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Metabolism and Target Organ Damage

Review

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New antidiabetic drugs' role in the management of testosterone deficiency and of the cardiovascular disease in hypogonadal diabetic men

Valentina Annamaria Genchi[1], Eleonora Zanni[2,3], Massimiliano Colzani[2,3], Celeste Lauriola[1], Angelo Cignarelli[1], Daniele Santi[2,3], Carla Greco[2,3]

[1]Department of Precision and Regenerative Medicine and Ionian Area, Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, University of Bari, Bari 70124, Italy.
[2]Unit of Endocrinology, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena 41125, Italy.
[3]Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria di Modena, Ospedale Civile di Baggiovara, Baggiovara 41126, Italy.

Correspondence to: Dr. Eleonora Zanni, Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria di Modena, Ospedale Civile di Baggiovara, Via Pietro Giardini 1355, Baggiovara 41126, Italy. E-mail: eleonora.zanni1995@gmail.com

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Abstract

The known hallmarks of type 2 diabetes mellitus (T2DM), such as hyperglycemia, insulin resistance, visceral adiposity, inflammation, endothelial dysfunction, and oxidative stress, are known to influence the hypothalamus-pituitary-gonadal axis, leading to functional hypogonadism. Both the consequent testosterone (T) deficiency and diabetes are recognized factors influencing cardiovascular (CV) risk. In this context, T replacement therapy showed an improvement in glycemic control and metabolic, anthropometric, and body composition parameters in hypogonadal diabetic individuals. Observational and randomized studies on T replacement therapy suggested the beneficial effect of this treatment on CV risk, although inconclusive results should still be evaluated, particularly when subgroups of patients have to be considered. In this setting, the novel antidiabetic drugs have demonstrated beneficial effects on T levels, due to their positive effects on the hypothalamic–pituitary–gonadal axis, in addition to a proven CV protective action. Thus, the combined metabolic and CV effects of T replacement therapy and novel antidiabetic drugs are of great interest. In this review, we aimed to summarize the present state of the art

concerning the association between T deficit and CV risk in diabetic people by analyzing the relationship between endogenous T and CV system in diabetic men. In particular, the impact of novel antidiabetic drugs on male hypogonadism, and the combined cardio-metabolic effects of T supplementation and novel antidiabetic drugs were discussed.

Keywords: Hypogonadism, testosterone, testosterone replacement therapy, diabetes mellitus, antidiabetic drugs, cardiovascular risk

INTRODUCTION

Diabetes mellitus (DM) is recognized as a condition at high cardiovascular (CV) risk, regardless of previous CV events. In particular, type 2 DM (T2DM) is usually accompanied by additional CV risk factors, such as obesity, hypertension, dyslipidemia, nonalcoholic fatty liver disease (NAFLD), and inflammation. Hyperglycemia, insulin resistance (IR), visceral adiposity, inflammation, endothelial dysfunction, and oxidative stress together represent the well-known hallmarks of T2DM. These conditions often alter the hypothalamus-pituitary-gonadal (HPG) axis function culminating in the development of functional hypogonadism consisting in low testosterone (T) circulating level and, in the long-term, in erectile dysfunction, reduced semen quality, and infertility as well[1-3]. Furthermore, functional hypogonadism could also lead to poorer glycemic control, lower insulin sensitivity, as well as increased fat mass in abdominal region due to the reduction of androgen-induced lipolytic effect[4]. Thus, T2DM is generally associated with hypogonadism, which, in turn, contributes to CV risk in diabetic males.

Hypogonadism in adult men is a clinical condition characterized by a decreased functional activity of the testes, resulting in decreased production and/or action of androgens and/or impaired sperm production[5]. The hypogonadism diagnosis requires serum T levels lower than the normal range (confirmed twice), together with the presence of specific clinical manifestations[5,6]. However, no validated serum T cut-off level has been established, but different thresholds have been proposed so far. Thus, either total T serum levels < 12 nmol/L (350 ng/dL), or T < 11 nmol/L (320 ng/dL) in middle-aged and elderly men[7,8] could be considered to define hypogonadism[5,8-10]. In general, T serum levels lower than 8 nmol/L (230.5 ng/dL) are widely accepted to define severe hypogonadism[5,9,10]. In the gray zone between 8 and 10-12 nmol/L, the presence of hypogonadism-related symptoms should be checked to confirm the diagnosis. In particular, sexual dysfunction (i.e., reduced libido, reduced spontaneous or stimulated penile erection, and erectile dysfunction), hot flashes, reduced semen volume, and decreased hair in androgen-dependent areas are the main signs and symptoms detectable [Figure 1].

Hypogonadism is strongly associated with metabolic disorders such as obesity, hypertension, diabetes, and dyslipidemia. Clinically, T deficiency is correlated with increased fat mass, reduced insulin sensitivity, impaired glucose tolerance, and elevated triglyceride and total cholesterol[11]. In particular, the association between DM[1], prediabetes[12] and male hypogonadism has been largely claimed and proven. In addition, many studies showed that T deficiency *per se* is an independent risk factor of CV and all-cause mortality[13], likely due to the direct effects of T on myocardial and vascular structure and function. Moreover, considering hypogonadism treatment and CV safety in the general population, and in particular in DM, the evidence from literature is still inconclusive. In this context, the potential effect of androgen therapy on the CV risk of males with DM remains far from being completely elucidated. With this in mind, the objectives of the review are to investigate: (1) evidence and controversies of T treatment and the CV risk in diabetes; (2) impact on male hypogonadism of novel antidiabetic drugs with proven CV protective effect; and (3) combined cardio-metabolic effects of T supplementation and novel antidiabetic drugs.

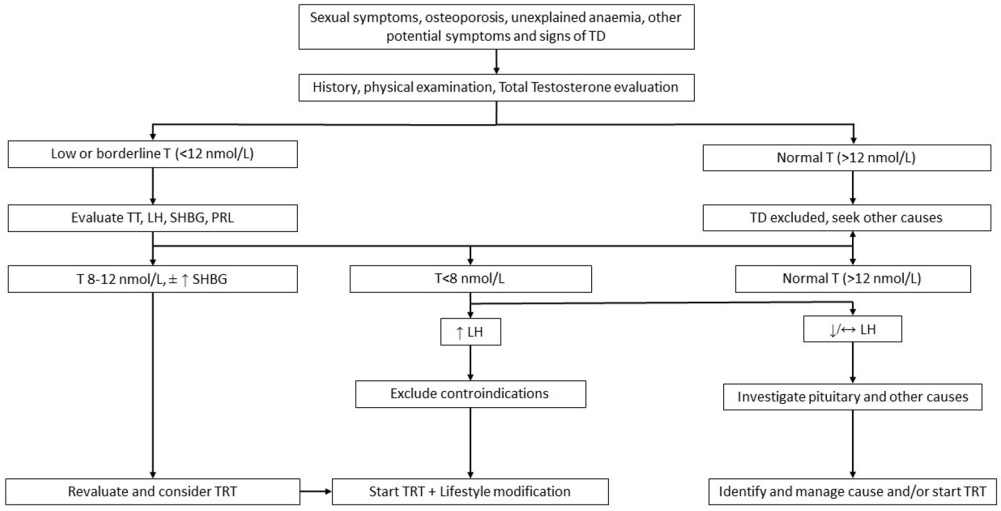

Figure 1. Evaluation and management of Testosterone Deficiency. TD: testosterone deficiency; TT: total testosterone; LH: luteinizing hormone; SHBG: sex hormone binding globulin; PRL: prolactin; TRT: testosterone replacement therapy.

DIABETES AND MALE HYPOGONADISM: A BIDIRECTIONAL RELATIONSHIP

Epidemiology

Several cross-sectional studies consistently demonstrated that subnormal T serum levels are common in men with diabetes, regardless of the type[14-20]. Overall, hypogonadism prevalence in males with T2DM ranges from 26% to 48%, considering total T (TT) serum levels[21-26], and from 19% to 57%, evaluating free T (FT)[21,22,24,25,27,28]. Thus, it could be expected that approximately more than one-third of T2DM men suffer from hypogonadism. Although hypogonadism is a common pathophysiological condition that occurs with increasing age, T deficiency has been observed in T2DM men also before 35 years[28], and already at the time of T2DM diagnosis[25], suggesting that this association is evident at a young age when diabetes is present. Accordingly, the prediabetes condition results are also associated with hypogonadism, with an overall calculated average prevalence ranging from 24% to 35%[12]. On the contrary, T deficiency prevalence seems to have a lower prevalence in type 1 DM (T1DM). The studies conducted in these subjects revealed a prevalence of hypogonadism ranging from 0 to 9.5% considering TT[21,22,24,28-30], and 3%-22% when FT levels were evaluated, respectively[21,22,24,28]. However, limited information is available on latent autoimmune diabetes in adults (LADA), in which hypogonadism prevalence is scantly reported, accounting for 8.2% of cases in one report[31].

As a confirmation of this association, whether hypogonadism is a common finding in diabetic men, a potential protective role of T on T2DM development has been suggested so far. Indeed, higher T serum levels in men seem to be protective against T2DM[32] and prediabetes[33] risk.

Overall, lower T serum levels in diabetics are generally associated with reduced gonadotropin (Gn) production, representing hypogonadotropic hypogonadism[27,34]. Only several diabetic subgroups populations show either T deficiency with inappropriately normal follicle-stimulating hormone (FSH) and luteinizing hormone (LH)[14], or high gonadotropins serum levels in subgroups of individuals with diabetic neuropathy[35], the latter representing hypergonadotropic hypogonadism.

Why are diabetes mellitus and hypogonadism associated?

The IR represents one of the main pathogenetic mechanisms of diabetes, at least considering T2DM. At the same time, several studies reported an association between IR and low T serum levels in men[36-38]. In line with this mutual influence, the relationship between DM and hypogonadism appears to be bidirectional[39].

From a molecular point of view, T and insulin can influence each other. Indeed, T leads to a non-genomic activation of several signaling factors which contribute to insulin receptor functioning, such as protein kinase B (Akt), extracellular signal-regulated kinase (ERK), and mechanistic target of rapamycin (mTOR), increases the expression of insulin receptor beta subunit (IR-β), insulin receptor substrate 1 (IRS-1), glucose-transporter-type 4 (GLUT4), and glycolysis enzymes[40]. Moreover, T increases the GLUT4 expression in cultured skeletal muscle cells, hepatocytes, and adipocytes[41], as well as membrane translocation, promoting glucose uptake in adipose and skeletal muscle tissue[42]. According to these *in vitro* studies, low T serum levels were found to induce IR *in vivo*[43,44]. Alongside these systemic T effects, the potential effect of this steroidal hormone on pancreatic beta cells is still not completely unraveled. Indeed, while some studies reported an increased androgen receptor-dependent hyperglycemic decomposition[45], other authors described a protective role[46].

By contrast, insulin has a role in restoring T and Gn serum levels[39]. In particular, insulin may increase the synthesis and the release of Gn-releasing hormone (GnRH) from the hypothalamus, and it may directly stimulate T secretion[47].

Low T serum levels increase adipogenesis and visceral obesity, which is associated with IR, chronic inflammation, and low sex hormone binding globulin (SHBG) levels[48]. This finding is in line with the positive effect of dihydrotestosterone on lipid tissue: it can inhibit lipid accumulation in human subcutaneous, mesenteric, and omental preadipocytes[49]. However, it is known that visceral obesity is more common in men than in premenopausal women[50]. In addition, it was found that androgen binding sites are two times higher in intra-abdominal preadipocytes than in subcutaneous preadipocytes[51], and that there is a direct positive transcriptional effect of androgens on the expression of the antilipolytic α2A-adrenoreceptor subtype in rodent mature adipocytes[52]. Nowadays, the role of androgens on body composition is still not completely understood.

SHBG is a protein secreted by the liver that, thanks to its steroid hormones binding property, has important regulatory actions on the levels and activity of steroid hormones, such as testosterone, dihydrotestosterone, and estradiol[53]. However, SHBG is also a protective molecule against metabolic syndrome (MetS), thanks to its suppressive action on adipocyte inflammation and lipid accumulation. Indeed, low levels of SHBG can be used as a marker of MetS, hepatic steatosis development, and IR, and also as a predictor of T2DM. As a matter of fact, chronic low-grade inflammation diseases, including obesity, IR, and T2DM, can decrease SHBG levels[54].

Increased fat mass seems to further reduce serum T. Adipose tissue converts circulating T into estradiol (E2) since it expresses the aromatase enzyme. An increase in serum E2 further contributes to a decrease in serum T since E2 exerts the main inhibitory effect (negative feedback) on Gn secretion both at hypothalamic and pituitary levels[55]. Conversely, IR might occur first (especially in obese diabetic patients), and then can lead to increased adipose tissue, triggering hypogonadism[56]. In particular, insulin and insulin-like growth factor 1 signaling are adipogenic, and as we described before, adipose tissue mass and its distribution can affect the circulating concentrations of T[57]. However, this is just one of the potential mechanisms linking adipose tissue excess and hypogonadism. Indeed, even more demonstrations suggested

that the correlation between obesity and hypogonadism is bidirectional, also sustained by leptin dysregulation and systemic inflammation[58,59]. Thus, in this complex scenario, other factors could lead to hypogonadism in diabetic subjects, such as the resistance to GnRH-stimulating effects of leptin in patients with obesity, the suppressive action of leptin on the stimulatory action of Gn on the Leydig cells, and finally, the increase of inflammation that leads to the suppression of hypothalamic GnRH secretion[60-62].

Finally, increased glucocorticoid activity in adipose tissue also appears to induce androgen inactivation due to increased activity of 11β-hydroxysteroid dehydrogenase type 1, leading to decreased androgen activity in adipose tissue[63] [Figure 2].

MALE HYPOGONADISM AND CARDIOVASCULAR RISK

It is well known that men have a higher CV risk compared to premenopausal women, suggesting a protective role of estrogens and, likely, a negative role of T on CV health. Recently, this hypothesis has been questioned because some evidence documented a relationship between hypogonadism, metabolic status, and CV risk. Indeed, low T serum levels were detected as a predictive marker for ischemic arterial diseases, such as coronary heart disease and stroke[64], and for CV-related mortality[65-67]. A recent meta-analysis confirmed this relationship, quantifying the association between low T levels and CV morbidity and mortality[68]. Indeed, CV risk and mortality were inversely related to mean age, and directly related to the prevalence of diabetes and the proportion of active smokers[68]. This association is particularly true in diabetic men, in which low T serum levels significantly predicted all-cause mortality during long-term follow-up[69]. However, the mechanism behind this correlation has not been completely understood. Studies in animal models suggest that low T could be involved in the regulation of inflammation in several tissues[70-73], worsening CV health. In humans, T has a vasodilatory effect through the downregulation of L-type voltage-gated calcium channels and the upregulation of calcium-activated potassium channels, increasing the cardiac contractility and cardiomyocyte relaxation, reducing the atheroma development, and reducing the lipid deposition in the artery wall[39]. Moreover, T decreases the production of inflammatory cytokines, such as tumor necrosis factor-alfa, interleukin-1b and interleukin-6, and increases the anti-atherogenic interleukin-10 levels[47]. Finally, T seems to have a weak anticoagulant activity, stimulating tissue factor pathway inhibitor and tissue plasminogen activator expression, and inhibiting plasminogen activator inhibitor type 1 secretion by the endothelium[47]. Alongside the direct T action on the endothelium, T could improve CV health, influencing the metabolic profile and reducing the risk of obesity, IR, metabolic syndrome, DM, and lipid profile impairment, which are widely reported in association with male hypogonadism[74]. As a confirmation, subjects treated with androgen deprivation therapy showed an increased risk of DM and coronary artery diseases[75], myocardial infarction[75,76], CV mortality and sudden cardiac death[77,78], and heart failure[79].

TESTOSTERONE TREATMENT AND CARDIOVASCULAR HEALTH IN DIABETES

It is largely demonstrated that hypogonadal men should be treated with exogenous T, also to prevent/reduce CV risk[80]. T replacement therapy improves sexual function[81,82], increases skeletal muscle mass[82,83], strength[84], and bone mineral density[82,83], and ameliorates lipid profile[85,86] and IR[43]. These effects are extremely beneficial in young men with hypogonadism, while in older men, the benefits and long-term risks must be properly evaluated[87].

Considering CV health, little evidence described a detrimental effect of T replacement therapy, increasing CV risk[88,89] and adverse outcomes[90], in particular in older men or in younger subjects with pre-existing heart diseases[89]. According to these controversies about the effect of T replacement therapy on CV risk, the US Food and Drug Administration (FDA) added restrictions through a warning statement on this

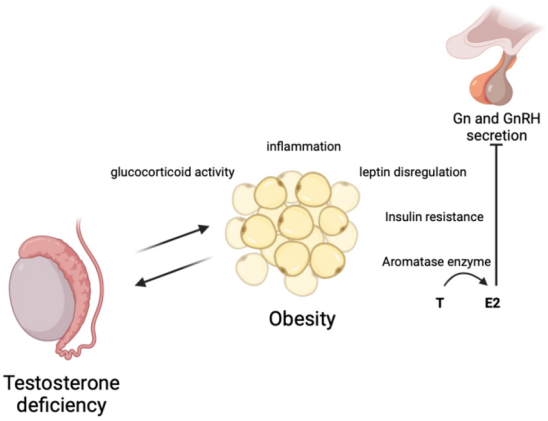

Figure 2. Bidirectional correlation between obesity and hypogonadism. Created with BioRender.com. T: testosterone; E2: estradiol; Gn: gonadotropins; GnRH:s Gonadotropin-releasing hormone.

substitutive treatment. However, these reports must be carefully considered, and recent analyses confirmed that, when prescribed according to the recommended dosage, T replacement therapy in hypogonadal patients improves angina symptoms in subjects with ischemic heart disease and exercise ability in patients with heart failure[91]. Obviously, the potential benefits of T treatment in reducing CV risk should be examined in longer-term trials with specific designs[68]. Indeed, T replacement therapy has been evaluated in specific conditions, such as men with heart failure, in whom T administration increases the cardiac output acutely[92] and improves functional capacity and symptoms[93], apparently via reduction of left ventricular afterload and/or change in cardiac morphology. Similarly, a beneficial effect has also been suggested in men with moderate/severe heart failure, in whom the supplementation of long-acting T resulted in improving functional capacity and baroreflex sensitivity for control of heart rate, together with the improvement of muscle strength and glucose metabolism[94]. With this in mind, exogenous T administration seems to be overall beneficial on the CV risk, particularly when TT basal levels were below 12.1 nmol/L. In these men, T-based therapy resulted in high patient satisfaction and reduced CV-related mortality[95].

The lack of a clear demonstration of the long-term safety of T replacement therapy on CV health led to confusion about when this treatment should be considered in hypogonadal men with T2DM. Indeed, many of the studies available in the literature evaluating the safety profile of T on CV health were not specifically designed for the diabetic population. Thus, the same considerations of the general population should be applied to diabetic men. Specifically considering diabetes, Muraleedharan *et al.* documented a significant survival improvement in 581 men with T2DM treated with T for six years[69]. Moreover, a randomized clinical trial has been designed with the purpose of answering the question of whether T therapy is associated with an increase in CV events. The testosterone replacement therapy for assessment of long-term vascular events and efficacy response in hypogonadal men (TRAVERSE) is a randomized, double-blind, placebo-controlled, parallel-group, non-inferiority, multicenter study that will determine the CV safety and long-term efficacy of exogenous T in middle-aged and older men with hypogonadism with or at increased risk of CV disease[96].

The association between T replacement therapy and CV risk in men with T2DM must consider other influencing factors. Indeed, the T action on CV risk could be mediated by the indirect effects on glycemic control, comorbidities, and additional diabetes-related CV risk factors[97]. As a confirmation, potential glucose metabolism improvement after androgen replacement therapy is suggested in diabetic men, allowing the reduction of glycated hemoglobin (HbA1c), fasting plasma glucose and homeostasis model

assessment of insulin resistance[85,98-102]. In addition, T supplementation seems able to improve the metabolic parameters in individuals with hypogonadism and metabolic syndrome[103] or prediabetes[12]. Indeed, androgen therapy restores the expression and phosphorylation of the adenosine 5'-monophosphate-activated protein kinase-α, a mediator of exercise-induced glucose uptake in skeletal muscle, contributing to insulin sensitivity and glucose homeostasis improvement[104]. Moreover, T replacement therapy in diabetic men improves lipid profile, reducing total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, and lipoprotein A, and increasing high-density lipoprotein cholesterol[101,102]. T supplementation shows a beneficial effect on blood pressure control, with a specific reduction of diastolic blood pressure in obese men[105], and an overall decrease in blood pressure in T2DM[101,106]. Finally, T replacement therapy in diabetic men improves anthropometric[101,107] and body composition parameters[43,101,106], inflammatory markers[43,108], and endothelial function[109,110]. Thus, all these demonstrations, although still sparse and not conclusive, suggest that T replacement therapy in T2DM men with hypogonadism contributes to CV risk improvement both directly and indirectly through the modulation of other influencing factors.

IMPACT OF NOVEL ANTIDIABETIC DRUGS WITH PROVEN CARDIOVASCULAR PROTECTIVE EFFECT ON MALE HYPOGONADISM

Considering the bidirectional link between T deficiency and DM-related complications, such as CV risk and mortality[4,111-113], hypoglycemic agents have been expected to exert a positive impact on HPG-related dysfunction in diabetic men.

Metformin represents one of the first hypoglycemic oral agents developed with favorable metabolic benefits. Beyond the well-known better glycemic control, accumulating evidence ascribed multiple functions to this drug, among these anti-obesity, renal/cardioprotective and anticancer roles[114]. For these reasons, metformin is still used as the first step drug in the management of glucose control in T2DM in combination with novel hypoglycemic agents[115,116]. Even in the presence of proven metabolic control and cardiovascular protection, experimental results described an anti-androgenic role of metformin as well as a negative impact on testicular and reproductive health[117,118].

Human studies reported the harmful effect of metformin on T production. Men with newly diagnosed T2DM, after rapid glycemic normalization by short-term intensive insulin treatment, showed the recovery of T levels in a eugonadal state whose concentrations were lowered when further exposed to metformin for 1 month[119]. Similarly, prolonged duration of metformin-based therapy reduced T levels and counteracted the T elevation accompanied with the improvement of blood glucose[120]. Low T levels have also been observed in patients under metformin regardless of age, duration of the disease, and HbA1c[121]. Notably, a recent study demonstrated that when fathers took one or more prescriptions for metformin during the development of fertilizing sperm, the likelihood of their male offspring having genital birth defects was increased[122].

These findings collectively indicated that the use of metformin may be another reason for the high prevalence of low T and reproductive abnormalities in males with T2DM. However, the mechanisms underlying the dangerous effects of metformin on human testicular health are still poorly clarified.

Conversely, new glucose-lowering agents have demonstrated a positive impact on body weight, waist circumference, hyperglycemia, atherosclerosis, and potentially on the HPG axis as well.

Glucagon-like peptide-1 receptor (GLP-1R) agonists (GLP-1Ra) and sodium-glucose cotransporter protein-2 inhibitors (SGLT2i) are currently used in T2DM management. GLP-1Ras are known to exert pleiotropic effects, including body weight control, glycemic control, and CV protection as well[123-125]. In accordance, SGLT2i inhibit renal glucose reabsorption, ameliorating blood glucose levels with additional effects on body weight and blood pressure, leading to improved renal and CV outcomes in subjects with T2DM, especially heart failure and kidney failure[126-131]. Thus, these drugs are efficient in protecting diabetic male patients from several players of disturbances of the HPG axis (i.e., advanced glycation end-products, reactive oxygen species, *etc.*)[132]. Considering the association between HPG failure and cardiometabolic outcomes, as well as a potential vasoprotective role of T replacement therapy in hypogonadal men[133], particularly with erectile dysfunction[132,134], a possible CV and metabolic benefit of T-based therapy is reasonable. However, conflicting results have been obtained regarding the effects of T replacement therapy on the occurrence of major adverse CV events, as will be discussed further[90,135-137]. Based on these considerations, herein we discuss current evidence about the effects of GLP-1Ra and SGLT2i on HPG function in hypogonadal diabetic males. Moreover, a potential additive effect on cardiometabolic outcomes from the combined administration of T replacement therapy and hypoglycemic agents will be further discussed.

Glucagon-like peptide-1 receptor agonists

Recent findings highlighted that GLP-1R is located in several cells related to the HPG axis as well, suggesting a potential GLP-1Ra effect on the HPG axis. Indeed, GLP-1R genetically abrogated in male mice resulted in poor development of gonads and seminal vesicles without modifications in the number and distribution of gonadotrophic cells within the anterior pituitary and in reproductive behavior[138]. However, GLP-1R is widely expressed in various central areas as hypothalamic nuclei orchestrating the release of GnRH and LH, and more recently was also identified in testicular cells[139]. Moreover, *in vitro* exposure of a neuronal cell line (GT1-7) to GLP-1 caused an increase in intracellular cAMP, together with the enhanced release of LH-releasing hormone[140]. This effect has also been confirmed in male rats where intracerebroventricular injection of GLP-1 induced a prompt increase in circulating levels of LH[140]. Further, *in vitro* analysis observed that increasing doses of GLP-1 stimulate hypothalamic GnRH neurons by enhancing the mRNA levels of kisspeptin-1 (KISS-1), an HPG axis gatekeeper, together with increased GnRH mRNA expression, effects inhibited in the presence of a selective GLP-1R antagonist[141].

The role of GLP-1 on gonadal function was elucidated by *in vivo* model of ischemia/reperfusion-induced testicular dysfunction. In this model, mice undergoing testicular torsion showed enhanced levels of oxidation (i.e., malondialdehyde, 3-nitrotyrosine), inflammatory [i.e., hypoxia-inducible factor-1β, tumor necrosis factor-α (TNF-α), *etc.*], and proapoptotic markers (i.e., caspase3, *etc.*) in association with downregulation of KISS-1 and its receptor (KISS-1R) in testis[142]. Notably, treatment with semaglutide before reperfusion alleviated dysfunction, inflammation, and oxidative stress of testis, probably due to the restoration of KISS-1 expression, which in turn improved testicular energy production and utilization[142]. Semaglutide injection also restored steroidogenesis pathway-related genes (i.e., steroidogenic acute regulatory protein, cytochrome P450 family 11 subfamily a member 1, *etc.*) and increased the expression of proliferating cell nuclear antigen in testicular cells, representing the key protein involved in DNA damage repair[142].

Effects on semen quality of GLP-1Ras have also been observed in obese male mice. This model of diet-induced obesity is typically characterized by impaired sperm quality through increased DNA damage, increased testicular inflammation (due to a rise in TNF-α, and monocyte chemoattractant protein-1), and abnormal sperm physiology[143]. All these conditions seem to be reversible after exenatide treatment[143].

Recent results support the functional role of the GLP-1/GLP-1R system in testicular somatic cells as well[144]. Indeed, GLP-1R has recently been identified in human Sertoli cells whose exposure to low doses of GLP-1 increased energy utilization, while at the highest concentration, it reduced mitochondrial membrane potential and oxidative damage[144]. Moreover, Rago *et al.* demonstrated that GLP-1Ra could directly ameliorate the seminal plasma quality since the expression of GLP-1R has been found in human spermatozoa[145]. Indeed, human sperm cells exposed to increasing concentrations of exenatide showed a significant increase in progressive motility and cholesterol efflux occurring through the activation of the cAMP/protein kinase a (PKA) pathway[145]. In concert, these findings suggest that GLP-1Ra-based therapy may bring additional advantages, improving the inflammatory status of testis and sperm quality and function not only directly by favoring GLP-1R activation in spermatozoa, but also indirectly through the activation of the GLP-1R in Sertoli cells.

Liraglutide, semaglutide and dulaglutide, the long-acting formulations, have demonstrated significant cardiovascular protective effects. In particular, liraglutide mitigated the risk of CV death[146], while semaglutide and dulaglutide conferred a risk reduction on non-fatal stroke[147,148]. Similar results were obtained by the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial, where exenatide ameliorated major adverse CV events even though to a less extent as compared with long-acting drugs[149-151]. These effects seem to be particularly mediated by an anti-atherogenic effect of GLP-1Ra as confirmed by animal models of hyperglycemia where liraglutide-based therapy reduced lipid deposition and plaque volume on the aortic surface according to glucose levels amelioration[152].

Based on the anti-atherogenic effects of GLP-1Ra, a possible action of these drugs on erectile dysfunction is reasonable. In this regard, Yuan *et al* recently demonstrated that liraglutide could improve erectile function in diabetes-induced erectile dysfunction by regulating smooth muscle relaxation, oxidative stress and autophagy, independently of the glucose-lowering effect, in a rat model of type 1 diabetes[153]. In addition, the supplementation of liraglutide to metformin therapy ameliorated endothelial functions of corpus cavernosum of male obese subjects with T2DM, resulting in the recovery of erectile performance[154]. Similar results were also obtained by the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial, where the long-term treatment with dulaglutide was also found to reduce the incidence of moderate or severe erectile dysfunction in middle-aged men with T2DM[155]. These beneficial effects on erectile function are probably mediated also by the recovery of normal T production. Indeed, incretin mimetics appear to bring T levels into the eugonadal range, as shown when exenatide-based therapy was combined with glimepiride or metformin treatment in hypogonadal middle-aged men with T2DM and obesity[156]. Similar results were obtained in a prospective randomized open-label study where the treatment of obese men with liraglutide induced a significant increase in TT serum levels (+ 2.6 ± 3.5 nmol/L) together with the improvement of LH and FSH secretion[157]. Thereafter, a recent retrospective study conducted in obese diabetic men with hypogonadism reported that the weight loss obtained with either liraglutide or dulaglutide, rather than the glycemic control, is the main driver of the improvement of T levels (≥ 300 ng/dL)[158]. Nevertheless, the beneficial testicular effects of these emerging therapies appear to vary according to basal levels of androgens, as emerged in a recent prospective cohort study where the exenatide-based therapy did not significantly change FT levels in diabetic men without hypogonadism[159], thus supporting a relevant role of incretin mimetics on male HPG axis, particularly in hypogonadism. Previously, experimental observations in healthy men documented no effect of GLP-1 on the pattern of LH secretion, but with intravenous infusion of physiological, low doses of GLP-1[160].

In summary, GLP-1Ra-based therapy may potentially act on each player of the HPG axis, fostering LH secretion by hypothalamic-pituitary neurons, T production by testis, ameliorating the semen quality and

improving erectile function [Figure 3 and Table 1]. Further elucidations are needed to clarify whether these effects are mediated by indirect actions of GLP-1Ra on glycemic control, body weight, inflammation, hormonal variation, or by direct interactions of these drugs with GLP-1R in different areas of the HPG axis.

Sodium-glucose cotransporter protein-2 inhibitors

Recent *in vivo* findings ascribed endothelial and anti-atherogenic functions to SGLT2i in terms of enhanced cardiac muscle remodeling, decreased vascular stiffness, and preventing the development of heart failure as observed in mice models of diabetes[161,162]. Similarly, studies conducted in diabetic patients reported that dapagliflozin-based therapy significantly improved systemic endothelial function and reduced both renal resistive index and aortic stiffness[163].

Despite the proven beneficial effects of SGLT2i in the setting of different diabetes-related cardiometabolic disorders, the contribution of these novel compounds to HPG axis function is still poorly explored. Data from a diabetic rat model with erectile dysfunction showed favorable effects of empagliflozin on erectile function, as compared to placebo, when the hypoglycemic treatment was followed by acute sildenafil administration[164]. This improved erectile response under SGLT2i was due to an increased cavernosal nitrergic relaxation, suggesting a positive effect of empagliflozin on the nerve injury[164]. Moreover, testicular benefits with SGLT2i treatment were demonstrated in leptin receptor-deficient diabetic mice, where the administration of dapagliflozin improved seminiferous tubule destruction, increased sperm concentrations and motility and protected testicular cells from apoptosis, increasing B-cell leukemia/lymphoma 2 protein and X-linked inhibitor of apoptosis protein, and oxidative stress, through the increase of superoxide dismutase and glutathione peroxidase activity[165]. Furthermore, dapagliflozin enhanced circulating levels of GLP-1 and the expression of GLP-1R within testicular tissue in a phosphatidylinositol-3 kinase (PI3K)/Akt-dependent manner [165]. Nevertheless, these effects on gonadal structure and sperm quality were partially lost after administration of GLP-1R antagonist exendin (9-39), thus suggesting that dapagliflozin may protect against diabetes-induced spermatogenic dysfunction via GLP-1R/PI3K/Akt-dependent pathway[165].

To date, only one human retrospective study demonstrated benefits on the HPG axis associated with SGLT2i-based therapy, highlighting that treatment with dapagliflozin increased T secretion in obese patients with uncontrolled T2DM and hypogonadism[158]. The enhanced T production observed was explained because of the amount of weight loss and the reduction in testis inflammation[158].

Even though the effects of SGLT2i on T synthesis are still poorly appreciable, *in vivo* experiments suggest a potential protective action of these drugs against cavernosal nerve alterations and sperm dysfunction [Table 1].

COMBINED CARDIO-METABOLIC EFFECTS OF TESTOSTERONE REPLACEMENT THERAPY AND NOVEL ANTIDIABETIC DRUGS

Several prospective cohort studies evaluated the association between endogenous T levels and the risk of CV disease. An inverse correlation was noted in the presence of severe hypoandrogenemia when the risk of CV death (RR 1.25, 95%CI: 0.97-1.60) and all-cause death (RR 1.35, 95%CI: 1.13-1.62) was higher in the setting of low T synthesis[166]. However, increasing endogenous T levels were significantly correlated with the decreased risk of CV death, with men in the highest quartile having an odds ratio of 0.53 (95%CI: 0.32-0.86) compared with men in the lowest quartile[67]. Therefore, low serum levels of endogenous T represent a risk factor for CV events, CV mortality, and all-cause mortality[167]. A similar association was also observed between gonadal functions and metabolic disturbances. Indeed, men with T deficiency have increased IR and low glucose tolerance regardless of age[43,44], as well as an increased risk of developing diabesity[168,169].

Table 1. Experimental findings supporting the actions of the novel antidiabetic drugs on hypothalamic-pituitary-gonadal axis and erectile function

	GLP1-Ra			SGLT2i		
	Experimental studies	Human trials		Experimental studies	Human trials	
		baseline	post-therapy		baseline	post-therapy
Hypothalamus-pituitary function	*In vitro* ↑ GnRH[140,141] ↑ KISS-1[141] *In vivo* ↑ LH[140] ↑ KISS-1[142]	Obese: LH (IU/L) [2.7 ± 1.2] FSH (mIU/L) [4 ± 1.7][157]	Obese: LH (IU/L) [3.4 ± 1.1] FSH (mIU/L) [4.9 ± 2.1][157]	None	None	
Gonadal function	*In vivo* Beneficial effect on steroidogenesis pathway-related genes[142] Beneficial effect on DNA damage repair system[140,142,143] ↓Inflammation[143] ↓ oxidative damage[144] Effect on seminal quality (↑ in progressive motility)[145]	Obese: TT (nmol/L) [7.6 ± 1.5][157] Obese with T2DM: TT (ng/dL) [262 ± 11][158]	Obese: TT (nmol/L) [10.2 ± 4.2][157] Obese with T2DM: TT (ng/dL) [> 300][158]	*In vivo* Effect on seminal quality (sperm concentrations and motility)[165] ↓ oxidative damage[165] Protect spermatogenic dysfunction via GLP-1R/PI3K/Akt-dependent fashion[165]	Obese with T2DM TT (ng/dL) [265 ± 11][158]	Obese with T2DM TT (ng/dL) [> 300][158]
Erectile function	Beneficial effects on smooth muscle relaxation, oxidative stress, and autophagy[153]	Obese with T2DM: ADAM and AMS positive results[156]	Obese with T2DM Improved ADAM and AMS after therapy[156]	Beneficial effect on erectile dysfunction by ↑ cavernosal nitrergic relaxation[164]	None	

ADAM: Androgen Deficiency in Aging Males; AMS: Aging Male Symptoms scale; FSH: follicle-stimulating hormone; GLP-1Ra: glucagon-like peptide-1 receptor agonist; GnRH: Gn-releasing hormone; KISS-1: kisspeptin-1; LH: luteinizing hormone; SGLT2i: sodium-glucose cotransporter protein-2 inhibitor; T: testosterone.

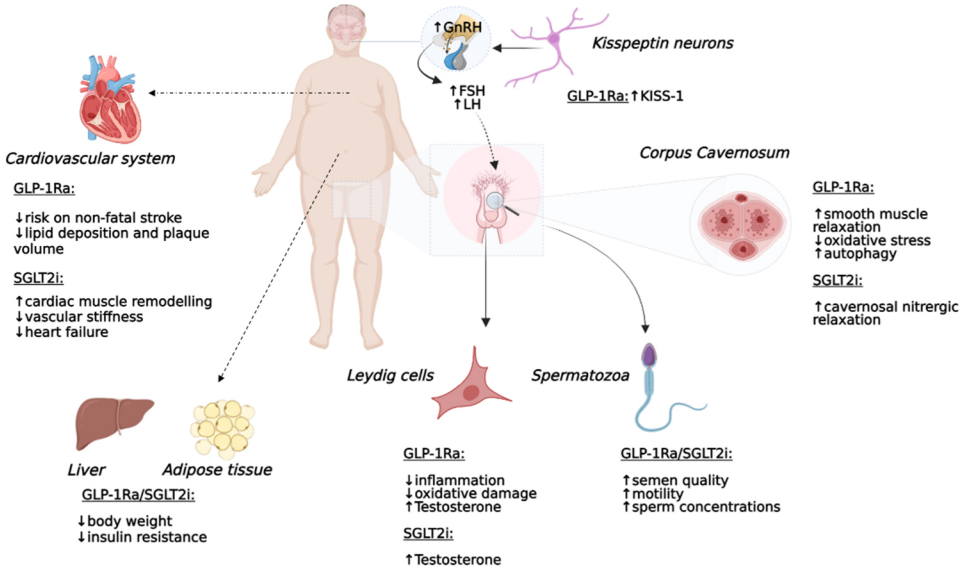

Figure 3. Potential direct and indirect effects of GLP-1Ra and SGLT2i on HPG axis function, CV system function and insulin resistance in diabetic hypogonadal men. FSH: follicle-stimulating hormone; LH: luteinizing hormone; GnRH, Gonadotropin-releasing hormone; GLP-1Ra: glucagon-like peptide-1 receptor agonist; KISS-1: kisspeptin-1; SGLT2i: sodium-glucose cotransporter protein-2 inhibitor; HPG: hypothalamus-pituitary-gonadal.

Indeed, Ding *et al.* showed that men with T concentrations above 15.5 nmol/L (447 ng/dL) had a 42% reduced risk of T2DM compared to men with T levels below 15.5 nmol/L[32]. The presence of hyperglycemia and reduced insulin sensitivity during T2DM could contribute to exacerbating HPG failure in hypogonadal men, thus sustaining an endless detrimental loop[132].

Considering the tight association between the disruption of the HPG axis and T2DM-related complications, the therapeutic efficacy of T replacement therapy on cardiometabolic outcomes is reasonable. As a matter of fact, Kapoor *et al.* reported that the administration of 100 mg/week of T for 3 months reduces HbA1c by 0.37%, fasting blood glucose by 1.58 mmol/L, total cholesterol by 0.4% and visceral fat in hypogonadal men with T2DM[170]. In line with this evidence, after 24 weeks of T replacement therapy, diabetic men with functional hypogonadism ameliorated insulin sensitiveness in terms of upregulation of key insulin signaling genes (IR-β, IRS1, AKT-2 and glucose transporter protein type-4) in the subcutaneous adipose tissue together with the improvement of lipid and inflammatory profile[43]. In contrast, a randomized clinical trial did not observe any improvement in glycemic control and IR as well as in visceral fat area in diabetic hypogonadal men when T replacement therapy was administered for a short period[85,107,171]. However, by extending the duration of T treatment to 2 years, both parameters achieved normal values[109,172].

The heterogeneity of study populations and differences in the duration of therapy could interfere with the real CV effectiveness of T replacement therapy. Since the effects of T on CV system are still debated, the cardiometabolic role of combined T and hypoglycemic therapies is still far from being investigated. Nevertheless, in a retrospective observational study conducted in men suffering from T2DM and overt hypogonadism, the supplementation of liraglutide to T replacement therapy allowed a consistent body weight reduction to be achieved and glycemic targets to be reached, together with a recovery in androgen levels[154]. However, in this study, no CV events have been reported in the medical history of patients enrolled[154]. Hence, further randomized, placebo-controlled studies with large cohorts of patients are needed to elucidate the effectiveness of co-administration of T and antidiabetic drugs on cardiometabolic outcomes in diabetic men with overt hypogonadism.

CONCLUSION

Clinical data on the effects of T treatment on CV outcomes produced contradictory and/or inconclusive results so far. However, in this context, it is essential to keep in mind the possibility that the risk is dose-dependent or higher in certain groups, such as the elderly. The trial TRAVERSE will address the uncertainty regarding CV safety of T replacement therapy among middle-aged or older men with or at high risk for CV disease. Taking into consideration diabetic people, impairment of glucose homeostasis and low T levels are strongly associated. In particular, in T2DM men, lowered serum T predicts DM-related comorbidities, high CV risk, and increased mortality. Furthermore, exogenous T showed beneficial effects on glycemic control and overweight/obesity, IR, dyslipidemia, hypertension, inflammation and endothelial dysfunction, all these recognized comorbidities and additional CV risk factors in T2DM. In this context, the novel GLP-1Ra and SGLT2i antidiabetic drugs have shown preliminary evidence of effects on T levels, in addition to a proven CV protective action [Figure 3]. The combined metabolic and CV effects of T replacement therapy and novel antidiabetic drugs are of great interest, and therefore requires further appropriately designed studies.

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Authors' contributions

Conception or design: Greco C
Drafting the work or revising: Greco C, Genchi V, Zanni E, Colzani M, Lauriola C
Final approval of the manuscript: Greco C, Genchi V, Zanni E, Colzani M, Lauriola C, Cignarelli A, Santi D

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All authors declared that there are no conflicts of interest.

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