]. Low serum total testosterone needs to be reconfirmed on another day, because 30% of men with an initial serum testosterone in the borderline hypogonadal range have a normal serum testosterone on repeat testing [2]. Serum testosterone between 2.3 and 3.5 ng/ml (8–12 nmol/l) should be re-evaluated on another day, together with SHBG measurement [35]. Serum testosterone can be low in the presence of an acute illness, and as such, must be measured a few weeks after the resolution of the acute illness to confirm the diagnosis of hypogonadism [9,33]. Similarly, serum testosterone can be influenced by a number of medications, including opioids, glucocorticoids, anabolic steroids, cimetidine, tricyclic antidepressants, chemotherapeutic agents and nicotine. A repeat assessment, off medication, if possible, is essential to confirm the diagnosis of hypogonadism [37,38].

Low serum testosterone should prompt measurement of LH and FSH to characterize the type of hypogonadism. In men with T2DM and hypogonadotropic hypogonadism, exclude organic causes of secondary hypogonadism; request for MRI pituitary, serum prolactin and anterior pituitary hormone profile. It is worthwhile to check serum Free T4 and TSH as uncorrected hypothyroidism can mimic many of the secondary symptoms seen in men with functional hypogonadism. Moreover, serum total testosterone <1.5 ng/ml (<5.2 nmol/l) necessitates a referral to an endocrinologist for a detailed evaluation of the cause of hypogonadism [34].

Consensus Statement 4a. The task-force recommends checking serum *total* testosterone from an accredited laboratory in a blood sample drawn between 7 and 11 a.m. (ideally 9 a.m.), or within 3 hours of waking up. LH and FSH must be checked to establish the nature of hypogonadism.

Consensus Statement 4b. The task force recommends avoiding collecting blood sample for checking serum testosterone during/immediately after an acute illness or when taking medications known to affect serum testosterone.

Consensus Statement 4c. The task force recommends a serum total testosterone of 2.3 ng/ml (8 nmol/l) as the normal lower limit to diagnose hypogonadism in men with type 2 diabetes mellitus.

Consensus Statement 4d. The task force recommends that all men with type 2 diabetes mellitus and serum total testosterone <1.5 ng/ml (5.2 nmol/L) be referred to an endocrinologist for further evaluation and management.

Consensus Statement 4e. The task force recommends against routinely relying on free serum testosterone to diagnose hypogonadism. Free testosterone estimation should be limited to men with type 2 diabetes mellitus with discrepancy between serum total testosterone and clinical symptoms or in conditions known to alter SHBG.

Consensus Statement 4f. Estimation of free testosterone by equilibrium dialysis method is preferable, when available. The task force recommends against using analog-based free testosterone immunoassays.

Consensus Statement 4g. The task force recommends a serum free testosterone of 46 pg/ml (160 pmol/l) as the normal lower limit to diagnose hypogonadism in men with type 2 diabetes mellitus.

Consensus Statement 4h. The task force suggests measurement of LH and FSH to characterize the type of hypogonadism. Check serum Free T4 and TSH to exclude hypothyroidism.

Consensus Statement 4i. In men with hypogonadotropic hypogonadism, exclude organic hypogonadism: request for MRI pituitary, serum prolactin and other anteriorpituitary hormones.

2.9. Does lifestyle modification have an impact on men with type 2 diabetes mellitus and functional hypogonadism?

Lifestyle modification is an important component in the management of people with T2DM. Adequate medical nutritional therapy and physical exercise are the first line interventions in T2DM. In the absence of any contraindications, moderate intensity aerobic physical activity for at least 150 min/week is recommended for adults aged 18–64 years. If properly adhered to, life style modification results in weight loss, especially loss of total fat mass, with resultant improvement in insulin resistance. Low testosterone, visceral obesity, and insulin resistance are intricately interrelated in men with T2DM; a reduction in weight and visceral obesity results in an improvement in insulin resistance that brings about an improvement in the serum total testosterone. Indeed, Khoo et al. reported that in obese middle-aged men, with or without diabetes, diet-induced weight loss of 10% or more was significantly associated with an increase in insulin sensitivity and serum total testosterone; the improvement in serum testosterone was proportional to the degree of weight loss [39]. Similarly, in a systematic review and meta-analysis on the effect of loss in body weight on sex hormones in obese middle-aged men, with or without diabetes, with hypogonadotropic hypogonadism, Corona et al. found that both a low-calorie diet and bariatric surgery induced weight loss led to a rise in serum total testosterone, free testosterone and SHBG; the increase in serum testosterone was proportional to the degree of weight loss [22].

However, the challenge lies in sustaining these life style changes. Dietary modification and exercise regimes are more often than not difficult to maintain, and in a significant majority of men with T2DM, the lost weight is regained, with a resultant drop in serum total testosterone [40].

Consensus Statement 5: The task force recommends lifestyle modification for all men with type 2 diabetes mellitus and functional hypogonadism. Adequate dietary modification, and in the absence of any contraindications, at least 150 min of moderate intensity aerobic exercise per week is recommended. Every attempt should be made to adhere to life style modifications made because the benefits disappear on regaining weight after stopping such measures.

2.10. Does testosterone replacement therapy have an impact on anthropometric and metabolic parameters in men with type 2 diabetes mellitus and functional hypogonadism (Table 5)?

It is well established that testosterone replacement therapy increases lean body mass and decreases total body fat mass in people with organic, primary or secondary hypogonadism [6,8]. In a randomized controlled trial (RCT) by Snyder et al. it was observed that increasing serum testosterone of normal men above 65 years of age to mid-normal range for young men increased lean mass and decreased fat mass; however, this did not result in an increase in muscle strength [41]. In a meta-analysis of 59 trials comparing 3029 men receiving testosterone supplementation with 2049 men acting as controls, Corona et al. found that testosterone supplementation was associated with a significant reduction in body fat and increase in lean mass. However, there was moderate-to-high degree of heterogeneity among the trials included in this meta-analysis; the age group of the men ranged from 27 to 76 years, some had late onset hypogonadism, and serum testosterone of the 'hypogonadal men' ranged from <3.7–12 nmol/L [42].

The results of RCTs on the effect of testosterone replacement therapy on body composition in men with T2DM and functional hypogonadism are mixed. Magnussen et al. in an RCT involving 43 obese men (BMI 31 kg/m2) with T2DM reported a 1.3 kg loss in total fat mass and 1.9 kg increase in lean body mass [43]. However, in an RCT involving 220 obese (BMI 33 kg/m^2) men, of whom 137 had T2DM and/or metabolic syndrome, Jones et al. did not find any significant effect of 2% testosterone gel on abdominal obesity, percentage body fat, BMI, or waist circumference [44]. Overall, the characteristics of the men included in these RCTs were heterogeneous. Most of them were obese; their BMI ranged from 30 to 39 kg/m^2 and the baseline serum testosterone was very variable, ranging between 6.7 and 13 nmol/L. Testosterone replacement therapy in these men with T2DM and functional hypogonadism resulted in no effect to up to 8.5 cm reduction in waist circumference, mostly no change in BMI, from none to 2.4 kg loss in total fat

Table 3
Symptoms suggestive of functional hypogonadism in men with type 2 diabetes mellitus [9, 32].

Core symptoms
★Erectile dysfunction
★Reduced frequency of early morning erection
★Low sexual desire
★Reduced frequency of sexual thoughts.
Common secondary symptoms
★Easy fatigability
★Poor concentration and cognitive impairment
★Decrease in initiative, motivation, energy and self-confidence
★Depression
★Disturbed sleep rhythm
★Reduction of muscle strength

mass, no change in visceral fat mass (in the studies that looked for it), and an uniform increase in lean mass ranging from 0.6 to 4.8 kg [6–8,42–47][Table 5].

As with the wide variability in the effect of testosterone replacement therapy in men with T2DM and functional hypogonadism on body composition, the effect on insulin resistance and glycemic parameters are equally mixed. The TIMES2 study, which failed to show any significant changes in body composition, did reveal a statistically significant reduction in HOMA-IR by 16% at 6 months among the 68 hypogonadal men with Type 2 DM on testosterone replacement therapy in comparison to the 69 on placebo [44]. Groti et al. evaluated the effects of testosterone replacement therapy in 55 obese (mean BMI 33 kg/m^2) hypogonadal men with T2DM over a period of one-year in a double-blind, randomized, placebo-controlled trial and reported a 41% reduction in HOMA-IR and 0.94% reduction in HbA1c [48]. However, a number of other trials did not find any significant change in HOMA-IR or HbA1c (Table 5).

Most trials assessing the effect of testosterone replacement therapy in men with T2DM and functional hypogonadism on insulin resistance and glycemic parameters are of short duration, have a small cohort size and multiple confounders. Moreover, there are significant discrepancies among the studies with respect to age and BMI of patients, baseline serum testosterone values, and methods used to measure insulin resistance were different.

In summary, well conducted RCTs, involving both obese and non-obese men with T2DM, with near uniform baseline serum testosterone that is unequivocally in the hypogonadal range, treated with a similar formulation of testosterone to achieve mid-normal target value, and assessed in a standardized fashion for changes in body composition, insulin resistance, and glycemic parameters are urgently required to clearly assess the effect of testosterone replacement therapy in men with T2DM with functional hypogonadism on body composition and metabolic parameters. Based on current evidence, our recommendation would be to follow the recommendations of the Endocrine Society and the European Association of Andrology, of not using testosterone replacement therapy for improving glycemic control in men with T2DM and functional hypogonadism [9,33].

Consensus Statement 6a: In the absence of high-quality evidence, the task force recommends that testosterone replacement therapy should not be considered in asymptomatic men with type 2 diabetes mellitus and functional hypogonadism for its purported beneficial effects on body composition.

Consensus Statement 6b: The task force recommends against testosterone replacement therapy in men with type 2 diabetes mellitus and functional hypogonadism to improve glycaemic parameters.

2.11. What are the effects of testosterone replacement therapy on sexual dysfunction, constitutional symptoms, and mood in men with type 2 diabetes mellitus and functional hypogonadism?

Reduced frequency of sexual thoughts, low sexual desire, reduced early morning erections, and erectile dysfunction (ED) are the core sexual dysfunction symptoms in hypogonadal men with T2DM. However, not all men with low serum testosterone complain of these symptoms; moreover, many men with normal serum testosterone also report these symptoms. Kapoor et al. studied 355 men with T2DM, among whom 20% had serum testosterone<2.3 ng/mL (<8 nmol) and in 49% it was>3.5 ng/ml (>12 nmol/L). Among those with serum testosterone<2.3 ng/ml, 72% complained of reduced libido, and 68% complained of ED; interestingly, among the 58% men with T2DM with normal serum testosterone (>3.5 ng/ml; >12 nmol/L), 68% and 54% complained of reduced libido and ED respectively [49]. As such, it is difficult to assess the effect of therapy on these symptoms. Despite these limitations, studies have suggested that testosterone replacement therapy results in a significant improvement in sexual functioning men with serum testosterone <2.3 ng/ml (<8 nmol/l), and possible benefit among men with borderline serum testosterone (2.3–3.5 ng/ml; 8–12 nmol/l). Therapeutic benefit is limited in symptomatic men with T2DM with serum testosterone >3.5 ng/ml (12 nmol/l) [5]. In a recent meta-analysis of six RCTs assessing the effect of testosterone therapy on sexual function in 587 men with T2DM, Algeffari et al. noted significant heterogeneity among the trials with respect to baseline serum testosterone, end-points assessed, and the dose and formulation of testosterone used; within these limitations, they reported that testosterone therapy moderately improved sexual desire and erectile dysfunction but had no effect on the other domains of sexual function [50].

Table 4
Laboratory diagnosis of testosterone deficiency [35].

- Measurement of serum ***total*** testosterone is the investigation of choice
- Collect sample for measurement of serum total testosterone at 9 a.m. Collection of samples between 7:00–11:00 a.m. or within 3 hours of waking is acceptable [36].
- Serum total testosterone >3.5 ng/ml (12 nmol/l) excludes significant testosterone deficiency
- Serum total testosterone <2.3 ng/ml (8 nmol/l) confirms significant testosterone deficiency
- Serum total testosterone between 2.3 and 3.5 ng/ml (8–12 nmol/l) should be re-evaluated. Repeat measurement of serum total testosterone and SHBG.
- Free testosterone should be measured only when there is a discrepancy between serum total testosterone value and clinical suspicion of hypogonadism.
- Alterations in SHBG can affect serum total testosterone. Therefore, free testosterone should be measured in conditions where SHBG levels are altered [9,36].
- Free testosterone is best measured using equilibrium dialysis. However, this is not readily available.
- Analog-based free testosterone immunoassays are inaccurate and should be avoided.
- Measurement of LH and FSH assists in differentiating between primary and secondary hypogonadism, and should be checked in all cases of suspected hypogonadism [9].
- Refer the patient to an endocrinologist for detailed evaluation when serum total testosterone is < 1.5 ng/ml (<5.2 nmol/l) [34].
- Hypothyroidism should be excluded in all patients, as symptoms of hypothyroidism may mimic those of hypogonadism.

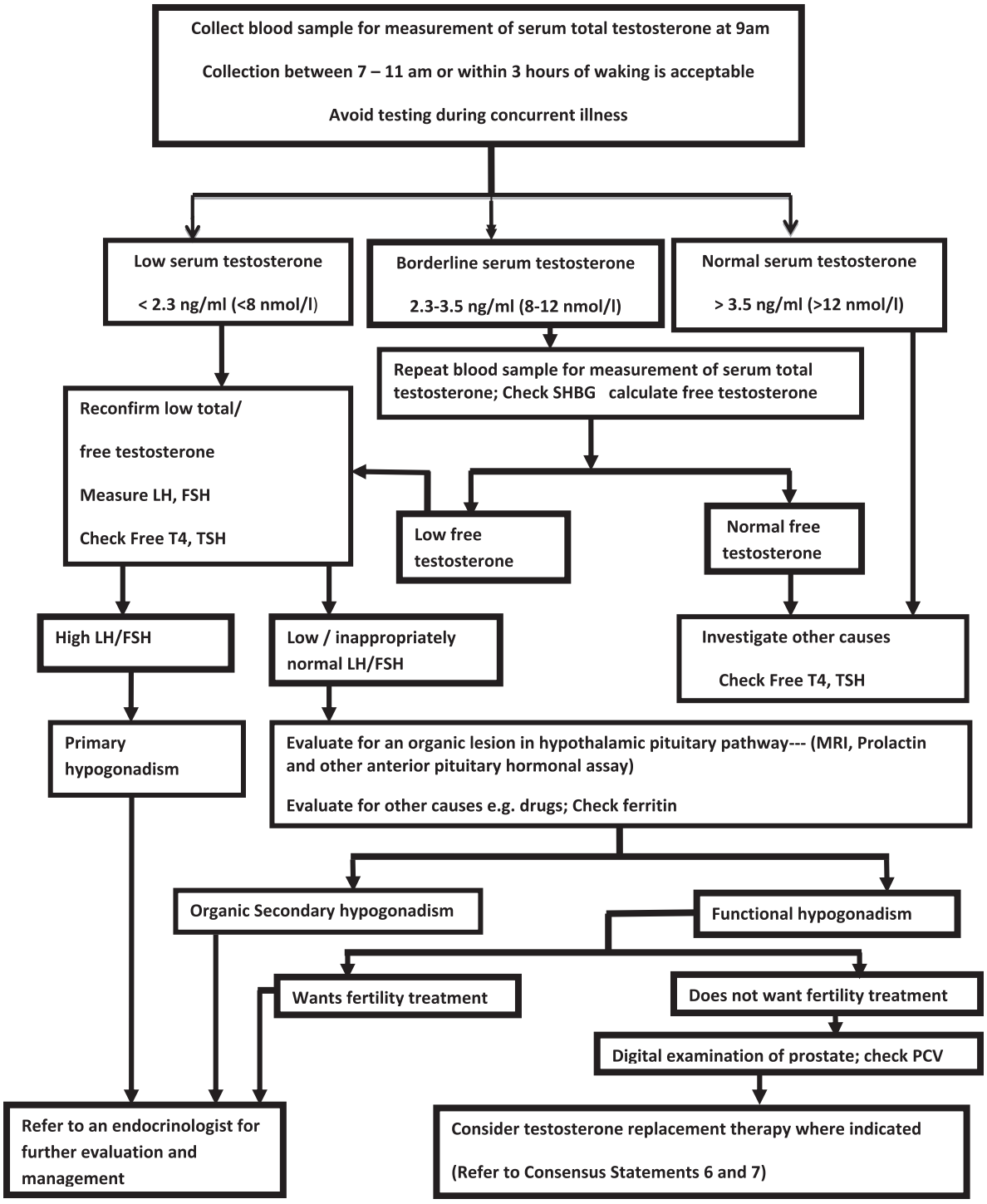

Fig. 2. Algorithm for diagnosis of functional hypogonadism in symptomatic men with type 2 diabetes mellitus [32].

Men with T2DM and functional hypogonadism complain of a number of constitutional symptoms. However, these symptoms, including lethargy, depression, easy fatigability, tiredness and inability to perform vigorous exercise are non-specific and difficult to causally relate to the low serum testosterone value. In fact, in a cross sectional study of 355 men with T2DM, of the 20% men with T2DM with functional hypogonadism (serum total testosterone <2.3 ng/ml; <8 nmol/L), 68%, 49%, and 42% complained of symptoms of easy fatigability, decreased muscle strength and mood changes respectively; interestingly, of the 49% men with T2DM with serum total testosterone>3.5 ng/ml (>12 nmol/L), 54%, 43% and 49% also complained of symptoms of fatigability, decreased muscle strength, and mood changes respectively [6]. Evidence for the effect of testosterone replacement therapy on these constitutional symptoms in men with T2DM and functional hypogonadism is at best weak. In the testosterone trials, an RCT assessing the effect of testosterone gel over one year in 790 men > 65 years of age with serum testosterone<2.75 ng/ml (<9.5 nmol/L), of whom 37% had

T2DM, there was no statistically significant improvement in vitality (as assessed by a scale that measures an individual's level of fatigue during usual daily activities) among men treated with testosterone when compared with those receiving placebo [51]. Similarly, Grossman et al. in a meta-analysis of seven RCTs including 833 men with T2DM and/or metabolic syndrome, found that testosterone treatment did not improve constitutional symptoms [52].

The evidence for the effect of testosterone treatment on depressive symptoms in hypogonadal men with T2DM is sparse. A few RCTs, including small number of non-diabetic men with borderline hypogonadism and dysthymia/major depression, have shown conflicting results. In a small RCT, including 23 men with dysthymic disorder with low or low-normal serum total testosterone (<3.5 ng/ml; <12 nmol/l), Seidman et al. found that testosterone treatment was effective in improving various scales of depression [53]. Similarly, Shores et al. in another small RCT involving 33 men aged 50 years or older with serum total testosterone<2.8 ng/ml (<9.7 nmol/l), found that compared to placebo, treatment with testosterone led to a higher remission rate of subthreshold depression (52.9% vs. 18.8%, $p = 0.041$) [54]. However, Pope et al. in an RCT involving 100 adult men with major depressive disorder and serum total testosterone <3.5 ng/ml (<12 nmol/l), did not find a significant difference in the Hamilton Depression Rating Scale score among the group receiving testosterone compared to the group on placebo [55]. Overall, these RCTs suggest that testosterone treatment does not have a major impact on the mood of patients with subnormal serum total testosterone.

Consensus Statement 7a. The task force recommends testosterone replacement therapy in men with type 2 diabetes mellitus and functional hypogonadism (serum total testosterone< 2.3 ng/ml; <8 nmol/l) with symptoms of sexual dysfunction (erectile dysfunction, reduced early morning erections, reduced frequency of sexual thoughts or low sexual desire), after discussing the non-availability of high-quality evidence to assess the risk-benefit ratio of such an approach.

Consensus Statement 7b. The task force recommends considering a trial of testosterone replacement therapy in men with type 2 diabetes mellitus and functional hypogonadism and borderline low serum total testosterone (2.3 −3.5 ng/ml; 8−12 nmol/l) with symptoms of sexual dysfunction after discussing the non-availability of high-quality evidence to assess the risk-benefit ratio of such an approach.

Consensus Statement 7c. The task force recommends against the use of testosterone replacement therapy in men with type 2 diabetes mellitus and functional hypogonadism for treatment of constitutional symptoms and/or depression.

2.12. Which testosterone formulation to choose for replacement therapy in men with type 2 diabetes mellitus and functional hypogonadism (Table 6)?

Testosterone is available in multiple formulations. It can be administered by deep intramuscular (i.m.) injection once every 2−3 or 10−12 weeks, taken orally as tablets, applied on the skin (gel or a patch), buccal mucosa (adhesive tablet), axilla (2% transdermal solution), or intranasal cavity (gel), or can be implanted as pellets subcutaneously every 3−6 months. There are no RCTs that have compared the efficacy and safety of the different routes of administration or the different formulations of testosterone on outcomes in men with T2DM and functional hypogonadism. The choice of formulation and route of administration thus depends upon many factors including bioavailability, injectable-or-not, availability, cost, patient preference, and formulation-specific advantages/disadvantages or side effects.

The oral and intramuscularly injectable formulations are easily available, and hence, are the most commonly used testosterone formulations in India. However, the only advantage of the oral formulation is its ease of administration; it has a number of disadvantages including variable bioavailability leading to variable serum testosterone concentrations, requirement of taking it thrice daily with a fatty meal, and being more expensive [35]. The shorter-acting intramuscular (IM) testosterone injections are relatively inexpensive and can be self-injected; however, disadvantages include need for frequent injections, wide fluctuations in serum testosterone levels (at times symptomatic), and pain and redness at the injection site. The longer acting injectable formulation, testosterone undecanoate, is inexpensive, can be injected once every 10−14 weeks, and has a smoother serum testosterone profile; however, the volume injected is higher, and the requirement for deep IM injection causes more pain when compared to the shorter-acting injectable formulations. Transdermal patches, gels, and solutions are easy to apply, have a better bioavailability with a smoother PK/PD profile mimicking normal circadian variation; however, they need to be applied daily. They can cause skin irritation, is affected by erratic absorption in tropical climates because of sweating, and carries risk of transfer during intimate contact.

Consensus Statement 8a. The task force recommends choosing the route of administration and type of formulation of testosterone based upon availability, cost, ease of administration, patient preference, and specific advantages/disadvantages of a particular route/formulation in a particular patient.

Consensus Statement 8b. The task force recommends using transdermal testosterone patches, where available and affordable, as it offers better bioavailability and smoother PK/PD profile. However, problems related to heat and humidity need consideration when using them in a tropical country.

Consensus Statement 8c. The task force recommends avoiding the oral route of testosterone replacement whenever possible because of the requirement of multiple daily dosing, variable bioavailability, and need for co-administration with a fatty meal for adequate absorption.

Consensus Statement 8d. The task force recommends using the longer-acting intramuscular testosterone formulations (once every 10−14 weeks) in preference to shorter-acting testosterone formulations to avoid symptomatic wide fluctuations in serum testosterone after injection of shorter-acting formulations.

Table 5
Randomized controlled trials on effect of testosterone replacement therapy on anthropometric and glycemic parameters in men with type 2 diabetes mellitus.

Year	Author	Patient (n)	Mean follow up in weeks	Mean age in years	Mean BMI change (kg/m2)	Mean HbA1C change	Mean HOMA-IR change[a]	Mean Lean mass gain in kg	Mean change in waist circumference	% loss of total body fat/loss of total body fat in kg
2006	Kapoor et al [6]	24	12	64	NS	−0.37%*	−39%*	NA	−1.6 cm*	NS
2010	Aversa et al [8]	50	52	57	NS	−0.2%*	−49%*	4.8 kg*	−8.5 cm*	↓19%*
2010	Gopal et al [46]	22	12	44	NS	NS	NS	NA	Nil	NA
2011	Jones et al. [44]	220	26	59.9	NS	−0.6%*	−16%**	NA	No change	No change
2014	Gianatti et al. [45] [b]	88	40	62	NS	NS	NS	2.08 kg*	No change	−2.38 kg*
2014	Hackett et al. [47] [c]	199	30	61.6	NS	NS	NS	NA	−2.5 cm*	NA
2016	Dhindsa et al. [7]	44	24	55	NS	No change	−34%*	3.4 kg***	No change	↓[d]
2016	Magnussen et al. [43]	43	24	61	NS	NS	NS	1.9 kg*	No change	−1.3 kg
2018	Groti et al. [48]	55	52	60	NS	−0.94%****	−41%****	NA	NS	NS

NA = Data not available. NS= Not significant *p < 0.05 **p = 0.049 ***p < 0.01 ****p < 0.001.
[a] Change in HOMA-IR in percentage.[HOMA-IR = fasting plasma glucose (mmol/l) X fasting insulin (mU/l)].22.5.
[b] Total volume of abdominal SC tissue reduced by 320 cc; no change in visceral adipose tissue.
[c] There was a significant difference in the outcome between the subgroup with underlying depression and those without depression. Significant reduction of HbA1c (p = 0.045), weight (p = 0.038), waist circumference (p = 0.02) and BMI (p = 0.02) noted in the group without depression, while these parameters showed worsening/ insignificant improvement in the depressed group.
[d] Trunk subcutaneous fat mass reduced by 2.5 kg (p = 0.03). No change in visceral fat.

Table 6
Testosterone formulations and their mode of administration [9,32].

	Active ingredient	Dose	Advantages	Disadvantages
Oral capsule	Testosterone undecanoate	40 mg 2−3 cap/day	User friendly	Variable serum concentrations with altered testosterone: dihydrotestosterone ratio
Buccal bio adhesive tablet	Testosterone enanthate	30 mg (1 tab) twice daily	Restores normal serum testosterone: dihydrotestosterone ratio in the physiological male range	Gingival adverse effects in 16% of patients
Transdermal gel	Testosterone	50−100 mg/day of 1% gel 40−70 mg/day of 2% gel	Restores normal serum testosterone: dihydrotestosterone ratio in the physiological male range. Easy to use Minimal residual effects Less fluctuation	Tissue irritation Variable bioavailability in tropical countries
Transdermal patch	Testosterone	1−2 patches/day (2-4 mg/day)	Restores normal serum testosterone: dihydrotestosterone ratio in the physiological male range. Easy to use	Inadequate testosterone levels in some Variable absorption in tropical countries Skin irritation
Axillary Solution	Testosterone	60 mg/day	Restores normal serum testosterone: dihydrotestosterone ratio in the physiological male range. Good skin tolerability	Potential of transfer to another person by direct skin-to-skin contact
Subcutaneous pellet	Testosterone	3−6(each containing 200 mg)600 −1200 mg every 6 months	Application frequency-Low Maintenance-Easy Testosterone levels-sustained (peaks at 1 month and then maintains plateau for 6 months)	Need for a surgical procedure Altered dihydrotestosterone: testosterone ratio
Nasal gel	Testosterone	11 mg 2−3 times daily	Rapid absorption Avoids first pass metabolism	Multiple daily intranasal dosing required Local nasal side effects; not appropriate for men with nasal disorders
Intramuscular	Testosterone Cypionate/ Enanthate	200 mg every 2−4 weeks	Most popular Inexpensive	Injectable Frequent injections Variable concentrations
	Testosterone Undecanoate	1000 mg every 10−14 weeks	Low application frequency Steady concentrations	Injectable Extra volume (4 ml)

2.13. What are the adverse effects of, and contraindications for, testosterone replacement therapy in men with type 2 diabetes mellitus and functional hypogonadism?

The adverse effects of, and contraindications for, testosterone replacement therapy in men with T2DM and functional hypogonadism are the same as that in men with organic hypogonadism receiving testosterone treatment. The 2018 Endocrine Society clinical practice guidelines on testosterone therapy in men with hypogonadism [9] and the 2015 Canadian Men's Health Foundation

Table 7
Monitoring of and adjustment in dose of testosterone in men with type 2 diabetes mellitus and functional hypogonadism [9].

Testosterone formulations	Time frame for evaluation of benefits of testosterone replacement therapy	Time frame for monitoring of side effects
Injectable Testosterone Enanthate or Cypionate	Monitor at 3–6 months; keep mid interval serum testosterone 3.5-6 ng/ml (14.1–24.5 nmol/l). Adjust dose/frequency of administration according to nadir value (low–mid normal range) at stipulated clinic visit	Local pain from injection- to be monitored after each injection
Injectable Testosterone Undecanoate	Measure serum testosterone just prior to the 4th dose and aim to achieve low-mid normal nadir value. Adjust injection frequency to every 10 weeks or every 14 weeks depending upon this value.	Local pain from injection to be monitored with every injection Monitor for cough (presumably due to pulmonary microembolisation of oil from the site of injection) after 1st injection (rare side effect)- if troublesome and recurrent might need change of route of administration
Transdermal gel	Measure serum testosterone 2–8 h after application and adjust dose after 1 week; target serum testosterone value at mid normal range	Monitor for local skin reactions after first 48 h
Transdermal patches	Measure serum testosterone 3–12 h after application; target serum testosterone levels as above	Monitor for local skin reactions after first 48 h
Oral testosterone undecanoate	Measure serum testosterone 3–5 h after ingestion with a fat-containing meal	Dose adjustment depending upon testosterone value
Buccal bio adhesive testosterone tablets	Measure serum testosterone immediately before or after application of fresh tablet	Monitor for gingival adverse effects
Subcutaneous pellets	Measure serum testosterone at the end of 6 months (before next dose). Adjust the number of pellets and/or the dosing interval accordingly; target testosterone value at mid normal range	Monitor for cellulitis at the site of implant after 48–72 h

Table 8
Evaluation for the benefits and adverse effects of testosterone replacement therapy in men with type 2 diabetes mellitus and functional hypogonadism [9,35].

Parameter	Frequency of evaluation	Method of evaluation and action to be taken
Erectile dysfunction	At baseline and 3 months; subsequently at 6 and 12 months; then annually	5-item version of the International Index of Erectile Function (IIEF-5) Questionnaire [30]
Libido	At baseline and 3 months; subsequently at 6 and 12 months; then annually	Clinical evaluation (EMAS questionnaire)
Anthropometric benefits (reduction in fat mass, increase in lean mass)	At baseline and every 3–6 months	Clinical; additional evaluation may be done with DEXA scan annually [33]
Monitoring for hazards		
FBC	At baseline and every 3–6 months; subsequently annually	Complete blood count **Stop if PCV > 48%** [9]
Evaluation of prostate by digital rectal examination (DRE) and PSA: For men 55–69 years of age and those in 40–69 years of age who are at increased risk for prostate cancer (family history of prostatic cancer/ occupational hazard)	At 3–12 months after initiating treatment	**Stop testosterone replacement if there is: (a) Any increase in size of prostatic nodule/indurations on DRE (b) ↑ in serum PSA concentration > 1.4 ng/mL within 12 months of initiating testosterone replacement, (c) Confirmed PSA > 4 ng/mL at any time (d)Significant worsening of lower urinary tract symptoms**

multidisciplinary guidelines task force on diagnosis and treatment of testosterone deficiency syndrome in men [35], have discussed these contraindications and adverse effects at length and our recommendations in this respect are similar.

In brief, metastatic prostate cancer, and breast cancer are absolute contraindications for administration of testosterone. The Endocrine Society also advises against using testosterone in men with unevaluated PSA >4 ng/ml, unevaluated prostate nodule or indurations, severe lower urinary tract symptoms with benign prostatic hypertrophy, poorly controlled heart failure, advanced liver disease or a hematocrit value > 48% [9].

The Endocrine Society has divided the adverse events of testosterone replacement therapy to those with a likely association to testosterone therapy including acne, oily skin, increase in hematocrit, reduced fertility, locally active prostatic carcinoma and progression of metastatic prostatic carcinoma, and those with a weak association with testosterone replacement therapy including gynecomastia, worsening of sleep apnea, and progression of carcinoma of the breast [9].

The effect of testosterone replacement therapy in hypogonadal men on the cardiovascular (CV) system remains unclear [56,57]. Retrospective studies, and the RCTs on CV events in men receiving testosterone replacement therapy have serious limitations. Similarly, a number of meta-analyses that have reported on the association between testosterone replacement therapy and CV events are limited by moderate to severe heterogeneity [4,58]; there is a wide variation in the baseline testosterone values among the study participants, with use of different routes, doses and formulations of testosterone, difference in duration of trials end-points reported [59,60]. Also, many of the individual trials in the meta-analyses had insufficient number of major adverse cardiovascular events (MACE). Therefore, the results of these meta analyses on the association between testosterone replacement therapy and CV events are conflicting. As such, the risk-benefit ratio of testosterone replacement therapy in hypogonadal men on the 3-point major adverse cardiovascular events is lacking. This conflict is further

reflected in the opposing views of the FDA, which has mandated a label change to include possible increased risk of cardiovascular events with use of testosterone, with that of the EMA, which has taken the position that the signal for an increased cardiovascular risk associated with the use of testosterone in hypogonadal men is weak and inconclusive [9].

Consensus Statement 9a. The task force recommends against the use of testosterone replacement therapy in men with type 2 diabetes mellitus andfunctional hypogonadism with locally active or metastatic prostatic cancer, breast cancer, severe lower urinary tract symptoms with BPH, unevaluated prostatic nodules or indurations, unevaluated PSA >4 ng/ml, and poorly controlled heart failure.

Consensus Statement 9b. The task force recommends against the use of testosterone replacement therapy in men with type 2 diabetes mellitus andfunctional hypogonadism with physiological or pathological polycythemia (hematocrit>48%)

Consensus Statement 9c. The task force recommends that men with type 2 diabetes mellitus and functional hypogonadism with symptoms of sexual dysfunction and stable cardiovascular disease can cautiously use testosterone replacement therapy after discussing the non-availability of high-quality evidence to assess the risk-benefit ratio of such an approach.

Consensus Statement 9d. The task force recommends against the use of testosterone replacement therapy in asymptomatic men with type 2 diabetes mellitus and functional hypogonadism for improvement in cardiovascular outcomes.

2.14. How to monitor testosterone replacement therapy in men with type 2 diabetes mellitus and functional hypogonadism (Tables 7 and 8)?

Following the initiation of testosterone replacement therapy in men with T2DM and functional hypogonadism, it is imperative to periodically monitor them for perceivable benefits or harm. The monitoring protocol is similar to that in men with organic hypogonadism. The 2018 Endocrine Society clinical practice guidelines on testosterone therapy in men with hypogonadism [9] and the 2015 Canadian Men's Health Foundation multidisciplinary guidelines task force on diagnosis and treatment of testosterone deficiency syndrome in men [35] have addressed these issues in detail.

Consensus statement 10a. The task force recommends periodic monitoring of men with type 2 diabetes mellitus, initiated on testosterone replacement therapy for functional hypogonadism, to assess response to therapy (Tables 7 and 8).

Consensus statement 10b. The task force recommends periodic monitoring of men with type 2 diabetes mellitus, initiated on testosterone replacement therapy for functional hypogonadism, to assess for adverse events that might necessitate discontinuation of testosterone replacement therapy, including periodic monitoring of hematocrit and prostate health.

3. Conclusion

In conclusion, the task force of thirteen specialists, under the banner of the Integrated Diabetes and Endocrine Academy, a not-for-profit academic organization from Kolkata, India, convened to formulate consensus recommendations for the evaluation and management of men with type 2 diabetes mellitus and functional hypogonadism. The task force has recognized that subnormal testosterone is common in men with type 2 diabetes mellitus, arising as a result of complex interactions between multiple mechanisms including visceral obesity, insulin resistance, SHBG and leptin levels, and various inflammatory markers. In the absence of good quality evidence on the risk-benefit ratio of testosterone replacement therapy in men with type 2 diabetes mellitus and functional hypogonadism who are asymptomatic or have non-specific constitutional symptoms/mood disorders, the task force has recommended against routine measurement of serum testosterone or offer of testosterone replacement therapy to such men. The task force recommends measuring serum testosterone in men with type 2 diabetes mellitus with sexual dysfunction, and offering testosterone replacement therapy only in those with serum total testosterone<2.3 ng/ml (8 nmol/L), with a clear understanding that good quality evidence on the risk-benefit ratio of such an approach is still lacking. The task force has recommended against the use of testosterone replacement therapy in asymptomatic men with type 2 diabetes mellitus and functional hypogonadism for improvement in cardiovascular outcomes. The taskforce has recommended which tests to use, when to test, which route and formulation of testosterone to choose, and how to monitor testosterone replacement therapy in symptomatic men with type 2 diabetes mellitus with functional hypogonadism.

The task force highlights the urgent need for further research to establish the risk-benefit ratio of testosterone replacement therapy not only in men with type 2 diabetes mellitus and functional hypogonadism who are symptomatic but also in those who are asymptomatic or have minimal symptoms. Well-designed/conducted RCTs, with adequate number of both obese and non-obese men with type 2 diabetes mellitus and functional hypogonadism, with serum total testosterone well matched and unequivocally in the hypogonadal or borderline hypogonadal range in both groups are urgently required. The RCTs must be of sufficient duration, have men treated with a similar formulation of testosterone to achieve mid-normal target value, who are assessed in a standardized fashion for changes in symptoms, body composition, insulin resistance, glycemic parameters, cardiovascular outcomes and adverse events.

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