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REVIEW ARTICLE

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The male hormone reset: how GLP-1RAs, lifestyle and testosterone transform obesity-linked problems

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ABSTRACT

Introduction: Functional hypogonadism, a manifestation of testosterone deficiency in simultaneously present comorbidities, profoundly impairs quality of life in men with overweight and obesity – yet remains persistently under-recognized in clinical practice.
Findings: Lifestyle modification constitutes first-line therapy, while pharmacological and surgical interventions increasingly complement it. Both promote substantial weight loss and may reverse obesity-related hypogonadism; bariatric surgery, in particular, elicits marked rises in circulating testosterone but entails risks of bone demineralization and uncertain long-term reproductive sequelae. Notwithstanding, testosterone deficiency itself represents a key driver of secondary osteoporosis, insulin resistance, anemia, fatigue, and depression as well as sexual symptoms. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have redefined obesity therapy through profound weight reduction and cardiometabolic benefit, yet concomitant losses of lean mass raise concern over sarcopenia and skeletal fragility.
Conclusion: This focused review article aims to present a comprehensive update on the latest data concerning combining testosterone therapy with contemporary anti-obesity pharmacotherapy as a new standard of care for obese men with functional hypogonadism, uniting metabolic, vascular, sexual, cognitive, and skeletal benefits within a comprehensive strategy to fortify corporeal resilience and enhance quality of life.

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Male hypogonadism; testosterone; GLP-1RAs; obesity; bones; osteoporosis

1 Introduction

Obesity is a chronic illness associated with several comorbidities (insulin resistance, leptin resistance, diabetes, etc.), that can lead to impairment of the hypothalamic–pituitary–testicular (HPT) axis, decreased testicular function, biochemical and clinical hypogonadism and subfertility in males.

Clinical evidence suggests that obesity is one of the most important risk factors for functional hypogonadism in men. The prevalence of hypogonadism in normal-weight adult males is around 32%, while about 75% of subjects with severe obesity (BMI > 40 kg/m^2) have hypogonadism [1]. Although the actual prevalence of male obesity-related secondary hypogonadism is still unclear, large-scale epidemiological studies, and small population-based surveys suggest prevalence rates as high as 45.0%–57.5% [2]. Male hypogonadism has been shown to be associated with excess morbidity and mortality in multiple clinical studies [3,4].

According to the guidelines [5,6] treatment of male hypogonadism include weight reduction and testosterone replacement, which is supported by many clinical studies. The aim is increase of testosterone level, which leads to improvement hormonal, metabolic, psychological, and general male health. This includes also weight loss in a long-term treatment. In last year's, we are witnessing enormous force in the field of medicaments' treatment for obesity, which treatment are with conflicting results, and possible serious adverse effects. On the other side is quite efficient metabolic surgery with excessive weight loss as a result in first years after the operative treatment. After massive weight loss are expected metabolic

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disturbances with decrease of bone mineral density (BMD) among others, which can lead to serious complications. Therefore, we aim to examine the multifaceted approach to treating obesity-related hypogonadism, including lifestyle changes, pharmacotherapy, metabolic surgery, and testosterone therapy (TTh) alongside their effects on health outcomes and to discuss about possible advantages of TTh in a long run for patients with obesity-related hypogonadism in this comprehensive review.

2 Understanding obesity-related functional hypogonadism

2.1 Definition and clinical presentation of obesity-related functional hypogonadism

Obesity-related functional hypogonadism is considered in males with body mass index (BMI) of ≥30 kg/m^2, with pathognomonic clinical symptoms of hypogonadism such as impaired sexual, physical or mental performance, along with gynecomastia, sleeping disorders, dysglycemia, anemia, flushing, low BMD, and evidence of biochemical hypogonadism – morning total testosterone level less than the lower limit for healthy young men as measured using a reliable assay, confirmed twice, or in the presence of abnormal sex hormone-binding globulin (SHBG), free or bioavailable testosterone less than lower limit for healthy young men in a reliable assay [2]. In order to confirm functional obesity-related hypogonadism, organic causes of hypogonadism must be systematically excluded according to the guidelines [5,6].

Clinical presentations vary dependent on the time of onset of testosterone deficiency, whether the defect is in testosterone production or spermatogenesis [7]. Men with functional hypogonadism commonly present with non-specific symptoms and modestly low testosterone levels. The most important symptoms, which were associated with testosterone deficiency in the European Male Ageing Study (EMAS), were sexual (only 3 out of 32 sexual) such as low libido, erectile dysfunction (ED), and decreased morning erections [8]. The symptoms most associated with hypogonadism beside sexual symptoms are decreased muscle mass and BMD, increased body fat, decreased vitality, and depressed mood. None of these symptoms is unique to hypogonadism, so one or more of these symptoms must be combined with a low testosterone concentration for the diagnosis to be made [9]. Both BMI and waist circumference, a clinical indicator of visceral obesity, are strongly related to the degree of HPT axis dysfunction and decrease of testosterone level [10], making assessment of both paramount during physical examination.

2.2 Physiological mechanisms linking obesity with low testosterone levels

There is a bidirectional relationship between obesity +/– metabolic syndrome (MS) and hypogonadism. The higher the number of MS components, the lower testosterone levels will be; and vice versa, the lower the testosterone level, the greater is the likelihood of metabolic complications [11]. Several complex mechanisms may negatively affect the HPT axis in obese individuals, such as: higher testosterone conversion to estradiol by aromatase activity in the adipose tissue (testosterone-estradiol shunt), increased reactive oxygen species (ROS) production, and the release of several endocrine molecules affecting the HPT axis by both direct and indirect mechanisms (hypogonadal–obesity–adipocytokine hypothesis) [12]. Adipose tissue is a source of inflammatory cytokines that are responsible for systemic inflammation. Testosterone may regulate inflammation by acting on adipose tissue [13]. Lipoprotein lipase present on the surface of adipocytes hydrolyzes circulating triglyceride-rich lipoproteins to free fatty acids that are taken up by the adipocytes and then esterified back into triglycerides for storage. Testosterone reduces the lipoprotein lipase activity in adipose tissue and inhibits the triglyceride storage. Testosterone deficiency is associated with enhanced triglyceride storage and subsequent increase in total body fat [12]. Insulin resistance in testosterone deficiency is mediated by body composition-dependent effects, including increased adipocyte differentiation (visceral obesity) and decreased myocytes differentiation (sarcopenia), and body composition independent effects such as increased inflammation (tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and IL-6), decreased adiponectin and reduced mitochondrial function [14]. Hyperinsulinemia acts on the kisspeptin neurons to decrease kisspeptin signaling, which, in turn, acts on the gonadotropin-releasing hormone (GnRH) neurons to decrease GnRH release and thereby luteinizing hormone (LH) secretion [15]. In obesity induced adipocyte dysfunction, there is increased leptin release from adipocytes, which, in turn,

causes a central leptin resistance at the hypothalamo-pituitary level. This decreases hypothalamic kisspeptin gene expression, which subsequently decreases GnRH and LH secretion and worsens testosterone deficiency [16]. Leptin directly inhibits the stimulatory effects of gonadotropins on the Leydig cells to further decrease testosterone secretion, via peripheral leptin resistance [17]. Testosterone suppresses leptin secretion from adipose tissue. Androgen receptors (AR) are present in adipose tissue, the density of which is positively regulated by testosterone. Testosterone and estradiol, activate androgen receptors (AR), and estrogen receptors (ERα and ERβ) within the visceral adipose tissue, with a resultant decrease in the release of adipokines (leptin, TNF-*α*, IL-6, osteoprotegerin (OPG), monocyte chemoattractant protein-1α) and increase in the release of adiponectin and visfatin [18]. Testosterone improves insulin sensitivity and reduces the C-reactive protein (CRP) from the liver [19]. Testosterone can decrease adipogenesis via a direct androgen-receptor-dependent mechanism [20]. The major hormones controlling lipolysis in adipose tissue are catecholamines, which are acting via adrenoreceptors. Testosterone upregulates the beta-adrenoreceptor number; activates adenyl cyclase to produce cyclic adenosine monophosphate which, in turn, stimulates hormone-sensitive lipase to accelerate lipolysis; and decreases total body fat mass [2]. In addition, androgen deficiency could further accelerate adipose tissue expansion (adipocyte hypertrophy and dysfunction) and therefore exacerbate obesity, which in turn enhances hypogonadism, leading to an endless loop in which abnormal adipose tissue expansion impairs testosterone production, resulting in further accumulation of adipose tissue [12].

2.3 Pathophysiological roles of sex hormones on bone metabolism

2.3.1 Effects of androgens on bone

Androgens, the most important of which is testosterone, affect bone remodeling in men directly by binding to androgen receptors (AR) and indirectly by binding to estrogen receptors (ER) [21]. ERα is mainly associated with bone metabolism. AR and ER are expressed by mesenchymal stem cells, osteoclasts, osteoblasts, and osteocytes [22]. In this way, testosterone affects bone growth during puberty as well as bone remodeling in adults. Androgens indirectly regulate the reproduction and activity of osteoclasts and thus bone breakdown through the modulation of the receptor activator of nuclear factor κB ligand (RANKL), which is secreted especially by osteoblasts and osteocytes, this process begins with the binding of RANKL to the RANK receptor on osteoclasts and their precursors. OPG acts as a natural antagonist that binds RANKL and thus blocks RANK activation [23].

Testosterone and even more potent dihydrotestosterone (DHT) also act anabolically by stimulating the proliferation and differentiation of osteoblasts and osteocytes [24]. Testosterone inhibits apoptosis of bone-building osteoblasts [25]. Locally generated DHT has a direct effect on bone [26]. Androgens also act on bone cells indirectly through cytokines. Testosterone controls local production of growth hormone and insulin-like growth factor 1 (IGF-1) [21]. Androgens help maintain bone mass and strength by slowing bone turnover and by maintaining the balance between breakdown and building through the RANKL–RANK–OPG system. They also affect the lifespan of osteoclasts [27].

Leydig cells of the testes, under the influence of LH, in addition to testosterone, form and secrete insulin-like peptide 3 (insulin-like peptide 3; INSL3), which plays an important role in the formation of osteoblasts [28]. Secretion of INSL3 is decreased in hypogonadal men [29]. Leydig cells express the CYP2R1 gene, which encodes 25-hydroxylase, one of the key enzymes for vitamin D activation [30]. Defect of Leydig cells leads to hypogonadism with decreased testosterone and INSL3. In addition to these, activation of vitamin D is disturbed, all of which contributes to the increased risk of osteoporosis [31]. Bone affects the functioning of Leydig cells through osteocalcin, which is produced by osteoblasts. It stimulates the formation of testosterone as well as the activation of vitamin D [32].

2.3.2 Effects of estrogens on bone

In men, estrogens, the most important of them estradiol, are produced by conversion from androgens with the help of the enzyme aromatase, which is present in many tissues, including in the bones in fibroblasts, osteoblasts, and osteoclasts, as well as in fat and bone marrow [33]. They work by binding to estrogen receptors on osteoblasts, osteoclasts, and osteocytes [27]. Through the RANKL–RANK–OPG system, they

stimulate apoptosis of osteoclasts, inhibit their differentiation and thus reduce bone degradation [34]. Estrogens direct the differentiation of mesenchymal stem cells into osteoblasts and thus increase their number, in addition to inhibiting osteocyte apoptosis. In addition to direct effects, estrogens have a beneficial effect on other hormones and cytokines involved in bone remodeling, especially growth hormone [35].

Testosterone deficiency due to aging leads to reduced aromatization and a relative lack of estrogens, which accelerates the physiological process of bone loss [36].

3 Comprehensive treatment strategies for obesity-related hypogonadism

Lifestyle modifications and increased physical activity is the mainstay of non-surgical therapies in males with functional hypogonadism. In selected cases testosterone treatment can be added according to the guidelines. Next option is pharmacological treatment with glucagon-like peptide 1 receptor agonist (GLP-1 RA) analogs, but most of the weight lost with diet, exercise, and after GLP-1 RA treatment is regained in the long-term in majority of patients. Consequently, bariatric surgery is another option for reducing body weight and treating hypogonadism associated with obesity. Anti-estrogens, including selective estrogen modulators or aromatase inhibitors still represent further possible off-label options, but long-term side effects of these drugs on sexual function and bone parameters constitute major limitations to their usage [37].

In a meta-analysis, diet-associated weight loss (mean 9.8%) increased testosterone by 2.9 nmol/L (84 ng/dL) and surgical weight loss (32%) by 8.7 nmol/L (251 ng/dL) [38]. Longitudinal data from EMAS have reported similar findings in older overweight men (mean age 58 years; BMI, 27.6 kg/m^2). During 4.4 years, weight loss of 5% was associated a significant rise in SHBG, probably because insulin resistance improved. This weight loss of 5% was associated with an increase in total testosterone by 2 nmol/L (58 ng/dL) but not in free testosterone. Weight gain was associated with opposite changes. Weight loss >15% was associated with more marked increases in total testosterone, LH, and free testosterone [39]. Significant weight loss can normalize the HPT axis, probably by amelioration of the obesity-associated hypothalamic–pituitary–gonadal axis suppression [40]. It is important to underline that increase of testosterone level in most of these studies never reached normal threshold of testosterone level [41].

3.1 Lifestyle modifications

A fundamental approach for weight loss is a calorie-restricted diet. In a meta-analysis of 22 studies on a sample of 567 obese patients with functional hypogonadism who lost weight with a diet, it was shown that for every 5 kg of weight loss, the value of total testosterone increases by 1 nmol/L [42]. Patients effectively lost weight with a diet with a very low calorie intake (up to 800 kcal/day) or with a diet with a low calorie intake (up to 1200 kcal/day). At the same time, concentrations of total testosterone and free testosterone and SHBG increased, insulin resistance and leptin concentration also decreased [43]. A meta-analysis found that significant weight loss can induce an increase in testosterone levels, along with an increase in SHBG, calculated free testosterone, LH, and follicle-stimulating hormone (FSH), and a reduction in estradiol [44]. This has been seen in several observational studies. Low-calorie diet caused a weight loss of 9.8% and therefore induced an average testosterone increase of less than 3 nmol/L, while bariatric surgery, with a weight loss of 32% resulted in testosterone levels increase that was three times higher (almost 9 nmol/L) [45].

With a Mediterranean diet and a 170–250 kcal lower daily energy intake in combination with moderate physical exercise for 150 minutes per week, study subjects improved their body composition and slightly increased the concentration of total testosterone in hypogonadal group, but remained in hypogonadal range [46]. Physical exercise also affects the increase in testosterone concentration, which was proven in a sample of obese men who were included in a 12-week program of 90-minute guided aerobic exercise one to three times a week [47]. Resorting only to diets with strict calorie restriction in treatment of functional hypogonadism is obviously not very effective. Furthermore, weight loss and physical activity are not effective in elderly and frail obese patients. This type of approach to the treatment of hypogonadism is therefore not recommended for this population.

3.2 Pharmacotherapy of obesity

Following the introduction of GLP-1 RAs, which enable effective weight loss, data are becoming available on their role in the treatment of functional hypogonadism. GLP-1 RAs are a group of incretin drugs that were initially used to treat type 2 diabetes (T2D), but they also act directly on the hypothalamus to inhibit gastric emptying [48]. The combined central and peripheral actions of GLP-1 RAs promote satiety, decrease hunger, and ultimately reduce food intake [49].

Results of a retrospective study on a sample of 51 patients with T2D who were treated with the GLP-1 RA exenatide for 6 months showed that patients lost an average of 2.27 kg during treatment. At the same time, the average concentration of testosterone in all patients did not increase significantly, but the results of additional analysis showed that the concentrations of total and free testosterone increased in the group of patients with lower values of total testosterone at baseline (<11.1 nmol/L) [50].

In a prospective 4-month study on a sample of 110 obese patients with functional hypogonadism, one group received injections of human chorionic gonadotropin at a dose of 2000 IU twice weekly, other injections of liraglutide at a dose of 3 mg daily, and third transdermal testosterone at a dose of 60 mg daily. In the group of patients treated with liraglutide, body weight decreased by 10.3%, BMI by 16.7%, and abdominal circumference by 8.3%. In patients treated with liraglutide, the concentration of testosterone increased more than in the other two groups, and they also achieved the best score of erectile dysfunction according to the IIEF questionnaire [51].

Results of a retrospective analysis of T2D patients with ED defined by the IIEF (International Index of Erectile Function) questionnaire and pre-pubertal (i.e. Klinefelter syndrome) and post-pubertal onset hypogonadism are also interesting. Patients were treated with both intramuscular injections of testosterone undecanoate at a dose of 1000 mg every 12 weeks and with metformin at a dose of 2000–3000 mg/day for at least 12 months. When response to treatment was poor, additional treatment with subcutaneous injections of the GLP-1 RA liraglutide was introduced. In these patients, by the 24th month of treatment, body weight and BMI decreased, testosterone levels normalized, and ED and glycemic control also improved [52].

The most common side effects of GLP-1 RA treatment are gastrointestinal adverse events (GI AEs). According to the literature addressing clinical trials, GI AEs usually develop in 40%–70% of treated patients, although they have sometimes been reported in up to 85% patients [53]. GI AEs effects mandate discontinuation of the drug. Review encompassing 30 trials focusing on GLP-1 RA safety in people with T2D concluded that the risk of inflammation of the gallbladder or pancreas associated with this medication was generally low [54]. Association between pancreatic, thyroid, breast and cholangiocarcinoma and GLP-1 RA is controversial and real-world evidence of GLP-1 RA-associated tumor risk is currently limited [55].

Important aspect of treatment of obese males is the rebound effect following medication withdrawal. One year after withdrawal of subcutaneous semaglutide 2.4 mg administered once-weekly and lifestyle intervention, participants regained two-thirds of their prior weight loss, with similar (negative) changes in cardiometabolic variables [56].

3.3 Metabolic surgery

The most effective long-term treatment for obesity is metabolic surgery, and the most common procedures are laparoscopic partial gastrectomy and Roux-en-Y gastric bypass (RYGB). Depending on the type of intervention, patients can lose more than 25% of their initial body weight, and then – in most cases – maintain the reduced body weight for more than 10 years [57]. The results of a meta-analysis of 45 studies showed that functional hypogonadism was present in 64% of patients with morbid obesity, but after surgical intervention as many as 87% of patients had normal testosterone level. The total testosterone concentration increased on average by 8.1 nmol/L, SHBG by 22 pmol/L, and the estradiol concentration decreased by 22 pmol/L [58]. In research on a sample of 33 obese patients with functional hypogonadism, their BMI value decreased by 9.1–18.8 kg/m^2 in 6–18 months after various metabolic surgeries [59].

Treatment of men with obesity and functional hypogonadism with metabolic surgery is successful in the long-term. After surgery, 34 obese adolescents with hypogonadism were followed for 5 years. They lost the

most weight by the second year after the procedure. Their BMI decreased by an average of 18.6 kg/m^2, after which the body mass began to gradually increase again. With a decrease in body weight, the concentrations of total testosterone (10.9 nmol/L) and free testosterone (170 pmol/L) and SHBG (19.3 nmol/L) increased. **The biggest hormonal increase was observed after two years**. The increase in body weight was associated with a decrease in the value of hormonal parameters. Despite partial weight gain, the proportion of patients with hypogonadism remained low (22%) after five years [60].

The mechanisms linking HPT axis, obesity and metabolic surgery are not completely understood, and surgical weight loss is sometimes not sufficient to ameliorate sexual function and, consequently, the quality of life (QoL) [61]. The improvement of testosterone plasma levels may favor a condition in which the restoration of muscle strength and resistance leads to increased physical activity, amelioration of obesity-related sarcopenia and positive effects on osteopenia [62]. Considering the experimental evidence regarding the influence of bone on testicular function, metabolic surgery may present some additional effects. Samavat et al observed that osteocalcin, a bone hormone produced by osteoblasts, which seems to play a role on the regulation of testis function, increased after bariatric surgery, and this increase was parallel with increase of free testosterone levels [63].

Metaanalysis of 54 studies showed that effects of bariatric surgery were associated with a significant increase in the levels of LH, FSH, total testosterone, and SHBG hormone levels with a significant decrease in the levels of estradiol and dehydroepiandrosterone (DHEA) [64]. Results of an observational study of 35 men undergoing bariatric surgery showed that a significant weight loss was observed 1 year after the surgery with an increase in total and free testosterone, SHBG and FSH and decrease in estradiol and prolactin [65]. Further studies have also demonstrated that decrease in visceral adipose tissue that is known to contain higher levels of aromatase enzyme, leads to increase in free testosterone and these effects are thought to be long lasting [61]. Studies have shown favorable outcomes in terms of reduction in pro-inflammatory mediators following bariatric surgery. This is seen in a study of 20 morbidly obese subjects undergoing gastric banding. One year post operatively they exhibited significant reduction in BMI and high-sensitivity CRP (hs-CRP) [66]. A significant improvement in adiponectin, leptin and some metabolic parameters (total cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides) are also observed in some studies [67,68]. Bariatric surgery also has beneficial effects on hunger, not only due to gastric restriction but also to the modulation of appetite-regulatory hormones coming mainly from the gut, such as ghrelin, cholecystokinin (CCK), peptide tyrosine tyrosine (PYY), and GLP-1 [69]. Insulin-like factor 5 (INSL5) is a hormone secreted primarily by the enteroendocrine cells of the colon and rectum that has been implicated in both mealtime hunger and the regulation of body weight in animals given its orexigenic properties. INSL5 belongs to the insulin superfamily of peptides (relaxins) consisting of insulin-like growth factors 1 and 2 (IGF-1 and IGF-2), and insulin-like peptides 3, 4, 5, 6, and 7 (INSL 3–7) [70]. Relaxins have many different roles, such as regulation of female and male reproductive tract functions, signaling in the central nervous system, vasodilation and heart stimulation in the cardiovascular system, regulation of fibrotic processes, and wound healing. It is also known that decrease in INSL 3, which is produced in Leydig cells, is associated with male hypogonadism, aging and obesity and also has important function in osteoblast function [30].

3.4 Testosterone therapy

For men with symptomatic hypogonadism, there are many potential clinical benefits of TTh, including improvements in libido, erectile function, muscle strength and body composition (including decreased fat mass, increased lean mass, and improved BMD), mood, and cognition [71–74]. The potential clinical benefits of TTh must be carefully weighed against potential risks. Potential adverse effects of testosterone replacement include erythrocytosis, increases in prostate-specific antigen (PSA) and worsening of prostate disorders (including benign prostatic hyperplasia), dermatologic effects, including acne and skin irritation, and worsening of an existing obstructive sleep apnea. In addition, exogenous testosterone administration leads to the suppression of LH, decreased intra-testicular testosterone concentrations, and reduced spermatogenesis, therefore TTh is not appropriate for hypogonadal men desiring fertility [5,6].

For patients undergoing TTh individual approach is important. Regular monitoring and follow-up according to the guidelines are crucial. This constitutes checking testosterone levels and clinical symptoms

of hypogonadism at every visit and allows discovery and management of any potential side effects. Key aspects of monitoring include checking hematocrit levels, lipid profiles, liver function, and PSA [5,6].

4 Impact of weight loss on obesity-related functional hypogonadism

4.1 Cardiometabolic effects of weight loss

Diabetes, arterial hypertension, and hyperlipidemia are among the most common risk factors for stroke and atherosclerotic cardiovascular diseases (CVD). Weight loss has multiple clinical benefits. A 3% weight loss significantly improved their insulin sensitivity, acute insulin response, triglycerides, non-HDL cholesterol concentration, LDL cholesterol, and high-density lipoprotein (HDL) cholesterol [75]. Modest weight loss of 5%–10% has been shown to substantially benefit in all metabolic risk factors for overweight individuals. Modest lifestyle interventions are also effective in reducing the risk of developing T2D in individuals with glucose intolerance [76]. Clinical guidelines from the American Heart Association and ADA recommend weight loss of 5%–8% for overweight and obese individuals to prevent CVD [77]. Findings of 16 years study on 63.567 patients suggest that clinically sustained weight loss significantly lowers incidence of cardiometabolic outcomes and favorably affects the incidence and severity of obesity-related disease [78].

4.2 Weight loss and quality of life

Significant bi-directional associations was found between a weight loss intervention and mental health and QoL, including substantial improvements in physical QoL with obesity treatment [79]. Losing weight helps improve many aspects of mental health, sleep, energy, vitality, and mood. All of these can have a direct impact on confidence, self-esteem and social life. Losing weight also improves many of the chronic conditions that can contribute to depression and other mental illnesses [80]. Results of a metaanalysis of 68 articles showed that weight loss resulted in improvement of sexual function in obese males [81]. Lifestyle modifications such as dietary restrictions, increased weekly exercise, lowering BMI, and glycemic management have been proposed as ways to lower the likelihood of developing ED or to mitigate complications when ED is already present [82]. Weight loss could improve sexual response through multiple pathways: it might have positive endocrine effects resulting from decreased adipose tissue; it might improve overall health and prevent comorbidities such as CVD, T2D, and MS, all known to affect sexual functioning; or it might influence psychological parameters such as self-esteem, confidence, body image, depression, and anxiety [83]. Furthermore, because endothelial dysfunction and dyslipidemia are associated with visceral adipose tissue accumulation, weight loss could improve hemodynamics and restore sexual function. Study involving 372 obese men evaluated the effects of weight-loss intervention, including dietary support group meetings and increased physical activity, on sexual and erectile function. At 1-year follow-up, 22% of men in the intervention group reported improved erectile function and 8% reported worsened erectile function. At 2-year follow-up, BMI had decreased further in the intervention group and sexual function scores had further improved compared to the control group, which showed unchanged sexual function scores [84]. ED occurring in abdominally obese men is positively correlated with endothelial dysfunction, chronic inflammation, and insulin resistance. In a study of 68 men with and without diabetes on a low-carbohydrate diet and regular physical activity, weight loss imparted significant effects. Although fasting glucose and lipid levels were not affected, insulin sensitivity significantly improved in the intervention group, and increased testosterone, improved erectile function, and increased sexual satisfaction correlated well with weight loss [43]. Esposito et al. reported that the intervention group showed significant decreases in body weight, BMI, blood pressure, and levels of glucose, insulin, total cholesterol, and triglycerides after 2 years. ED symptoms appeared to be alleviated, as evidenced by 31% of men regaining sexual function [85].

4.3 Changes in bone mineral density after weight loss

Observational studies showed a **significant decrease in BMD and increased bone turnover** in subjects in the first year after bariatric surgery due to rapid weight loss, with the decrease in BMD continuing even after

weight stabilization. **This reduction is primarily in the cortical bone**, which means a higher risk of non-vertebral fractures [86]. Reductions in BMD and cortical bone thickness and area assessed above the tibia by high-resolution computed tomography (CT) were more pronounced after RYGB gastric bypass [87]. Although successful in treating obesity, metabolic surgery is not a cosmetic procedure, but rather a surgical procedure that changes the digestive tract anatomically and physiologically, so the risk of complications is relatively high. Changes in gastrointestinal tract motility and nutrient digestion, hypoglycemia, malabsorption, and dysbiosis may also occur, as well as gastroesophageal reflux, abdominal pain, malnutrition and deficiency of vitamins and minerals, gallstones, and surgical complications [88].

Despite the positive effects of bariatric surgery, concerns have been raised over potential adverse effects on the skeletal system, e.g. **increased bone loss and bone fragility** [89]. The bone loss that occurs after bariatric surgery is multifactorial. Proposed mechanisms include skeletal unloading, abnormalities in calciotropic hormones, as well as changes in gut hormones. Increased bone turnover may be associated with physiological adaptation of the skeleton to unloading, or it may be associated with pathophysiological changes like increased parathyroid hormone (PTH) [90].

Long-term complications after gastrectomy **include osteoporosis and osteomalacia**. This may be explained by secondary hyperparathyroidism, which may occur after surgery due to malabsorption of vitamin D and decreased calcium intake and absorption, increased PTH due to lower vitamin D absorption; decreased plasma leptin and ghrelin, and increased concentration of adiponectin [91]. Osteomalacia is characterized by low BMD and increased risk of fractures. Additional features like bone pain and muscle weakness, raised serum alkaline phosphatase, hypocalciuria and secondary hyperparathyroidism are often not recognized. This may lead to a misdiagnosis of osteoporosis and prescription of antiresorptive therapy. Such treatment carries a high risk of hypocalcemia if the underlying vitamin D and calcium deficit is not corrected with high-dose supplementation first [92]. Bariatric surgery not only causes vitamin D malabsorption but also reduces calcium absorption by bypassing the duodenum and proximal jejunum, which are the predominant sites of calcium uptake (active, transcellular, 1,25(OH) D-mediated calcium uptake). Based on a study that examined the effects of RYGB on intestinal fractional calcium absorption (FCA), FCA decreases dramatically after RYGB even with calcium intake and vitamin D ≥ 30 ng/mL level. The authors advised the patients to increase their calcium intake for preventing calcium-induced disorders and maintaining calcium homeostasis [93]. Sleeve gastrectomy affects bone metabolism through several mechanisms; decreased mechanical unloading following weight loss, decreased ghrelin secretion, decreased calcium absorption due to decreased gastric acid secretion, and increased gastric emptying rate [94]. In general, the results of studies show that despite adequate levels of vitamin D (30 ng/mL) and recommended calcium intake (1200 mg/day) with the help of diets and calcium citrate supplements, calcium absorption in the intestine remains much lower than average in patients who underwent RYGB surgery 6 months after the procedure [93].

In addition to bone density and bone turnover, microarchitecture is an important property contributing to bone strength and fracture risk [95]. Bone biopsies at baseline and 4 years post-operatively in a group of patients who underwent bariatric surgery demonstrated **decreased cortical thickness**, while trabecular bone volume increased [96]. A detailed discussion of the complex and procedure specific hormonal changes that occur after bariatric surgery includes declines in leptin after bariatric surgery, which may be associated with increased osteoclast activity [97]. Decrease in leptin after RYGB correlated with an increase in bone resorption [98].

Development of secondary bone loss after bariatric surgery and resultant increase in skeletal fragility is therefore an important issue of bariatric surgical procedures [90]. That is why guidelines emphasize the periodic evaluation of BMD in patients undergoing bariatric surgery [89]. To maintain calcium homeostasis – in addition to PTH and vitamin D – several endocrine and paracrine factors such as prolactin, estrogen, and insulin-like growth factor directly stimulate intestinal calcium absorption. This cycle is controlled by negative self-regulation. A significant point is a decrease in calcium absorption by intestinal epithelial cells at high calcium concentrations in the gastrointestinal tract [99].

5 Role of testosterone therapy in managing obesity-related functional hypogonadism

Men with functional hypogonadism who do not experience improvement in symptoms after non-pharmacological measures can be treated with testosterone treatment for at least six months according

to the current guidelines on hypogonadism [6]. After this period, the clinical benefit of the treatment is assessed and, in the absence of clinical improvement, the causes of hypogonadism are re-examined, the testosterone preparation is changed, or the treatment is discontinued. Long-term treatment with testosterone produces various beneficial effects on metabolic parameters including weight loss and decreased waist circumference independently of diet and exercise. Long-term studies have been shown that **these effects are superior to other drugs alone or in combination with behavioral and lifestyle modifications** [100,101].

Guidelines on obesity from 2016 suggest TTh as an approach to weight loss in men with confirmed hypogonadism and obesity who are not seeking fertility in addition to lifestyle intervention [102].

5.1 Cardiometabolic effects of testosterone therapy

There is considerable evidence from large randomized clinical trials that testosterone treatment improves glycemic control, individual parameters of metabolic syndrome, and sexual symptoms in hypogonadal men with metabolic syndrome and/or T2D [100,101]. The improvement is due to the direct effect of testosterone on the reduction of insulin resistance through an increase in muscle mass or through a reduction in BMI and a reduction in visceral obesity [103]. Testosterone leads to an increase in the proportion of lean body mass, which cannot be achieved with antidiabetic or obesity drugs [104]. Some studies have observed a neutral effect of testosterone treatment on certain parameters, such as glycated hemoglobin (HbA1c) and lipid profile, as well as on endothelial function [105,106]. Differences in the mentioned results may be the result of different research design, number and selection of subjects, use of different forms and doses of testosterone, and different treatment duration. In studies with the parenteral form of testosterone (testosterone undecanoate), almost 100% concordance was found, while with the transdermal form it was at least 80% [100,107].

The results of long-term treatment with testosterone in men with impaired glucose tolerance and a marginally reduced testosterone value are also encouraging. In 316 men, after 8 years of treatment, it was found that treatment with testosterone prevents the formation of T2D, normalizes glycemia (fasting glucose and HbA1c) and significantly reduces the risk of cardiovascular events and mortality compared to men who do not receive testosterone. To improve the symptoms of sexual function and other symptoms of hypogonadism, the normalization of the testosterone level, which occurs almost immediately after the first injection of testosterone, is key. In the group receiving parenteral testosterone, the average value of total testosterone was 16.8 nmol/L [101]. In the same study, prediabetes progression to T2D was observed in 40.2% of men after 8 years in the group not treated with testosterone. In addition, testosterone treatment resulted in a statistically significant loss of body weight of 8.6% (9.2 kg), compared to an increase of 9% (8 kg) in the untreated group of men.

Even longer, 11 years of testosterone treatment in 823 men with hypogonadism (among whom 57.6% were obese, 34.7% overweight fed and 7.7% normal weight) resulted in weight loss, decreased waist circumference and BMI, while body weight increased in the untreated group. It is also interesting that there was a 20% weight loss in the group of obese men, the magnitude of which is comparable to the effects of bariatric surgery. This study also observed a statistically significant increase in testosterone levels (by 8.5 ± 0.2 nmol/L) [100].

A multicenter Australian study (T4DM) compared the impact of lifestyle changes and supplemental TTh in obese men without hypogonadism (total testosterone > 12 mmol/L) and high-risk for T2D. They studied whether testosterone treatment improves the benefits of lifestyle changes in terms of prevention or remission of T2D. After two years, the prevalence of T2D was statistically significantly lower in the group receiving testosterone compared to the group not receiving testosterone. Subgroup analysis showed that in the group of men with MTG, i.e. in those who had a high risk of developing T2D at the beginning of the study, testosterone treatment reduces the risk of developing T2D by 50%, while in the group with baseline newly detected T2D, testosterone treatment led to regression of T2D. In the aforementioned research, unlike the group that was treated only with lifestyle changes, an improvement in body composition, loss of visceral fat and increase in muscle mass as well as an improvement in the values of sexual parameters (assessed with questionnaires for the assessment of erectile function) were observed after two years. In the

group that did not receive testosterone, a decrease in muscle mass and an increase in visceral fat were observed. Since the subjects did not have hypogonadism, the effect of testosterone treatment to prevent T2D is probably independent of the baseline serum testosterone concentration. However, approximately three quarters of the study population had testosterone levels of 12 nmol/L or less, and it can be safely assumed that majority also had signs and symptoms of hypogonadism, in addition to the elevated waist circumference, which was an inclusion criterium [108]. The results of the T4Bone study, part of the larger T4DM study, which studied the effects of testosterone on bone microarchitecture in 1007 men aged 54–74 for two years, showed improvements in cortical and total bone in the group of men who received testosterone in addition to lifestyle changes [109].

Other benefits of testosterone treatment include reduction of insulin resistance and intima-media thickness, improvement of endothelial function and fatty infiltration of the liver, and better subjective well-being [103,110,111]. There is evidence that testosterone treatment also improves lipid profile [101], vitality, depressed mood [112], and cognitive function [113], which is an additional benefit of treatment of symptoms of testosterone deficiency. Low testosterone levels can contribute to poor motivation for a healthy lifestyle. Some studies have shown that testosterone treatment can increase motivation to eat and exercise [40].

5.2 Testosterone therapy and quality of life

TTh has demonstrated improvement in sexual function in young men with primary or secondary hypogonadism as well as in middle-aged men with mildly or moderately low testosterone levels [114]. While the effects on sexual activity in older men were controversial in older studies, the T trials demonstrated modest improvement in sexual interest and activity with TTh in elderly males with hypogonadism, with greater effects seen on libido and sexual activity than on erectile function. A meta-analysis showed that TTh is most effective when serum testosterone is <10.4 nmol/L [115].

The Sexual Function Study within the TRAVERSE trial aimed to find the efficacy of TTh in improving hypogonadal symptoms (sexual activity, libido, and erectile function) among middle-aged and older hypogonadal men reporting low libido with the primary outcome being change in sexual activity score. TTh was associated with significant improvement in sexual activity compared to placebo. The beneficial effects of TTh were maintained at 24 months, testosterone improved hypogonadal symptoms and sexual desire, but not erectile function [116].

TTh is thought to affect mood, energy, and health in multiple ways. Some trials have demonstrated significant improvements in the QoL with TTh. However, there are also shorter trials showing no significant effects of TTh on health-related QoL, such as 6 week lasting RCT on 32 men [117]. As pointed out TRAVERSE trial showed that TTh is associated with small improvements in mood and energy in hypogonadal men with and without significant depressive symptoms.

A meta-analysis on TTh in hypogonadal men vs placebo evaluated 23 randomized controlled trials (21 were placebo-controlled, two were active-controlled) involving 3090 participants. Compared with placebo, treatment with any TTh significantly improved QoL. The effect was largely attenuated in men with symptoms of depression [118]. Positive effects of testosterone on QoL were seen in large cohort of hypogonadal men of more than 1000 patients [119]. A smaller uncontrolled study comparing two different intramuscular testosterone for TTh in 40 hypogonadal men over a period of 90 weeks described marked improvements in scales of sociability, concentration, agitation, self-confidence, listlessness, dizziness, activation, depression, fatigue, anxiety, good mood, and aggression [120].

5.3 Impact of testosterone therapy on bone metabolism

A number of studies have shown positive effects of testosterone replacement therapy on BMD – particularly lumbar spine BMD – in testosterone-deficient men, although none of the studies were designed with the primary objective of determining the effect on a possible reduction in fracture incidence [121]. In young hypogonadal men, TTh prevents further bone loss and ensures the attainment of genetically determined

maximal bone mass [87]. The role of TTh in elderly men with osteopenia or osteoporosis and hypogonadism is less clear. Testosterone does increase lumbar spine BMD compared to controls, but there is a higher risk of treatment complications than in younger men [122].

There is evidence from The Bone Trial, that TTh improved volumetric bone density and estimated bone strength in the lumbar spine and at the hip in 211 men with functional hypogonadism after one year of testosterone treatment; benefits are more pronounced in the lumbar spine and trabecular bone [123].

In subgroup analysis of men with osteoporosis from a hypogonadism registry, 12 men with functional hypogonadism and osteoporosis at baseline had their osteoporosis markedly improved or even resolved, depending on the duration of TTh and regardless of bisphosphonate treatment [124].

In The Fracture Trial in 5000 men, a subtrial of the TRAVERSE trial, determined whether testosterone treatment reduced the risk of clinical fractures. The 3-year cumulative incidence of all clinical fractures was 3.8% in the testosterone group and 2.8% in the placebo group. The fracture incidence was also numerically higher in the testosterone group for all other fracture end points [125].

The effect of testosterone on increase of BMD is very important in the context of the effect of weight loss on BMD in men with functional hypogonadism. Men with functional hypogonadism on TTh can expect testosterone to help prevent further bone loss and increase BMD, especially in men with very low baseline serum testosterone [126]. The effect of testosterone on BMD increase is proportional to the degree of hypogonadism [127]. TTh in men with functional hypogonadism and osteoporosis increases BMD to a lesser extent than anti-osteoporosis drugs do [128]. There is no evidence that TTh reduces the risk of osteoporotic fractures. TTh should therefore be combined with one of the anti-osteoporosis drugs, which have been shown to reduce fracture risk, in men with functional hypogonadism and either severe osteoporosis or are at very high risk for bone fractures [129].

TTh is effective in ensuring bone anabolism and preventing sarcopenia, whilst also improving physical performance, which is an important factor against falls and frailty, both key factors involved in the occurrence of fractures, femoral bone fractures in particular [130,131].

6 Mechanism of action of GLP-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are pharmacological analogs of the endogenous incretin GLP-1, and they exert their therapeutic effects through pleiotropic actions on several organ systems. At the level of the pancreas, GLP-1RAs potentiate glucose-dependent insulin secretion from β-cells while simultaneously suppressing glucagon release from α-cells, thereby reducing hepatic glucose production and improving glycemic control. In the gastrointestinal tract, these agents slow gastric emptying, a property particularly evident with short-acting molecules, which mitigates postprandial glucose excursions [132]. Beyond peripheral effects, GLP-1RAs also act centrally by stimulating hypothalamic and brainstem GLP-1 receptors involved in appetite regulation, leading to increased satiety, decreased hunger, and reduced caloric intake. Collectively, these mechanisms translate into clinically meaningful reductions in body weight, improved glycemic indices, and favorable cardiometabolic outcomes [133]. Large outcome studies have confirmed their potential not only as glucose-lowering drugs but also as agents with cardiovascular and renal protective properties, which has expanded their role far beyond glycemic control alone [56].

7 General adverse effects of GLP-1 receptor agonists

Although GLP-1RAs are generally well tolerated, their use is accompanied by a characteristic adverse-event profile that warrants careful monitoring. Gastrointestinal intolerance, particularly nausea, vomiting, diarrhea, abdominal pain, and dyspepsia, represents the most common side-effect constellation [134]. These symptoms occur in a substantial proportion of patients, especially during the initial dose-escalation period, but tend to diminish with continued therapy and slow titration [135]. Beyond the gastrointestinal tract, gallbladder and biliary disorders, including cholelithiasis and cholecystitis, are observed more frequently among patients receiving GLP-1RAs, probably due to rapid weight loss and altered gallbladder motility [136]. Concerns about drug-induced pancreatitis have persisted for more than a decade, yet large meta-analyzes of randomized

controlled trials have not demonstrated a convincing increase in risk; nonetheless, vigilance remains prudent. Particular attention has been drawn to diabetic retinopathy complications, which were more common in semaglutide-treated individuals in the SUSTAIN-6 trial, especially in those with pre-existing retinopathy and rapid improvements in glycemic control [137]. With regard to thyroid safety, rodent studies have shown an increased risk of C-cell tumors, but observational data in humans remain inconclusive, with some analyzes suggesting a modest association and others finding no signal [138]. Finally, discontinuation of therapy is often followed by rapid weight regain, as demonstrated in the STEP-1 extension study, underscoring the chronic nature of GLP-1RA treatment in obesity management [139].

8 GLP-1 receptor agonists and loss of muscle mass

While the weight-reducing effects of GLP-1RAs are largely attributable to reductions in fat mass, accumulating evidence indicates that absolute lean body mass also declines during therapy [140]. In the STEP-1 body-composition substudy with semaglutide, patients lost a substantial amount of total and visceral adipose tissue, but lean mass was reduced by approximately three kilograms. Similar observations have been reported with tirzepatide in the SURMOUNT-1 trial, where dual GLP-1/GIP receptor agonism resulted in profound fat mass loss accompanied by measurable declines in lean tissue [141]. Meta-analyzes of randomized trials confirm that decreases in lean mass account for approximately one quarter to one third of total weight loss in patients treated with GLP-1Ras. Although the relative proportion of lean mass as a percentage of body weight may increase, the absolute loss of muscle tissue raises clinical concerns. Loss of skeletal muscle not only reduces physical strength and functional capacity but may also compromise long-term metabolic health, as muscle is a critical determinant of insulin sensitivity and energy expenditure. These findings highlight the importance of considering strategies to preserve or restore lean mass in individuals undergoing GLP-1RA-mediated weight reduction [142].

9 The potential role of testosterone therapy in obese, hypogonadal men treated with GLP-1RAs

Testosterone replacement therapy (TTh) constitutes the standard of care for men with confirmed, symptomatic hypogonadism, and its clinical benefits have been documented across multiple physiological domains. TTh consistently increases lean muscle mass and reduces fat mass, thereby exerting favorable effects on body composition. In addition, testosterone enhances sexual desire, erectile function, mood, and overall vitality, while also improving bone mineral density and correcting anemia through stimulation of erythropoiesis [143]. Beyond these established benefits, randomized clinical studies have demonstrated that testosterone therapy can improve insulin sensitivity and glycemic control in hypogonadal men with type 2 diabetes, suggesting an important metabolic role. In the context of GLP-1RA therapy, testosterone offers a biologically plausible means of counteracting the lean-mass losses observed during pharmacologically induced weight reduction. For obese men with functional hypogonadism, the addition of testosterone therapy may therefore represent a complementary strategy, enhancing muscle preservation, improving sexual and general well-being, changing body composition in favor of lean body mass and supporting comprehensive management of obesity-associated metabolic dysfunction [144]. Improvement in body composition may facilitate lifestyle changes – physical activity in particular – leading to further improvements.

The safety profile requires regular monitoring of hematocrit and prostate health, and fertility considerations remain important, but when prescribed according to established guideline recommendations, testosterone therapy has the potential to synergize with GLP-1RAs to address both the metabolic and androgen-deficiency components of disease [145].

10 Sports, weight loss, and testosterone

In men with obesity-related hypogonadism, structured exercise programs combining aerobic and resistance training offer the greatest benefits for testosterone restoration, muscle preservation, and fat reduction.

Resistance training should be based on progressive overload principles – starting with 2–3 sessions per week, targeting all major muscle groups (legs, back, chest, shoulders, arms, and core). Compound exercises such as squats, deadlifts, lunges, bench presses, overhead presses, and rowing are especially effective, as they recruit multiple large muscle groups and stimulate higher testosterone responses. Initial training can be performed at moderate intensity (e.g. 60%–70% of one-repetition maximum [1RM]) with 2–3 sets of 8–12 repetitions. Over time, resistance should be increased gradually by 2–5% for upper body exercises and 5%–10% for lower body exercises every 1–2 weeks to ensure continual adaptation and hypertrophy. Aerobic training should complement resistance sessions, with 150–210 minutes per week of moderate-intensity activities such as brisk walking, cycling, or swimming [47]. Studies confirm that such combined programs not only promote weight loss but also sustain lean body mass, improve insulin sensitivity, and raise serum testosterone [45]. This integrated approach is superior to diet alone and mitigates the risk of sarcopenia frequently observed during caloric restriction or GLP-1 receptor agonist therapy.

11 Diet and protein intake

Nutritional strategies for obese men with functional hypogonadism should avoid extreme regimens such as ketogenic diets and instead focus on a balanced, sustainable approach that supports both weight loss and muscle preservation. A Mediterranean-style diet, rich in vegetables, fruits, legumes, whole grains, nuts, fish, and olive oil, with reduced processed foods and refined sugars, has been shown to improve metabolic parameters and modestly elevate testosterone concentrations [46]. Caloric restriction of approximately 500–750 kcal/day below maintenance promotes gradual fat loss while minimizing muscle catabolism. Protein intake should be prioritized at 1.2–1.6 g/kg/day, distributed evenly across meals (20–30 g per meal), to maximize muscle protein synthesis and prevent sarcopenia. Lean animal sources (poultry, fish, low-fat dairy) as well as plant-based proteins (legumes, soy, pea, lentils) should be incorporated. Randomized studies demonstrate that high-protein, low-fat diets improve endothelial and sexual function, as well as reduce systemic inflammation, more effectively than low-energy diets alone [43]. Carbohydrates should be moderate (45%–55% of total energy), emphasizing complex, fiber-rich sources, to sustain training performance and metabolic flexibility, while fats should come primarily from monounsaturated and polyunsaturated sources (olive oil, nuts, fatty fish). This dietary framework provides both the macronutrient balance necessary for resistance training progression and the metabolic milieu to support normalization of hypothalamic–pituitary–testicular axis function and testosterone recovery.

12 Comprehensive treatment strategies

The management of obesity-associated functional hypogonadism necessitates a multifaceted and synergistic therapeutic paradigm, harmonizing pharmacologic, nutritional, and kinetic interventions to restore homeostasis within the metabolic–gonadal axis. Singular modalities – whether dietary restriction, pharmacotherapy, or testosterone replacement – rarely suffice when employed in isolation, given the intricate pathophysiological reciprocity between adiposity, inflammation, and androgen deprivation. A polytherapeutic construct that amalgamates GLP-1 receptor agonists (GLP-1RAs), testosterone therapy (TTh), resistance-oriented physical activity, and a protein-enriched, anti-inflammatory diet offers the most physiologically consonant and durable restoration of endocrine and somatic equilibrium. GLP-1RAs facilitate profound adipose depletion and amelioration of cardiometabolic risk, yet frequently precipitate decrements in lean mass; the concomitant administration of TTh mitigates such catabolic sequelae by invigorating myoanabolic pathways, augmenting bone mineral density, and reinstating androgen-dependent vigor. Concurrent progressive resistance training potentiates these effects through mechanotransductive stimulation, while a Mediterranean-style regimen furnishes the requisite substrates for cellular regeneration and endocrine recalibration. Collectively, this integrative therapeutic choreography not only reconstitutes hormonal and metabolic symmetry, but also engenders salutary transformations in body composition, vitality, and long-term cardiovascular resilience – heralding a refined standard of care for men with adiposity-driven hypogonadism, see Figure 1.

Figure 1. Comparative overview of therapeutic approaches for male hypogonadism and metabolic dysfunction. The figure summarizes the key advantages and disadvantages of three main management modalities: GLP-1 receptor agonists (GLP-1 RAs), lifestyle modification (diet and exercise), and testosterone therapy (TTh). GLP-1 RAs provide substantial weight loss and cardiovascular benefit but may lead to muscle loss, mood disturbances, and rebound weight gain upon discontinuation. Diet and exercise remain foundational but are limited by adherence challenges. Testosterone therapy exerts direct androgenic effects, supports muscle mass, and offers multi-systemic benefits, but may increase hematocrit and suppress spermatogenesis.

13 Conclusion

Testosterone plays an essential role in maintaining bone mineral density (BMD) and skeletal integrity in men. The molecular mechanisms through which testosterone influences bone metabolism are well established, and clinical studies consistently demonstrate benefits of testosterone therapy (TTh) on BMD, particularly in hypogonadal men with osteopenia or osteoporosis. However, no study to date has been designed primarily to assess whether TTh reduces osteoporotic fracture incidence, and there is currently no evidence that TTh alone decreases fracture risk. In men with functional hypogonadism and concomitant osteoporosis, the BMD gains achieved with TTh are smaller than those observed with dedicated anti-osteoporotic drugs. For hypogonadal men with severe osteoporosis or a very high fracture risk, it is therefore advisable to combine testosterone with an osteoporosis-specific drug, which has been shown to reduce fracture incidence in this population.

TTh should nonetheless be considered an important therapeutic option to improve both hypogonadal symptoms and BMD in symptomatic men with low bone mass. Beyond skeletal effects, testosterone exerts broad systemic actions: it reduces fat mass, increases muscle mass and strength, enhances sexual function, improves mood and cognition, corrects anemia, and favorably influences cardiometabolic parameters. The normalization of testosterone concentrations, particularly when combined with weight reduction and improved glycemic control, is associated with favorable metabolic and vascular outcomes in men with obesity-related hypogonadism.

The management of obesity itself requires a multimodal therapeutic strategy that integrates dietary modification, structured physical activity, pharmacotherapy, and, in selected cases, bariatric surgery. Lifestyle interventions alone are often insufficient in men with established hypogonadism, especially in elderly or frail obese patients, in whom sustained weight loss is rarely achieved. In such contexts, pharmacological agents such as GLP-1 receptor agonists have emerged as highly effective tools for substantial and durable weight reduction. However, these agents are consistently associated with concomitant decreases in lean body mass, including skeletal muscle. This unintended consequence may compromise physical function and bone health if not counteracted.

Table 1. Details on multi-systemic effects of testosterone therapy (TTh).

System	Primary effects	Clinical implications
Metabolic	Improves insulin sensitivity, reduces visceral fat, increases lean body mass	May decrease HbA1c and fasting glucose in hypogonadal men with T2DM or metabolic syndrome
Cardiovascular	Enhances endothelial function, reduces arterial stiffness, and improves lipid profile (↓ LDL, ↑ HDL modestly)	Evidence suggests reduced all-cause and cardiovascular mortality in adequately replaced men
Musculoskeletal	Increases muscle mass, strength, and bone mineral density	Reduces sarcopenia and fracture risk, particularly in older or obese men
Neurocognitive	Enhances mood, motivation, and cognitive performance	Associated with reduced depressive symptoms and improved executive function
Hematologic	Stimulates erythropoiesis (↑ hematocrit, ↑ hemoglobin)	Requires monitoring to prevent erythrocytosis
Sexual	Improves libido, erectile function, and sexual satisfaction	Particularly effective in hypogonadal men with ED unresponsive to PDE5 inhibitors
Inflammatory/ Immunologic	Decreases pro-inflammatory cytokines (e.g., IL-6, TNF-*α*)	May confer anti-inflammatory cardiovascular protection

In this setting, the combination of GLP-1RA therapy with TTh represents a rational therapeutic concept. While GLP-1RAs effectively reduce adiposity and improve glycemic control, TTh can preserve or restore lean muscle mass, stabilize BMD, and improve sexual and general well-being in hypogonadal men. Such an integrated approach addresses both the excess adiposity driving functional hypogonadism and the androgen deficiency that exacerbates musculoskeletal decline. It is particularly relevant when substantial weight loss is anticipated, as monitoring for bone and muscle loss becomes critical. In selected men, TTh prior to bariatric surgery may also help ameliorate the bone loss associated with rapid postoperative weight reduction.

The long-term safety of TTh in obese men with hypogonadism still requires clarification, particularly in combination with novel pharmacotherapies such as GLP-1RAs. This underscores the importance of a cautious, individualized treatment strategy, balancing potential benefits against risks. Large-scale, long-duration studies are needed to determine the combined effects of GLP-1RA therapy and testosterone on bone health, fracture risk, body composition, and cardiometabolic outcomes. Until such data are available, clinical practice should be guided by careful patient selection, guideline-based monitoring, and a personalized approach that integrates lifestyle measures, modern weight-loss pharmacotherapy, and hormone replacement where indicated Table 1.

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