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Systemic effects of the hormonal treatment of male hypogonadism with preliminary indications for the management of COVID-19 patients

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***Abstract*:** Male hypogonadism, defined as an inadequate production of testosterone (T), is associated with a greater morbidity and mortality. Epidemiological studies identified T deficiency as a risk factor for cardiovascular disease. Also, low serum T levels impact on glucose homeostasis through a worse glucose uptake, utilization, and disposal, and the general negative impact on metabolism. The aim of this review is to provide a comprehensive and updated overview of the effects of T replacement therapy on metabolic and cardiovascular systems and prostate tissue in patients with hypogonadism, including molecular mechanisms through which T exerts its actions. Furthermore, recent findings on novel coronavirus disease (COVID-19) epidemiology have shown a greater mortality in male compared with female patients and a role of T in promoting the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection of the host cells has been demonstrated. Hence, the secondary aim of this review is to provide preliminary indications on the management in patients with COVID-19.

Keywords: benign prostate hyperplasia, hypogonadism, obesity, obstructive sleep apnea, prostate cancer, prostatitis, testosterone replacement therapy, type 2 diabetes mellitus

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Introduction

The term male hypogonadism refers to a dysfunction of Sertoli, germ or Leydig cells, resulting in spermatogenetic failure and infertility or in an abnormal steroidogenesis. Specifically, Leydig cell failure to secrete adequate levels of testosterone (T) is defined as testosterone deficiency (TD).[1] Its diagnosis is established when specific symptoms and signs of hypogonadism combine with low T levels. In particular, the last Endocrine Society guidelines consider 9.2 nmol/l (265.1 ng/dl) as the lower limit (corresponding to the 2.5th percentile) of normal total T in healthy nonobese young men.[2] Hence, at least two values of total T $\leqslant$ 9.1 nmol/l and specific signs (e.g. incomplete sexual development, loss of body hair, small testis), suggestive symptoms (e.g. reduced libido, erectile dysfunction, low bone mineralization) or nonspecific symptoms (e.g. anemia, fatigue, increase of body fat) are warranted to make the diagnosis of hypogonadism.[2]

A great amount of evidence supports that T is an important biomarker of man's health. Accordingly, TD associates with aging, obesity, poor health, metabolic syndrome, and cardiovascular disease (CVD).[3] More in detail, epidemiological studies identified TD as a risk factor for myocardial infarction, ischemic stroke and other adverse cardiovascular events.[4] Patients with TD show an increase of the all-cause mortality risk in a 4–16-year follow-up period.[3,5] Lastly, normal serum T levels promote glucose homeostasis through a better glucose uptake, utilization and disposal, thus supporting a general improvement of metabolism. As a consequence, T deficiency favors hyperglycemia, and associates with metabolic syndrome (MetS) and type II diabetes mellitus (T2DM).[6] Furthermore, T deficiency has been shown to alter the lipid profile and to change body composition promoting the accumulation of visceral fat by causing insulin resistance.[7] Based on the

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hypogonadal–obesity–adipocytokine hypothesis, central obesity (often related to MetS and T2DM) associates with lower T levels due to the aromatization into estrogens occurring in adipocytes. In turn, the activity of lipoprotein lipase, involved in the storage of triglycerides into the adipocytes, and the differentiation of pluripotent stem cells into mature adipocytes are favored by the low T levels.[8] The subsequent adipocyte accumulation and enlargement leads to insulin resistance. Finally, T is able to affect prostate cell proliferation under a specific range of values, and the impact of T replacement therapy (TRT) on prostate disorders is often matter of discussion.

Several lines of clinical evidence have been released so far on the impact of TRT on the general health of patients with hypogonadism. The primary aim of this review is to provide a comprehensive and updated overview of the effects of TRT on metabolic and cardiovascular systems and prostate tissue in patients with hypogonadism. Conditions which may benefits from TRT and those representing contraindications to T prescription are also included.

The amount of the epidemiological data recently accrued on the SARS-CoV2 infection revealed pivotal aspects deserving consideration. These include the age- and comorbidity-dependent mortality, and the increased risk in males than females, which leads to speculate on a possible influence of T on the virus infection.[9] Hence, the secondary aim of this review is to resume the available evidence on this matter and the implications in the management of patients with SARS-CoV2 infection.

To accomplish the aims of the study, we performed a search on PubMed, Scopus, Ovid and Science Direct, and the following keywords were used: hypogonadism, TD, TRT, blood pressure, hypertension, ischemic heart disease, heart failure, stroke, obesity, insulin, diabetes, metabolic disorders, prostatic hyperplasia, prostate cancer, COVID-19, and SARS-CoV2.

Benefits of testosterone replacement therapy on metabolic disorders

Relationship between metabolic disorders and hypogonadism

Metabolic disorders are some of the most relevant problems of our time. MetS includes insulin resistance, hypertension, dyslipidemia, abdominal fat accumulation, which are all cardiovascular risk factors. In particular, the comorbidities associated with obesity are multidisciplinary (metabolic, vascular, gastrointestinal, respiratory, oncological, osteoarticular, psychological), and the risk of comorbidities caused by obesity has been stratified according to the World Health Organization classification. Obesity, MetS, insulin resistance, T2DM and hypogonadism are closely linked in men.[10,11] Strong evidence has been reported on the relationship between the maintenance of normal metabolic parameters and the testicular function. Both MetS and T2DM associate with TD and levels of total and free T are inversely correlated with the body mass index (BMI).[12] Furthermore, men with obesity have low luteinizing hormone (LH) pulse amplitude in comparison with normal weight controls, and those with T2DM were found to have a reduced gonadotropin-releasing hormone (GnRH) pulsatility. However, there is a bidirectional association link between metabolic disorders and male hypogonadism.[12] In fact, hypotestosteronemia can increase body fat accumulation and worsen the carbohydrate metabolism.

In hypogonadal patients TRT has been shown to improve glucose control, lipid profile, blood pressure, and waist circumference. Therefore, the maintenance of normal serum T levels in hypogonadal patients has long-term effects on the development of MetS and the quality of life (QoL) in general. Genetic and environmental factors seem to be also involved in this complex model of interaction. However, mechanisms specifically linking TD with fat mass accumulation and dysmetabolism are still far to be understood.

Molecular mechanisms of metabolic decay in hypogonadism

A vicious cycle between obesity and insulin resistance has been reported. Indeed, the adipose tissue and T are strictly related, as adipocytes host the aromatase enzyme. An important relationship between the adipose tissue and T lays in the "adipose tissue-aromatase" hypothesis, which states that aromatase activity makes the adipocytes larger, due to fat accumulation, leading to higher rates of conversion of T into E2. This generates a negative feedback on the hypothalamic–pituitary–gonadal axis that results in lower T levels.[13]

An increased adiposity decreases serum T levels even before the onset of phenotypic obesity by suppressing the testicular leptin and JAK–STAT pathway.[14] An oxidative damage of the Leydig cells in obesity due to increase in inflammatory pathways [e.g. interleukin (IL)-1 receptor] has also been shown. High fat-diet-induced obesity also leads to insulin resistance through several signaling molecules [such as tumor necrosis factor (TNF)-α, IL-1, IL-6, IL-8 and monocyte chemotactic protein (MCP)-1] and release of free fatty acids (FFAs) that affect the liver leading to hepatic insulin resistance, lipogenesis and gluconeogenesis.[3] Furthermore, FFAs can compete with glucose as an energy source in the muscle.[15]

Hypogonadism can be the initial trigger of the vicious cycle of metabolic decay. The molecular pathways have been shown in rats, and there is consensus on a protective role of T on β-cells through antioxidant and antiapoptotic effects. There are many experimental evidences of these effects at various levels, exerted by T binding to the androgen receptor (AR), as AR experimental blocking (with the antiandrogen flutamide) impairs glucose-stimulated insulin secretion.[16] Studies have shown that T regulates the production of enzymes with antioxidant properties in β-cells.[17] Moreover, evidence has recently shown that the androgens interfere with the signaling of glucocorticoids responsible of pancreatic β-cell apoptosis. Androgens also hinder the dexamethasone-induced increase of the thioredoxin-interacting protein, which has pro-apoptotic effects in β-cells.[18] T can also decrease markers of oxidative damage, which have been induced by orchiectomy in the hippocampus of rodents.[19] Lastly, recent studies in patients with T deficiency showed that exogenous T inhibits JNK, IKK-β and TNF-α, which in turn are the major inflammatory cytokines involved in development of insulin resistance, which may suggest that T protects against inflammation-induced insulin resistance.[19,20] Recent evidence has shown that the anti-inflammatory effect of T, displayed by triggering the AR, has wider implication than thought before. Another effect of T deficiency is the increase in body fat, especially visceral fat, which is more T-related than subcutaneous fat.[21] The reason is the subsequent increase in lipoprotein lipase activity in adipose tissue, which in turn brings to a poor triglycerides control, together with a lower response to catecholamine-mediated lipolytic activity.[22,23] The sensitivity of fat tissue to T could also be related to other hormones, as a study showed that TRT in T2DM patients improves leptin/adiponectin ratios and leptin levels,[24] and also T-stimulated growth hormone (GH) exerts various effects in adipose tissue (inhibition of proinflammatory cytokines, such as TNF-α, IL-6, soluble Fas and Fas ligand).[25,26]

There are no exhaustive studies that show a direct role of TRT on dyslipidemia yet, but visceral fat decrease is clearly associated with a better lipid profile. A study enlightened interesting molecular mechanisms on hypogonadal patients: proatherogenic lipoprotein-associated changes were found which explain a reduced cholesterol efflux and an increased influx, providing a possible explanation for the increase of CVD risk. However, high-density lipoprotein (HDL)-C concentrations did not correlate with T levels.[27] However, the effect on the HDL subtypes was not reported.[27] Another study showed an elevated triglyceride (TG)/HDL-C ratio in patients with hypogonadotropic hypogonadism (HH); the TG/HDL-C ratio represents an index of atherosclerosis and insulin resistance, being also an independent predictor of CVD risk.[28]

A summary of the relationship between hypogonadism, diabetes and visceral fat is shown in Figure 1.

Effects of testosterone administration on metabolic diseases

TRT efficacy on metabolic disorders and body composition has clearly showed positive results. Fui and colleagues reported that 56 weeks of TRT leads to a reduction in visceral fat, and a trend towards an improvement of carbohydrate metabolism in obese patients with TD (<12 nmol/l).[13] Another study showed that 100 mg/week of TRT for 3 months lowered glycated hemoglobin by 0.37%.[29] In agreement with these data, other authors reported the amelioration of subcutaneous fat, but no reduction in visceral and hepatic adipose tissue following 24 weeks from TRT in T2DM patients with TD.[20] Of note, both the glucose infusion rate and insulin signaling gene expression (e.g. IR-β, IRS-1, AKT-2, and GLUT4) increased while, by contrast, FFAs, C-reactive protein, IL-1β TNF-α and leptin decreased in the fat tissue after TRT. Hence, this study showed a greater improvement in the molecular signaling pathways than in the phenotypic appearance.[20] Another study on obese,

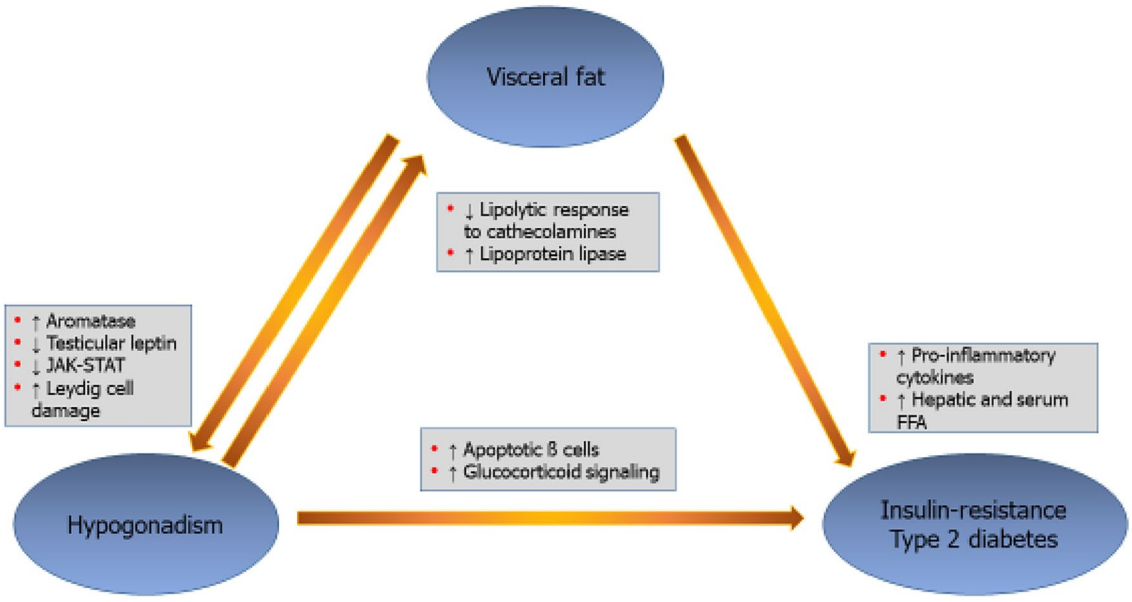

Figure 1. Relationships between hypogonadism, visceral fat and insulin resistance: the vicious cycle.
FFA, free fatty acid.

nondiabetic, eugonadal men, showed a reduction of visceral fat and an improvement of insulin resistance, glycemia, diastolic blood pressure and serum cholesterol, with no change of prostate-specific antigen (PSA) levels, following an 8-month-long TRT.[30] However, other authors did not find ameliorations of insulin resistance, glucose control or visceral fat in T2DM patients with TD after 40 weeks of TRT.[31]

According to these studies, TRT is necessary in hypogonadal patients with metabolic abnormalities because it improves several endocrine pathways and body composition.[13,20,29,30]

Given the availability of different types of TRT, and the need of multidisciplinary approach for the treatment of metabolic abnormalities, additional clinical trials are needed to clarify the potential role of TRT in metabolic disorders.

Effects of testosterone replacement therapy on the cardiovascular system

The effects of TRT on the cardiovascular system are still reason for debate in scientific literature. Among eugonadal men, a lower incidence of major adverse cardiovascular events (MACEs) has been recorded in patients with T levels in the higher quartile.[32] In patients with low T levels, several studies have highlighted a higher prevalence of cardiovascular events.[33,34] In 2011, two meta-analyses were performed: the first included 70 studies with over 12,500 patients and showed that patients with CVD have significantly lower T and higher E2 levels than patients without CVD. This finding was confirmed by a logistic regression, after adjustment for age and BMI.[12] The second meta-analysis, including 12 studies and about 11,000 men, concluded that low endogenous T levels are associated with increased risk of all-cause and CVD death.[5] However, it is still not clear whether low T levels are merely a consequence of the underlying diseases or hypogonadism itself promotes the atherosclerotic progression.

The basis of most cardiovascular diseases is endothelial dysfunction. It has been shown that ARs are present in both endothelial cells (ECs) and endothelial progenitor cells (EPCs). Androgens stimulate EC proliferation and viability enhancing vascular endothelial growth factor (VEGF) synthesis and subsequent cyclin expression. Furthermore, T stimulates the synthesis of nitric oxide (NO) that is able to potentiate EC proliferation and to decrease EC apoptosis by suppressing the expression of caspases and decreasing p38/MAPK activity. EPCs are bone-marrow-derived cells involved in the repair of injured endothelium, vessel remodeling, and

vasculogenesis. The binding of androgens with AR activates the PI3K/Akt signaling pathway that leads to EPC proliferation. Indeed, patients with central hypogonadism have reduced EPC number that increase following TRT.[35] On the other hand, TRT has also been shown to increase the levels of endothelin-1, intracellular adhesion molecule type 1 (ICAM-1), and vascular adhesion molecule (VCAM), thus enhancing vasoconstriction and thrombosis.[35,36]

Some evidence indicate that TRT could indirectly improve cardiovascular health in some categories of patients acting on cardiovascular risk factors. For example, in obese hypogonadal patients with T2DM, it has been demonstrated that TRT reduces HOMA index and glycated hemoglobin and improves flow-mediated dilatation.[37] Accordingly, other authors provide evidence on the benefits of TRT on flow mediated dilation (FMD) in a cohort of nondiabetic nondyslipidemic male patients.[38] In newly diagnosed T2DM patients with functional hypogonadism, TRT also lower BMI, waist circumference, adipohormones such as leptin and resistin, and markers of endothelial dysfunction and inflammation such as ICAM-1, p-selectin, and C-reactive protein.[36]

Conversely, other categories of patients may be more susceptible to adverse effects of TRT. Erythrocytosis, the most frequent adverse event associated with TRT, is a risk factor for neuro-occlusive or cardiovascular events.[39] However, the hematocrit value above which the risk increases significantly is unknown. The increase in hemoglobin and hematocrit depends on T doses and circulating concentrations and is more likely in older than in young men.[2] Furthermore, TRT increases salt and water retention that could contribute to worsen cardiovascular function.[40]

The Testosterone in Older Men with Mobility Limitations (TOM) trial was a placebo-controlled, randomized study design aimed at assessing the impact of TRT on muscle strength in aging males with TD and limited physical function. The trial was interrupted early due to the increased prevalence of adverse cardiovascular events in the TRT group.[40] Since then, a debate has arisen on the cardiovascular safety of TRT. However, data obtained in TOM trial were not generalizable because the T doses administered were higher than those used in clinical practice. Furthermore, the population study was composed by frail elderly men with limited mobility and an increase in the prevalence of chronic diseases (e.g. previous heart diseases, obesity, diabetes, hypertension), and so more predisposed to cardiovascular events than general population.[40,41]

The Testosterone Trials were a group of seven placebo-controlled trials designed to evaluate the effects of TRT on men $\geqslant$65 years of age with low T levels. Among them, the Cardiovascular Trial showed an increase in noncalcified coronary artery plaque volume by computed tomographic angiography in participants who received T. However, the prevalence of MACEs and the levels of markers of inflammation, fibrinolysis, or myocardial damage (D-dimer, C-reactive protein, IL-6, and troponin) did not differ among groups.[42,43] It has been hypothesized that the observed increase in plaque volume may represent the initial phase of a healing response induced by T leading to a more stable plaque. Indeed, in other studies a reduction in carotid intimal media thickness has been reported.[44] In animal models, T deficiency promoted the formation of lipid streak, the first stage of atherosclerotic plaque, while TRT protected against it.[44]

To date, there is no conclusive evidence that TRT is associated with MACEs. It has been hypothesized that the etiology and the duration of the hypogonadism, patient age, and any comorbidities may have a greater influence on cardiovascular risk than TRT itself. In young patients with primary or secondary hypogonadism TRT is always indicated and safe for the cardiovascular system. Conversely, in late-onset hypogonadism associated with chronic illness the risk–benefit balance must be evaluated. In this category of patients, that usually have a greater cardiovascular risk *per se*, low T levels may represent an index of poorer healthy status. Their normalization with exogenous T administration not always improves cardiovascular health and, conversely, may expose patients to the adverse effects of TRT (e.g. increased hematocrit).[45]

In 2017, a meta-analysis including 39 randomized controlled trials (RCTs) and 10 observational studies with a total of about 5500 patients did not find any significant association between TRT and myocardial infarction, stroke, or mortality, even if the quality of the evidence was low.[46] More recently, a retrospective study on a cohort of almost 3500 middle-aged men who underwent

TRT, matched for age and comorbidities with men who did not undergo TRT, revealed that TRT improves cardiovascular event-free survival, mainly lowering the incidence of coronary artery disease.[47] These findings agree with other recent population studies reporting a reduced prevalence of MACE in hypogonadal patients receiving TRT,[48] and especially in those who obtain the normalization of T levels during replacement.[49]

The impact of TRT on blood pressure, ischemic heart disease and stroke is following discussed.

Blood pressure

According to the most recent guidelines of the American College of Cardiology/American Heart Association, hypertension is defined as an average systolic blood pressure ⩾130 mmHg and/or an average diastolic blood pressure ⩾80 mmHg. In 90% of cases hypertension is essential, while in approximately 10% of cases a secondary cause of hypertension can be identified.[50]

Androgens are involved in the regulation of vascular tone. Indeed, they are able to induce vasodilatation through several mechanisms. Through a genomic effect, T and dihydrotestosterone (DHT) binding with AR activates in ECs the PI3K/Akt and ERK1/2 pathways that enhance endothelial NO synthase (eNOS) expression and induce NO release in a dose-dependent manner. NO, in turn, acts on vascular smooth muscle cells were activates guanylate cyclase. The subsequent increase in cyclic GMP (cGMP) concentrations induces a decrease in Ca^{2+} influx leading to muscular relaxation and vasodilatation.[35] Furthermore, the activation of AR induces the enzyme cystathionine-γ lyase, which catalyzes the production of H2S, a gas with vasodilator effects, from amino acid L-cysteine. Another genomic mechanism through which T seems to induce vasodilatation may be the induction of cyclooxygenase-2 (COX-2), which increases prostacyclin production. On the other hand, the activation of COX-2 may also produce compounds with vasoconstrictor activity such as thromboxane A2 and 20-hydroxyeicosatetraenoic acid, thus partially denying the benefits of TRT on vascular health. Some effect on endothelin-1 has been also described: it has been demonstrated that hypogonadal men have increased concentrations of endothelin-1, a potent vasoconstrictor, which decrease following TRT.[35] In addition, T and its metabolites exert a rapid vasodilator action through nongenomic mechanisms: they are able to block the L-type voltage-operated Ca^{2+} channel and to open the potassium channels, leading to hyperpolarization and relaxation.[51]

In animal studies, chronic T treatment in nonhypogonadal spontaneously hypertensive rats caused an increase in mean blood pressure in young animals, probably due to the activation of renin–angiotensin system, but not in aging male rats, whose blood pressure decreased.[52] Conversely, in orchidectomized normotensive rats, T deprivation induced an increase in blood pressure, prevented by TRT.[51]

Regarding evidence on humans, it has been shown that arterial stiffness is higher in hypogonadal patients and it improves after TRT.[53] In parallel, in aging men, T levels showed a significant negative correlation with systolic pressure.[54] Despite this evidence, some clinical trials reported an increase in blood pressure in patients following TRT. This effect may probably be related to the increase in tubular sodium and water reabsorption and the activation of renin–angiotensin system due to the achievement of supraphysiological androgen levels during injective TRT.[55]

Ischemic heart disease

Ischemic heart disease indicates a condition in which heart muscle is not supplied with a sufficient amount of blood and/or oxygen. Ischemia can occur in the presence of an increase in myocardial oxygen demand and/or a reduction in coronary flow. The most frequent cause is atherosclerosis, characterized by the presence of plaques with high cholesterol content (atheromas) in the coronary arteries, which can obstruct or reduce blood flow. When the shrinkage becomes important, it alters the normal circulation and promotes the formation of blood clots that can detach from the arteriosclerotic plaque and obstruct smaller-sized vessels. Furthermore, in turn, thrombus itself stimulates the synthesis of thromboxane, a powerful vasoconstrictor, able to determine a vessel spasm and aggravate the obstruction. Ischemic heart disease includes different clinical manifestations such as stable and unstable angina pectoris and myocardial infarction.[56]

T has anti-thrombotic properties. Indeed, it increases the expression of tissue plasminogen activator (t-PA) and tissue factor pathway inhibitor

and decreases the expression of plasminogen activator inhibitor type 1 (PAI-I) and factor VII.[35] Instead, the effects on the endothelial expression of adhesion molecules are controversial. The adhesion of monocytes to ECs induces vascular inflammation that represents an initial stage of atherogenesis. Some studies showed a direct correlation between testosterone and the expression of vascular cell adhesion molecule-1 (VCAM-1) and endothelial selectin. Conversely, other studies demonstrated a reduction in inflammatory molecules and markers of endothelial dysfunction including ICAM-1, VCAM-1, PCR, p-selectin, and resistin in ECs exposed to testosterone and in hypogonadal patients who underwent TRT.[5,37] Furthermore, T stimulates the production of IL-10, a cytokine with anti-inflammatory and anti-atherogenic effects.[44]

An observational study showed no association between endogenous T and DHT levels and incident myocardial infarction in older men.[57] Similarly, in hypogonadal patients receiving TRT many studies did not find an increased risk of myocardial infarction.[58,59] Recently, this finding was confirmed by a large retrospective cohort study that compared myocardial infarction rates between over 200,000 T-treated men and as many matched untreated hypogonadal patients. The calculated odds ratio did not significantly differ between the two groups, even if it tended to be lower in treated patients.[60] In other studies, myocardial risk resulted slightly reduced in hypogonadal patients who achieved normal T levels during TRT.[61]

Regarding men already diagnosed with ischemic heart disease, several RCTs have shown that T has beneficial effects on myocardial ischemia. Indeed, T reduces ST depression and angina symptoms, prolongs time to ST depression during exercise-induced cardiac ischemia, and reduces the frequency of angina episodes. These effects are probably due mainly to ability of T to enhance coronary blood flow with a rapid non-genomic action and a slower genomic mechanism.[44] Conversely, in animal models results are contrasting: some studies reported a reduced myocardial contractility in hypogonadal rats treated with T after myocardial infarction;[62] other studies found a decreased myocardial angiogenesis and consequent reduced capillary density, worsened cardiac function, increased infarct size and cardiomyocyte apoptosis in castrated rats with myocardial infarction, but these effects were reversed by TRT.[63]

A summary of the available evidence mainly coming from prospective randomized placebo-controlled trials administering TRT to hypogonadal patients with coronary heart disease and heart insufficiency is provided in Table 1. Overall, these data suggest the benefits of TRT and the lack of side effects when TRT is not overdosed, even in case of demonstrated coronary artery obstruction.

Brain stroke

Brain stroke consists of a loss of brain function, caused by insufficient blood supply to the organ or to one or more of its areas. Stroke can be hemorrhagic or ischemic. In the latter case it may be caused by a thrombus or an embolus. Transient ischemic attack means a cerebral ischemia whose symptoms resolve within 24 h.

Among eugonadal men, those with T in the highest interquartile range show lower incidence of stroke. It has been estimated that men with T levels at or below the 10th percentile have a 40% increased risk of ischemic stroke compared with men with T concentrations at 11–90th percentiles.[76] A relation between ischemic stroke and DHT has also been found. In men without prior stroke or heart disease, calculated free DHT was inversely correlated with incident ischemic stroke risk, while total DHT showed a nonlinear relation with the lowest risk at levels of 50–75 ng/dl and greater risk at total DHT levels above or below this range.[77] Conversely, other studies found a linear inverse association also between total DHT levels and stroke, with a calculated risk approximately half for men with DHT in the highest compared with the lowest quartile of values.[57]

In aging patients with low T levels not related to testicular or hypothalamic–pituitary diseases, the effects of TRT on stroke risk are unclear. A population study on about 4700 patients with low baseline T levels revealed a trend to a higher stroke rate in patients who achieved high T levels during TRT, while TRT, administered at dose adjusted to keep serum T levels in the normal range, was correlated with reduced MACEs and risk of death among a 3-year-long observation.[49] In a population study on a cohort of about 15,400 UK men aged 45 years or older with low T levels, patient who underwent TRT showed a 21%

Table 1. Summary of the evidence on the effects of testosterone replacement therapy in hypogonadal patients with heart failure.

Author	Study design	Duration	Sample	Evidence
English *et al.*[64]	Prospective double-blind, randomized, placebo-controlled trial	14 weeks	46 patients with stable angina	TRT significantly delayed time to ischemia, after 4 and after 12 weeks of treatment
Malkin *et al.*[65]	Prospective randomized single-blind placebo-controlled	4 weeks	10 men with CAD (coronary artery stenosis >70% or previous proven MI)	TRT delayed time to ischemia as time to 1 mm ST segment depression increased by 74 s at exercise treadmill testing
Webb *et al.*[66]	Prospective placebo-controlled trial	8 weeks	22 patients with CAD	TRT modestly supported myocardial perfusion supplied by not obstructed coronary arteries
Mathur *et al.*[67]	Prospective randomized parallel group-controlled trial	12 months	13 patients with hypogonadism and angina: • 7 on TRT • 6 on placebo	A trend towards the decrease of CIMT in the TRT group was observed. T increased time to ischemia.
Cornoldi *et al.*[68]	Prospective placebo-controlled trial	12 weeks	87 diabetic patients with proved CAD	A significant 34% reduction of the number of angina attacks per week was found in the TRT group. Silent ischemic episodes and total ischemic burden decreased significantly by 26% and 21%, respectively
Stout *et al.*[69]	Prospective randomized placebo-controlled	12 weeks	41 patients with HF	Echocardiographic indexes, N-terminal pro-brain natriuretic peptide, and inflammatory markers were mostly unchanged in both groups
Toma *et al.*[70]	Meta-analysis of prospective RCTs	Up to 52 weeks	198 patients with stable HF (LVEF < 40%), including NYHA II and III	TRT was associated with a significant increase in exercise capacity, 6-minute walk test, shuttle walk test and peak oxygen consumption. No significant adverse cardiovascular events were reported
Mirdamadi *et al.*[71]	Prospective double-blind, placebo-controlled trial	12 weeks	50 male patients with HF: • TRT group ($n = 25$): 20 NYHA II, 5 NYHA III, 0 NYHA III • Placebo group ($n = 25$): 13 NYHA II, 10 NYHA III, 2 NYHA IV	Patients on TRT showed a significant improvement of the 6-min walk mean distance parameter. Although changes in left ventricular echocardiographic measures were almost comparable between the two groups, the diastolic functional state (assessed by the Tei index) significantly increased in the TRT group.
Abd Alamir *et al.*[72]	Prospective double-blind, placebo-controlled trial	1 year	165 men with coronary noncalcified plaques	A non-significant trend toward a lower plaque volume compared with baseline was observed with the increase of T levels
Navarro-Peñalver *et al.*[73]	Prospective Randomized Double-Blind Controlled Pilot Study	12 months	29 patients with HFrEF, LVEF 30 ± 6%, NYHA II	TRT showed no effect on NYHA class, Framingham score, Minnesota Living Heart Failure Questionnaire, 6-minute walk test, LVEF and N-terminal pro-B-type natriuretic peptide levels
Oni *et al.*[74]	Retrospective cohort study	—	1470 men with previous MI: • Group 1 ($n = 755$): TRT and T normalization • Group 2 ($n = 542$): TRT without T normalization • Group 3 ($n = 173$): no TRT	T normalization was associated with decreased all-cause mortality compared with those without T normalization or untreated. No increased risk of MI recurrence was reported in the TRT groups
Tao *et al.*[75]	Meta-analysis of RCTs	3–12 months	8 RCTs (170 patients with HErEF - NYHA II and III)	No damaging effect on cardiac function was observed

CAD, coronary artery disease; CIMT, carotid intima media thickness; HF, heart failure; HFrEF, heart failure and reduced ejection fraction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; RCTs, randomized controlled trials; TRT, testosterone replacement therapy.

higher risk of the composite outcome ischemic stroke/transient ischemic attack/myocardial infarction. While an increased risk was observed up to the first 2 years of treatment and in 45–59 year aged men, the authors found a significantly lower risk of all-cause mortality in patients in TRT.[78] In 2017 a systematic review examined the studies where the risk of stroke was assessed as a noncomposite endpoint. It included 15 publications, of which seven were observational studies and eight were RCTs. Two observational studies reported a marked reduction in the risk of stroke in patients who underwent TRT and especially in men who achieved normal T levels. A study reported an increased risk of the composite outcome stroke/myocardial infarction/death among T-treated patients. In the other studies the risk of stroke did not differ between treated and untreated patients. Among RCTs the frequency of stroke was too low to draw conclusions about the association between TRT and stroke, so the risk remains unclear.[79]

Effects of the treatment in patients with prostatic diseases

Testicular androgens play an important role in embryogenesis for the formation of the prostate. In prepubertal phase, T (by conversion into DHT) is believed to induce prostate cell proliferation, leading to an increase in prostate volume. In old age, a further growth of the prostate is seen, despite the low T levels. Specifically, an increase in prostate cell proliferation compared with cell death is often observed in this phase. The imbalance of such mechanisms can lead to benign prostatic hyperplasia (BPH) or prostate cancer (PCa) in men. The reasons for such imbalance are yet not well understood, however T is not the only factor associated with abnormal prostate growth.[80]

Given that, some prostatic disorders represent absolute contraindications to TRT in patients with hypogonadism, such as untreated prostate cancer or severe obstructive prostate hyperplasia, according to the current guidelines.[81] Following, the impact of TRT on BPH and PCa is discussed.

Prostatic hyperplasia

BPH is defined as an increase in prostate volume. Glandular hyperplasia often leads to the manifestation of lower urinary tract symptoms (LUTSs), characterized by symptoms of the filling phase and symptoms of the emptying phase. Symptoms of the filling phase (which may also be associated with inflammatory bladder processes, bladder or prostatic carcinoma) include urinary frequency (diurnal and/or nocturnal), urinary urgency and urge incontinence. Among the symptoms of the emptying phase we recall the hypo-valid urination, interrupted urination. The lengthening of the voiding time and the post-voiding dripping are instead included among the post-voiding symptoms. With the progression of prostatic hyperplasia and of the symptomatology, detrusor hypertrophy first occurs and subsequently, as the degree of obstruction progresses, fibrosis is added, which is the infiltration by the connective tissue associated with the deposition of adipose tissue and reduction of sympathetic innervation. All of these events lead to obstructive detrusor instability.

There has been a concern raised that TRT could theoretically worsen LUTSs by increasing prostate size. This concern resulted in the US Food and Drug Administration declaration stating that TRT in men with BPH puts patients "at an increased risk for worsening signs and symptoms of BPH".[82–85] However, despite low T levels, the prevalence of BPH increase with aging,[84] thus suggesting that T is not involved in prostate growth in this phase. A number of studies suggest that prostatic receptors for androgens are totally saturated at levels close to castration (50 ng/dl), although the prostate has numerous ARs.[82] In particular, the AR becomes saturated in human prostate tissue at about 8 nmol/l *in vivo*. Beyond this saturation point (8 nmol/l) T does not appear to further increase prostate volume. This provides explanation for the increase in PSA in men with T below the saturation point when TRT is started, while PSA unlikely increases when serum T is higher than this level. This is commonly called "saturation theory". In line with this theory, although the high T levels reached in young men, they do not develop LUTSs or BPH compared with the norm, contrary to what happens in the elderly with minimal T values.[82]

NO is a powerful regulator of the innervation of the smooth muscle of the prostate. It is believed that NO synthase (NOS) is altered in patients with BPH and therefore it can be assumed that lower levels of NO lead to more severe LUTSs, due to a greater smooth muscle tone at the level of the bladder neck, and to its increased proliferation at the prostate level, which leads to a

worsened urinary flow. T modulates cGMP levels by stimulating high levels of NOS and inhibiting cGMP degradation by phosphodiesterase type 5 (PDE5).[82] The increased NO availability provided by normal serum T levels may positively impact on LUTSs in patients with BPH.

A meta-analysis conducted on 19 randomized trials comparing placebo *versus* T therapy, which overall included 651 patients over 45 years, with low to normal serum T levels, found no statistically significant differences in PCa, PSA growth levels above 4.0 ng/ml or in urinary symptom scores among those who have received T therapy and those who received placebo.[83]

Recently, a systematic review has summarized the data from patients with mild LUTSs randomized to TRT or no treatment in 14 studies ($n = 2029$). No significant difference in International Prostate Symptom Score (IPSS) was observed from baseline on a mean follow-up of 34.4 months. In addition, observational studies have found that TRT can reduce IPSS (IPSS used for the calibration of urinary symptoms and LUTSs). No significant data are available on TRT in men with severe LUTSs (IPSS > 19).[86]

In numerous multicenter studies provided data on the impact of a 1% transdermal TRT on QoL in patients suffering from T deficiency and chronic prostatitis. There were positive changes regarding body weight, waist circumference, pelvic pain, and a reduction in LUTSs, albeit in a median follow-up period of about 6 months. These data demonstrate how TRT not only does not have a clear correlation with the severity of the LUTS, but also can have positive effects on the patient suffering from hypogonadism and chronic prostatitis in the face of a good handling and safety of the treatment.[87] Furthermore, a prospective, open-label trial of 25 men assessed the influence of TRT on urodynamic parameters, reporting a reduction of detrusor pressure at maximum flow after treatment and no relationship between TRT and average flow rate or post-void residual urine.[84]

In conclusion, several systematic reviews of the literature revealed no definite evidence that TRT worsens the symptoms of LUTS or increases the volume of prostate in men with hypogonadism. Hence, further prospective tests are needed to definitively draw up guidelines that can safely and effectively recommend TRT in men with hypogonadism and BPH/LUTSs.

Prostate cancer

Since the 1940s, when Huggins demonstrated how castration and thus the drastic lowering of T values or estrogen therapy caused the regression of PCa, we became aware that high levels of T caused an increase in growth of PCa. This is why TRT is avoided for many years for those who had had a "history" of PCa or who had undergone primary treatment.[88]

In literature there are scientific articles describing the use of T in men treated surgically for organ-confined prostate cancer. In a 2004 retrospective review, seven cases of hypogonadal men undergoing radical prostatectomy were included, all showing symptomatic TD. Each man under examination had received a TRT. After variable follow-up periods, no biochemical or clinical evidence of cancer recurrence was reported.[89]

Again, in a study by Rhoden and Morgentaler, only 1 in 20 patients with hypogonadism and a history of high-grade prostate intraepithelial carcinoma found at prostatic biopsy had PCa after 1 year of TRT.[90]

Unfortunately, today the data regarding the association between TRT and PCa are sometimes few and immature. *In vitro* studies have shown that at low physiologic T levels (< 2.4 ng/ml), prostate cancer cell proliferation is androgen dependent.[80] These findings may provide explanation for PCa recurrence after androgen-deprivation therapy (ADT). Indeed, following treatment suspension, low androgen levels hinder tumor cell growth, but serum T levels increase from castration to low after 12–33 months. After a prolonged period of exposure to deprivation therapy, many men develop a form of castration-resistant prostate cancer (CRCP), probably related to wild-type ARs and independent ligand variants, AR gene amplification and AR mutations. However, CRCP cell lines may be inhibited by maintaining super physiological levels of T led to the stabilization of ligand-bound AR in the nucleus, thus facilitating apoptosis.

No association has been reported in an analysis of 18 prospective studies, collectively comparing 3886 PCa patients with 6438 age-matched

control cases. In addition, no difference in the relative risk of PCa was found in patients with higher T levels and in those with low values. More recently, REDUCE trial, aimed at assessing the role of dutasteride in PCa prevention by the analysis of data coming from 3255 men who underwent prostate biopsy at 2 and 4 years, revealed the absence of association between T, DHT and PCa risk. Also, the latter did not differ among patients with higher T levels and those with lower ones.[91]

The guidelines of the European Urology Association (EAU), the British Society for Sexual Medicine, the International Society of Sexual Medicine, the Endocrine Society and the International Study of Male Aging support that there is no association between TRT and PCa risk.[83]

A nested case–control study drew data from nationwide, population-based Swedish registries. To this end, the risk classification of the PCa has been simplified in two categories: favorable risk (low- and intermediate-risk PCa) and aggressive (high-risk, locally advanced, regional, and distant metastatic PCa), tracing the classification present in the EAU Guidelines.[92] From the results it was deduced that the patients who had received TRT (mostly gel type) did not register an increased rate of overall PCa risk but rather a lower risk of aggressive PCa.[93]

The increasing number of patients now surviving PCa after primary treatment and who had hypogonadism has stimulated a change in attitude towards this topic, with a growing number of doctors now recommending TRT to men who appear to have no recurrence of cancer. Recent scientific publications indicate that there appear to be relapses of PSA with TRT, only in a small number of patients with undetectable PSA levels following radical prostatectomy, even if this number of patients is comparable with the rates of PCa detection reported in screening programs.[88]

Among patients suffering from hypogonadism, and who have undergone radical prostatectomy, there is still fear of TRT as it may stimulate the recovery of the disease. In several retrospective reviews of patients with TD undergone to TRT following prostatectomy, no evidence of local recurrence or widespread neoplastic disease was found within quite long follow-up times (1–12 years). Furthermore, patients undergoing radical prostatectomy and treated with transdermal or intramuscular TRT found no detectable PSA (>0.01 ng/ml), after a median follow-up of 19 months. In these cases, the total mean serum T levels raised from 197 to 591 ng/dl, with improvements also in QoL scores. In a more recent study, 103 hypogonadal men undergoing RP and transdermal TRT were compared with 49 eugonadal men who were also undergoing RP and were divided into low, intermediate, and high-risk PCa. A significant increase of T in the TRT group was reported after 27.5 months. Despite a small increase in PSA in men treated with TRT, the calculated velocity PSAs did not support the thesis of prostatic tumor growth, recalling that the increase in PSA was found in all patients in both the high-risk and the nonhigh-group risk. It should be noted that, while no evidence of PCa recurrence was reported in low- or intermediate-risk subgroups, it was detected in eight patients from the high-risk subgroup. These results don't support a protective role of TRT towards patients with a history of PCa, but encourage broaden research in this way.[91,94]

It is also important to understand whether TRT can be administered to patients undergoing radiation therapy for PCa, and indeed results similar to those proposed above have been found. One of these prospective studies analyzed five patients with PCa undergone to external-beam radiotherapy, which presented with TD, finding a symptomatic response to TRT in the treated patients, such as a reduction in hot flushes, fatigue, and an improvement of libido, and erectile function. One patient showed a temporally increase of PSA levels but nobody had cancer recurrence.[95]

These data are encouraging, but in addition to these positive findings, it must be borne in mind that, after the treatment, there have been cases of increased PSA and biochemical recurrence (a recurrence of the disease reported up to several months earlier by a PSA relapse, after primary treatment), albeit at low rates. The lack of long-term scientific research that focuses on the safety of the treatment of patients makes it difficult to draw firm conclusions. However, it is possible to suggest TRT in those patients whose poor QoL due to untreated hypogonadism would expose them to worse sequelae, and in any case with close monitoring.[91]

Finally, the EAU Guidelines state locally advanced or metastatic PCa as a main contraindication to TRT. Additional contraindications to treatment

refer to the lack of evaluation of suspected prostatic nodules on urological examination, PSA level above 4 ng/ml (or >3 ng/ml in high-risk men for PCa, such as African Americans and those with relatives of first degree that have PCa).[89] The American Urological Association (AUA) and EAU Guidelines recognize the lack of long-term follow-up data as an important limitation of the available studies. However, no increase in PCa relapse was observed, and this is why TRT is supported. The EAU Guidelines recommend that TRT be "treated with monitoring and caution" at least 1 year after low-risk PCa treatment without signs of relapse; TRT is contraindicated in men with locally advanced or metastatic carcinoma. No strong recommendations are given for patients with previous or current cancer.[86,94]

To conclude, some recent evidence encourages the use of TRT in patients with a history of PCa, concluding that it is safe in those with low risk of progression and relapse of PCa. The available data on patients with high-risk disease are scarce, even if the available evidence shows a similar risk of disease relapse among those who take TRT and those who do not, suggesting, in some studies, a potential protective response due to treatment. Therefore, taking into account the current knowledge, TRT may be considered for those patients with a history of PCa at nonhigh risk, in which the benefits of the treatment of hypogonadism are superior to the risks, even if these patients will have to be constantly monitored.

Effect of testosterone on SARS-CoV2 infection: possible implications for the management of COVID-19

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is the pathogen involved in the etiology of the novel coronavirus disease (COVID-19), a pandemic SARS recently affecting more than 5 millions of people and causing >35,000 deaths in over 100 countries (www.worldometers.info/coronavirus).

Epidemiological data provided evidence for the sex influence in SARS-CoV2 infection. An Italian report on 1591 patients with biochemically confirmed COVID-19, reported a significantly higher prevalence of men among infected people, representing 82% of the entire cohort.[96] Another study carried out among Chinese patients failed to confirm the higher frequency of infection in men, but stated a significant 2.4-fold higher mortality in men compared with women. Also, men showed more serious complications than women.[97,98] Similar data have been confirmed elsewhere.[98,99] Finally, a scoping review on 59,254 individuals from 11 countries confirmed a higher mortality rate in the male than the female sex.[100]

From a molecular point of view, androgens are able to impact on the virus infection in peripheral tissues, as T could influence the expression of SARS-CoV2 molecular targets. SARS-CoV2 is an RNA virus, whose genetic material is surrounded by the envelope, a membrane showing several protein antigens in the surface, such as the so-called "spike" protein. The latter is the ligand of angiotensin converting enzyme 2 (ACE2), which is the human receptor used by SARS-CoV2 to enter into the host cells.[9] ACE2 expression is androgen dependent, as shown by animal models. Particularly, the expression of ACE2 is higher in the myocardium of male than female mice and, opposite to what happens in ovariectomy, orchiectomy is able to decrease ACE2 expression in the myocardium.[101] Hence, circulating T could be able to enhance ACE2 expression, thus prompting to SARS-CoV2 infection (Figure 2). In addition, the TMPRSS2, a protein triggering the fusion of the viral and the host cell membranes, which facilitates viral infection, displays an androgen-modulated expression.[102]

This evidence could explain the higher severity and mortality in men than women and may prompt to consider novel therapeutic strategies in COVID-19 patients. A recent population-based retrospective study was performed on 4532 biochemically confirmed COVID-19 male cases from Veneto. Considering the population with PCa, the authors reported a four-fold lower risk of infection in PCa patients on ADT compared with those not on ADT,[103] which suggests that the evidence from the mice model may likely be applied to humans.

The capability of SARS-CoV2 to infect testicular cells is a debated issue. Intriguingly, ACE2 is expressed in Leydig cells, although no overlapping expression with the TMPRSS2 has been found in human testicular tissue.[104] This suggests that the infection of SARS-CoV2 in testicular cells unlikely occur.[102] However, the virus has been detected in the semen of COVID-19 patients,[105] reopening the discussion of a possible urogenital infection of SARS-CoV2. A preliminary and yet unpublished report showed an

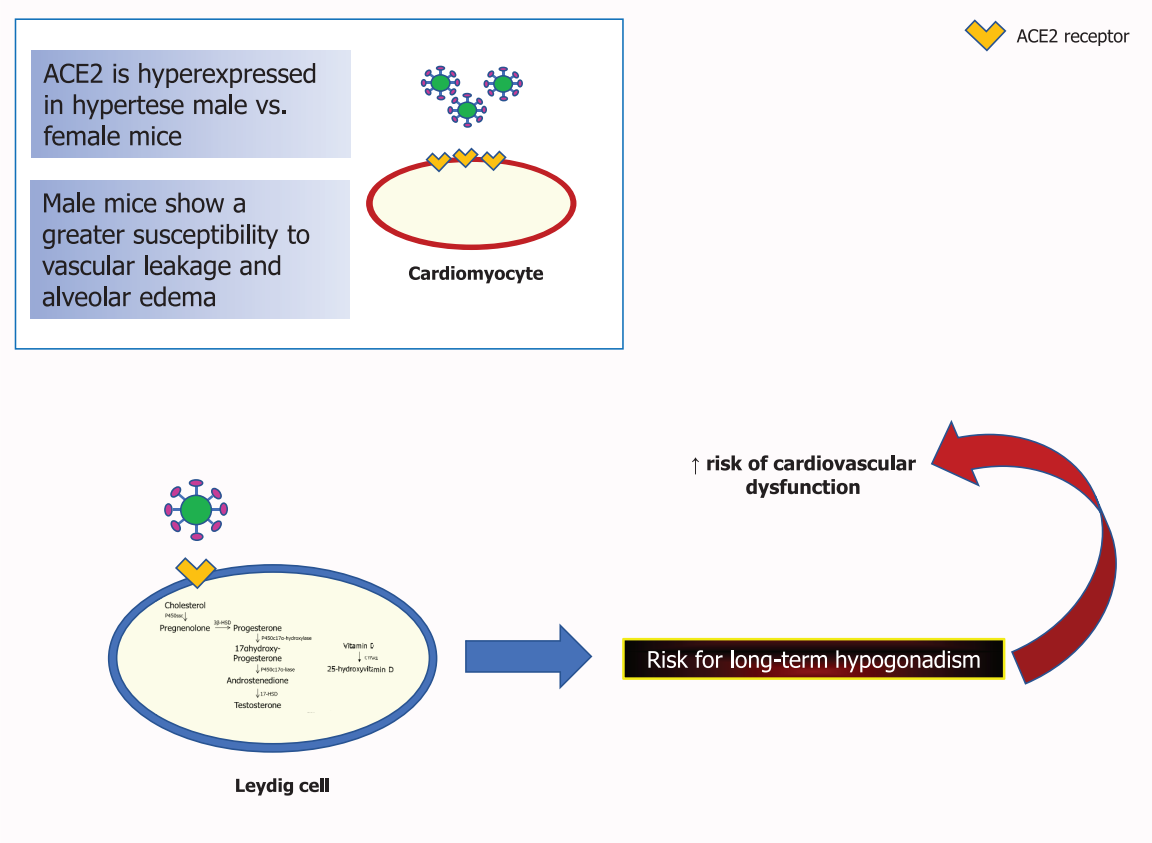

Figure 2. Androgen-related mechanisms of SARS-CoV2 infection. Serum T levels can influence the expression of ACE2 in the myocardium, thus increasing the susceptibility to infect the host cells. SARS-CoV2 can impact on testicular steroidogenesis. Low T levels increases the risk of cardiovascular risk in the long-term. Hypovitaminosis D, which can result from Leydig cell dysfunction, is able to worsen SARS.
ACE2, angiotensin converting enzyme 2; SARS, severe acute respiratory syndrome; T, testosterone.

abnormal LH/T ratio in COVID-19 patients, suggesting that SARS-CoV2 may impair testicular steroidogenesis.[106] Although the reliability of this finding is unknown, the detection of SARS-CoV2 in the seminal fluid implicates that the virus is able to reach the testis. Its impact on steroidogenesis and Leydig cell function may deserve to be prospectively assessed.

In conclusion, based on these considerations, TRT may be temporally discontinued in COVID-19 patients with hypogonadism. ADT might be considered in severe cases with no hypogonadism to oppose to the influence of androgens on SARS-CoV2 infection. However, the quality of the existing evidence is low as only observational studies but not randomized controlled studies are available. Finally, testicular function may deserve monitoring after the acute phase in post-COVID-19 patients.

Author contribution(s)

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