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Review

The interaction of drugs to treat cardiovascular diseases and testosterone therapy, their effects and characteristics

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Abstract

Testosterone is used in the treatment of primary or acquired hypogonadism, constitutional growth retardation, and delayed puberty in male patients. Today, there is a fact that cardiovascular diseases present a high frequency in males with a marked tendency to increase soon. Therefore, the number of men using drugs to treat cardiovascular diseases is increasing rapidly. Cardiovascular drugs, which are frequently used and/or recently introduced, may cause undesirable effects under the heading of drug-drug interaction with testosterone therapy. The number of male patients exposed to these agents may increase rapidly quite soon. In this paper, we reviewed the potential drug-drug interactions between drugs to treat cardiovascular diseases and testosterone treatment considering the pharmacokinetic parameters and experimental animal studies in the literature.

Keywords

Testosterone; Drug interactions; Drug-induced; Cardiovascular drugs

1. Introduction

Testosterone is the main androgen in the body and is used for the treatment of primary or acquired hypogonadism in men. Besides, it is also used in adolescent male patients with growth retardation and delayed puberty.

Today, it is known that cardiovascular diseases are frequently seen in male patients. Therefore, the number of men using drugs to treat cardiovascular diseases is increasing rapidly. Cardiovascular drugs, which are frequently used and/or recently introduced, may cause undesirable effects regarding drug-drug interaction with testosterone therapy. A big amount of novel pharmacologic agents have been developed for cardiovascular treatments and are frequently prescribed. The number of male patients exposed to these agents will likely increase soon.

In epidemiological studies in older men, low endogenous testosterone concentrations have been associated with a higher risk of cardiovascular events [1–3]. However, randomized controlled trials in older men also reported adverse effects of testosterone therapy [4]. Whether testosterone exerts beneficial, neutral or, adverse effects on the cardiovascular system remains unclear and needs elucidation in further studies.

Data on the drug interactions are mostly based on animal studies, case reports or retrospective studies, and a small number of prospective studies. Drug interactions with unproven safety may cause adverse consequences for the patient using the drug. While considering this concept, patient benefits and clinical indications should also be considered.

In this review, we aimed to provide information about the drugs to treat cardiovascular diseases that interfere with testosterone-based drugs and their roles in the possible drug-drug interactions (Table 1). We explained the pharmacological properties of these drugs with their pharmacokinetic background and clinical use drugs to treat cardiovascular diseases and their interactions with testosterone.

1.1 Ambrisentan (moderate)

Ambrisentan is an endothelin (ET) receptor antagonist used in pulmonary arterial hypertension. It inhibits the endothelin receptor subtypes ET A and ET B in vascular endothelium and smooth muscle. ET A and ET B receptors perform opposing actions. ET A receptors are involved in vasocon-

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TABLE 1. Summary of the interactions of testosterone and drugs in cardiovascular diseases.

Drugs	Category	Metabolic pathway	Interaction with testosterone	Risk grade
Ambrisentan	endothelin receptor antagonist	CYP3A4, CYP2C19, UGT 1A9S, 2B7S, 1A3S. Substrate of organic anion transporting polypeptides 1B1, 1B3, P-gp	Increases the oral absorption of ambrisentan.	moderate
Carvedilol	non-selective beta- and alpha-adrenergic blocker	CYP2C9, 2D6, 3A4, 2C19, 1A2, 2E1. Aromatic ring oxidation and glucuronidation.	Carvedilol and testosterone are both substrates and inhibitors of P-gp. Changes in concentrations may occur.	moderate
Conivaptan	non-peptide antagonist of arginine vasopressin V1A and V2 receptors	CYP3A4	Conivaptan is a CYP3A4/P-gp inhibitor, and testosterone is a CYP3A4/P-gp substrate. Concomitant use may increase serum testosterone levels.	major
Dabigatran	direct thrombin inhibitor	Hydrolyzed by hepatic esterases. Hepatic glucuronidation to form active acyl glucuronide isomers.	Dabigatran is a P-gp substrate, co-administration with testosterone, a P-gp inhibitor, may increase serum concentrations of dabigatran.	moderate
Dronedarone	non-iodinated analog of amiodarone, antiarrhythmic	CYP3A4	Dronedarone is a CYP3A and P-gp inhibitor, and is metabolized by CYP3A. Testosterone is a substrate for CYP3A4 and P-gp. Co-administration may increase the level of testosterone.	moderate
Edoxaban	oral Xa factor inhibitor	Minimally via hydrolysis, conjugation and oxidation by CYP3A4	Edoxaban is a P-gp substrate and testosterone is a P-gp inhibitor. Co-administration causes an increase in edoxaban concentration.	moderate
Propranolol	nonselective beta-adrenergic blocker	Aromatic hydroxylation, N-dealkylation, and direct glucuronidation. Aromatic hydroxylation is catalyzed primarily by CYP2D6, side chain oxidation is mainly via CYP1A2 and CYP2D6. Weak inhibitor of CYP2D6.	Testosterone cypionate increases the clearance of propranolol. Efficacy of propranolol may be reduced.	moderate
Ranolazine	anti-ischemic	CYP3A (major) and 2D6 (minor)	Ranolazine is a substrate of P-gp, and testosterone is an inhibitor of P-gp. Co-administration increases the absorption of ranolazine. Ranolazine inhibits CYP3A and may increase plasma concentrations of testosterone since testosterone is metabolized by CYP3A4.	moderate
Rivaroxaban	oral inhibitor of factor Xa	CYP3A4/5 and CYP2J2	Co-administration of testosterone, a P-gp inhibitor, and rivaroxaban, a P-gp substrate, may result in increases in rivaroxaban concentrations and thereby increase the risk of bleeding.	minor
Ticagrelor	oral reversible inhibitor of platelet activation and aggregation	CYP3A4/5	Co-administration of testosterone, a P-gp inhibitor, and ticagrelor, a P-gp substrate, may result in increases in ticagrelor concentrations and thereby increase the risk of bleeding.	moderate
Tolvaptan	non-peptide antagonist of arginine vasopressin V2 receptor	CYP3A4	Co-administration of testosterone, a P-gp inhibitor, and tolvaptan, a P-gp substrate, may result in increases in tolvaptan concentrations.	major
Warfarin	active coumarin derivative, anticoagulant	CYP2C9, CYP2C8, 2C18, 2C19, 1A2, 3A4	Testosterone may increase the anticoagulant effects of warfarin and reduce procoagulant factors, resulting in severe bleeding consequences.	moderate
Dapagliflozin	sodium-glucose co-transporter 2 inhibitor, antidiabetic	UGT1A9, CYP (minor)	Testosterone may result in changes in insulin sensitivity or glycemic control, and may reduce the blood glucose levels.	moderate
Empagliflozin	sodium-glucose co-transporter 2 inhibitor, antidiabetic	UGT2B7, UGT1A3, UGT1A8, UGT1A9	Testosterone may result in changes in insulin sensitivity or glycemic control, and may reduce the blood glucose levels.	moderate
Ertugliflozin	sodium-glucose co-transporter 2 inhibitor, antidiabetic	UGT1A9 and UGT2B7-mediated O-glucuronidation. CYP-mediated metabolism is minimal.	Testosterone may result in changes in insulin sensitivity or glycemic control, and may reduce the blood glucose levels.	moderate

striction, growth, and inflammation while ET B receptors are related to vasodilation and antiproliferation. Ambrisentan binds to the ET A receptor with 4000 times higher affinity compared to the ET B receptor [5].

The protein binding rate of ambrisentan is 99%. Its metabolism occurs via hepatic CYP3A4, CYP2C19, and, uridine 5'-diphosphate glucuronosyltransferases (UGTs) 1A9S, 2B7S, and 1A3S. It is also a substrate of organic anion transporting polypeptides 1B1 and 1B3 and P-glycoprotein (P-gp). Half-life elimination is approximately 9 hours. The time to reach the peak level in plasma is approximately 2 hours. Its excretion is primarily nonrenal [5].

Testosterone implication leads to an increase in the oral absorption of ambrisentan and a decrease in its metabolism since testosterone is a P-gp inhibitor. Therefore, ambrisentan-testosterone interaction poses a moderate risk, and patients should be closely followed for side effects if ambrisentan is co-administered with testosterone [6, 7]. In animal studies, it has been reported that male rats given ambrisentan developed testicular tubular atrophy. At higher doses, a decrease in testicular size was observed at 10 mg/kg /day [8].

1.2 Carvedilol (moderate)

Carvedilol is a non-selective beta- and alpha-adrenergic blocker with no intrinsic sympathomimetic activity and is indicated in heart failure and hypertension. In hypertensive patients, it leads to a decrease in cardiac output, exercise or beta agonist-induced tachycardia, reflex orthostatic tachycardia, peripheral vascular and renal vascular resistance, and plasma renin activity. Its effects in chronic heart failure are related to a reduction in pulmonary capillary wedge and pulmonary artery pressure, heart rate, systemic vascular resistance, and right atrial pressure [9].

Alpha blockade in the antihypertensive effect starts within 30 minutes and beta-blockade starts within 1 hour. The antihypertensive effect reaches the maximum after 1-2 hours. Absorption is rapid in oral consumption, but due to the first-pass effect, the R (+) enantiomer can reach plasma concentrations 2-3 times higher than the S (-) enantiomer. Food intake may delay this effect. The volume of distribution is 115 L. It may distribute into the extravascular fluid. The protein binding rate of carvedilol is higher than 98%. Carvedilol is specifically bound to albumin. Its metabolism occurs in 98% hepatic way, via CYP2C9, 2D6, 3A4, 2C19, 1A2, and 2E1. It is predominantly metabolized by aromatic ring oxidation and glucuronidation. Oxidative metabolites undergo conjugation through glucuronidation and sulfation. The effects of carvedilol depend on the various parameters. Due to the first-pass effect, plasma concentrations in the elderly patients and cirrhotic patients are detected 50% and 4-7 times higher, respectively. In humans that poorly metabolizing the CYP2D6 isoenzyme, the R (+) enantiomer is 2-3 times higher in plasma. Its bioavailability is 25% to 35% for immediate release (due to a significant first-pass effect). Half-life elimination is approximately 7-10 hours. The time to reach the peak level in plasma is approximately 5 hours in the extended-release. Its excretion is primarily via feces [9].

When testosterone and carvedilol are used together, changes in their concentrations may occur. Carvedilol and testosterone are both substrates and inhibitors of P-gp. If concomitant use is necessary, follow-up for side effects is required [10–12]. Therefore, carvedilol-testosterone interaction poses a moderate risk. Preclinical studies have reported adverse effects of carvedilol at 200 mg/kg/day on fertility in rats [13]. On the other hand, no adverse fertility effects were seen at 60 mg/kg/day. This dose level was equal to 10-fold higher than the human dose. In diabetic rats induced with streptozotocin, carvedilol 1 or 10 mg/kg daily for four weeks has been reported to prevent histological damage to the testis caused by diabetes. Caspase 3 expression, an indicator of apoptosis, was increased with diabetes, but this level was decreased with carvedilol [14].

1.3 Conivaptan (major)

Conivaptan is a non-peptide antagonist of arginine vasopressin (AVP) V1A and V2 receptors. It is administered intravenously in the treatment of hyponatremia. Under normal physiological conditions, AVP exerts an antidiuretic effect by activating the V2 receptor, which promotes the balance of water and electrolyte in renal collecting ducts. In euvolemic or hypervolemic hyponatremia, serum AVP levels increase, causing serum sodium dilution. Antagonizing the V2 receptor by conivaptan results in an increase in the urine output, decrease in urine osmolality, and recovery of normal serum sodium concentrations [15].

Conivaptan's protein binding rate is 99%. Its metabolism is converted to four minimally active metabolites via hepatic CYP3A4. Half-life elimination is between 5.3 and 8.1 hours. It is excreted in feces (~ 83%) and urine (12%) [15].

Conivaptan is a CYP3A4/P-gp inhibitor, and testosterone is a CYP3A4/P-gp substrate. Therefore, co-administration should be avoided. Conivaptan-testosterone interaction poses a major risk. Concomitant use may increase serum testosterone levels. Co-administration of conivaptan with other CYP3A substrates has exerted a 2- to 3-times increase in mean AUC values. Previous studies stated that simultaneous use with testosterone is not recommended, and maybe initiated 1 week after the ending of conivaptan treatment [10, 16–18].

1.4 Dabigatran (moderate)

Dabigatran etexilate is a direct thrombin inhibitor administered orally. After oral dosing, dabigatran etexilate is converted to the active ingredient dabigatran. Dabigatran is also metabolized to acyl glucuronides which have similar actions like the main component. Plasma protein binding is approximately 35% and a half-life of 12-17 hours [19, 20]. The daily treatment dose of dabigatran is 2 $\times$ 150 mg or 2 $\times$ 110 mg to inhibit coagulation by preventing thrombin-mediated effects [21].

The volume of distribution is 50-70 L. Dabigatran etexilate is completely hydrolyzed to active dabigatran by hepatic esterases. It also exhibits hepatic glucuronidation to form active

acyl glucuronide isomers. Its bioavailability is 3% to 7%. The time to reach the peak level in plasma is 1 hour. Its excretion is primarily via urine (80%) [21].

Since dabigatran is a P-gp substrate, co-administration with testosterone, a P-gp inhibitor, may increase serum concentrations of dabigatran. In this case, side effects may occur due to increased serum concentrations of dabigatran. If dabigatran is administered for the treatment or prophylaxis of deep vein thrombosis/pulmonary embolism, concomitant use of P-gp inhibitors such as testosterone should be avoided. Besides, concomitant administration of testosterone should also be avoided in patients using dabigatran with non-valvular atrial fibrillation and severe renal impairment, since serum dabigatran levels are increased in these patients compared to patients with normal renal function. P-gp inhibition and renal failure are independent factors that increase dabigatran concentrations [10, 22]. Therefore, dabigatran-testosterone interaction poses a moderate risk.

1.5 Dronedarone (moderate)

Dronedarone is a non-iodinated analog of amiodarone that is administered orally in the treatment of cardiac arrhythmias. This drug can be involved in four antiarrhythmic classes. It inhibits sodium (INa) and potassium (Ikr, IkS, Ik1, and Ik-ACh) channels, causing prolongation of action potential and refractory time in the myocardial tissue. It reduces AV conduction and sinus node function through inhibition of calcium (ICa-L) channels and beta-1 receptor blocking activity. It also inhibits alpha-1 receptor-mediated increases in the blood pressure like amiodarone [23].

The protein binding rate is over 98%. Half-life elimination ranges from 13 to 19 hours. The volume of distribution is approximately 1400 L. Its metabolism occurs via hepatic CYP3A4 to active N-dibutyl metabolite and other inactive metabolites. Its bioavailability is 3% to 7%. The time to reach the peak level in plasma is 3-6 hours. Its excretion is primarily via feces (84%), and urine (~6%) [23].

Dronedarone is a CYP3A and P-gp inhibitor and is metabolized by CYP3A. Testosterone is a substrate for CYP3A4 and P-gp. Co-administration of dronedarone with CYP3A4 and P-gp substrates such as testosterone may increase the level of the substrate [24]. Hence, dronedarone-testosterone interaction poses a moderate risk.

1.6 Edoxaban (moderate)

Edoxaban, an oral Xa factor inhibitor, inhibits prothrombinase activity, and thrombin-induced platelet aggregation.

The drug is transformed into active metabolites with minimal metabolism. Plasma protein binding is approximately 55% and its elimination half-life is 10-14 hours [19, 25]. The daily treatment dose of edoxaban is 1 × 60 mg. The volume of distribution is approximately 107 L. Its metabolism occurs minimally via hydrolysis, conjugation, and oxidation by CYP3A4. Its bioavailability is 62%. The time to reach the peak level in plasma is 1-2 hours. Its excretion is primarily via urine [26].

Co-administration of edoxaban and testosterone causes an increase in edoxaban concentration and side effects of edoxaban may occur since edoxaban is a P-gp substrate and testosterone is a P-gp inhibitor. Hence, edoxaban-testosterone interaction poses a moderate risk. Dosage reduction of edoxaban may be considered for patients treated for deep venous thrombosis or pulmonary embolism [10, 17, 27]. Rats given edoxaban at up to 162-fold higher than the human dose had no effects in fertility [28].

1.7 Propranolol (moderate)

Propranolol, a nonselective beta-adrenergic blocking agent, is frequently used in the treatment of hypertension, tachyarrhythmias, idiopathic hypertrophic subaortic stenosis, hyperthyroidism, and migraine. It is classed in class II antiarrhythmics, competitively blocks beta1- and beta2-adrenergic stimulation resulting in decreases in heart rate, myocardial contractility, blood pressure, and myocardial oxygen requirement. Nonselective beta-adrenergic blockers like propranolol also decrease portal pressure, thereby reduce portal blood flow [29].

The protein binding rate is approximately 90%. Half-life elimination in the immediate-release formulation is 3-6 hours; in extended-release formulations is 8-10 hours. The volume of distribution is 4 L/kg in adults, and it crosses the blood-brain barrier. It represents an extensive first-pass effect, and hepatically metabolized to active and inactive compounds. The main metabolic pathways are aromatic hydroxylation, N-dealkylation, and direct glucuronidation. Aromatic hydroxylation is catalyzed primarily by CYP2D6, side-chain oxidation is mainly via CYP1A2 and CYP2D6. 4-hydroxypropranolol is a weak inhibitor of CYP2D6. Its bioavailability is 25%. The time to reach the peak level in plasma is 1-4 hours in immediate-release, 12-14 hours in extended-release, 6 hours in the long-acting capsule. Its excretion is primarily via urine (96% to 99%) [29].

Testosterone cypionate has been shown to increase the clearance of propranolol. Thereby, the therapeutic efficacy of propranolol may be reduced [30]. Hence, propranolol-testosterone interaction poses a moderate risk.

1.8 Ranolazine (moderate)

Ranolazine exhibits anti-ischemic effects and is used in angina pectoris without changing hemodynamic parameters. Ranolazine inhibits the late phase of the inward sodium channel (late INa) in myocytes during cardiac repolarization, decreasing intracellular sodium concentrations, and thus reducing calcium influx through Na^{+}-Ca^{2+} exchange. A decrease in intracellular calcium reduces myocardial oxygen consumption. At higher concentrations, ranolazine inhibits fast-delay rectifier potassium current (IKr), prolonging the ventricular action potential time and QT interval [31].

The protein binding rate is approximately 62%. Half-life elimination is 7 hours. The volume of distribution is 4 L/kg in adults, and it crosses the blood-brain barrier. Its metabolism occurs via hepatic CYP3A (major) and 2D6 (minor). Its bioavailability is 76%. The time to reach the peak level in plasma is 2-5 hours. Its excretion is 75% via urine

and 25% via feces [31].

Ranolazine is a substrate of P-gp, and inhibitors of P-gp such as testosterone increase the absorption of ranolazine. Additionally, ranolazine inhibits CYP3A and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A4 such as testosterone [2, 32]. Hence, ranolazine-testosterone interaction poses a moderate risk.

1.9 Rivaroxaban (minor)

Rivaroxaban is an oral inhibitor of factor Xa. Rivaroxaban undergoes partial metabolism and turns into inactive metabolites. The rate of plasma protein binding, especially to albumin, is 92-95% and the elimination half-life is 5-9 hours [15, 33]. The daily treatment dose of rivaroxaban is 1 × 15-20 mg. Rivaroxaban inhibits platelet activation and fibrin formation through selective and reversible inhibition of factor Xa [34].

The volume of distribution is approximately 50 L. Its metabolism occurs via hepatic CYP3A4/5 and CYP2J2. Its bioavailability is 80-100 %. The time to reach the peak level in plasma is 2-4 hours. Its excretion is 66% primarily via active tubular secretion and 28% via feces [34].

Co-administration of testosterone, a P-gp inhibitor, and rivaroxaban, a P-gp substrate, may result in increases in rivaroxaban concentrations and thereby increase the risk of bleeding [35]. Hence, rivaroxaban-testosterone interaction poses a minor risk.

1.10 Ticagrelor (moderate)

Ticagrelor is an oral reversible inhibitor of platelet activation and aggregation and is grouped as cyclopentyl triazolopyrimidine. It is metabolized to its metabolite approximately equal in potency. Both parent drug and metabolite are highly bound to plasma proteins (> 99%) and half-lives are approximately 7 and 9 hours, respectively [15, 36]. The daily treatment dose of ticagrelor is 2 × 90 mg.

It reversibly binds to the adenosine diphosphate (ADP) P2Y12 receptor on platelets to prevent ADP-mediated activation of the GPIIb/IIIa receptor complex. This situation reduces platelet aggregation.

The volume of distribution is 88 L. Its metabolism occurs via hepatic CYP3A4/5. Its bioavailability is 30-42%. The time to reach the peak level in plasma is 1.5 hours for the parent drug and 2.5 hours for the active metabolite. Its excretion is via feces (58%) and urine (26%) [37].

Co-administration of testosterone and ticagrelor, a P-gp substrate, may result in increases in ticagrelor concentrations and thereby increase the risk of bleeding. Monitorization for evidence of bleeding is recommended [38, 39]. Hence, ticagrelor-testosterone interaction poses a moderate risk.

1.11 Tolvaptan (major)

Tolvaptan is a non-peptide antagonist of the arginine vasopressin (AVP) V2 receptor. It is administered orally in the treatment of hyponatremia. It has an affinity for AVP receptor subtypes V2 and V1a in a ratio of 29 : 1. Antagonizing the V2 receptor by tolvaptan results in an increase in the urine output, decrease in urine osmolality, and recovery of serum sodium concentrations [40].

The protein binding rate is approximately 98%. Half-life elimination is 3 hours in 15 mg doses; ~12 hours in ≥ 120 mg doses, since half-life increases with higher doses due to more prolonged absorption. The volume of distribution is 3 L/kg. Its metabolism occurs almost exclusively via CYP3A4. Its bioavailability is 42-80%. The time to reach the peak level in plasma is 2-4 hours. Its excretion is 59% via feces and 40% urine [40].

Co-administration of testosterone, a P-gp inhibitor, and tolvaptan, a P-gp substrate, may result in increases in tolvaptan concentrations, thereby a reduction in the dose of tolvaptan may be required [41]. Hence, tolvaptan-testosterone interaction poses a major risk.

1.12 Warfarin (moderate)

Warfarin is an active coumarin derivative, like dicumarol, phenindione, acenocoumarol, diphenadione, phenprocoumon, anisindione. Warfarin (Coumadin) is the most commonly used anticoagulant agent. Vitamin K is required for the hepatic synthesis of coagulation factors II, VII, IX, and X, proteins C and S. These coagulation factors are activated by the addition of carboxyl groups to glutamic acid residues. Vitamin K is activated by epoxide reductase complex 1 (VKORC1). Warfarin inhibits the subunit of the multi-unit VKOR complex, thus depleting functional vitamin K reserves and reducing the synthesis of active coagulation factors [42].

The protein binding rate is 99%. Half-life elimination is 20-60 hours which is variable among humans. The volume of distribution is 0.14 L/kg. Its metabolism occurs via hepatic CYP2C9. Also, minor pathways include CYP2C8, 2C18, 2C19, 1A2, and 3A4. The time to reach the peak level in plasma is approximately 4 hours. Its excretion is via urine (92% primarily as metabolites) [42].

Testosterone may increase the anticoagulant effects of warfarin and reduce procoagulant factors, resulting in severe bleeding consequences in some patients. Therefore, it may be necessary to reduce the warfarin dose during testosterone therapy. In patients receiving such oral anticoagulants, frequent monitoring of INR, and prothrombin time at the beginning and end of androgen therapy is recommended. It is unclear whether testosterone would increase the anticoagulant response to heparin therapy or whether testosterone could alter the effect of other non-coumarin oral anticoagulants similarly [43, 44]. Hence, warfarin-testosterone interaction poses a moderate risk.

1.13 Dapagliflozin (moderate)

Dapagliflozin is an inhibitor of sodium-glucose co-transporter 2 in the proximal renal tubule. This medication prevents reabsorption of filtered glucose resulting in calorie loss in the urine. It is also used to reduce the risk of cardiovascular death and hospitalization in adults with

reduced ejection fraction. Dapagliflozin decreases sodium reabsorption and potentiates the sodium delivery to the distal tubule. Consequently, it can reduce cardiac preload/afterload and decrease sympathetic activity [45].

Its protein binding rate is approximately 91%. Half-life elimination is 12.9 hours. Its metabolism is primarily mediated by UGT1A9 and also CYP (minor). Its bioavailability is 78%. The time to reach the peak level in plasma is 2 hours. Its excretion is via urine (75%) and feces (21%) [45].

Androgen therapy like testosterone may result in changes in insulin sensitivity or glycemic control. In diabetic patients, the metabolic effects of androgens may reduce the blood glucose levels, therefore, antidiabetic agent dosage should be reduced. If coadministration occurs, blood glucose and HbA1C levels should be monitored. Hence, dapagliflozin-testosterone interaction poses a moderate risk [46–51]. No adverse effects on fertility presented in male rats treated with 1708 times the human dose or in female rats treated with 998 times the human dose [52]. Adverse effects on spermatogenesis in males were associated with generalized toxicity [53].

1.14 Empagliflozin (moderate)

Empagliflozin is a sodium-glucose co-transporter 2 inhibitor used in type 2 diabetes mellitus. It initiates the loss of glucose in the urine and reduces cardiovascular mortality in patients with type 2 diabetes mellitus [54].

Its protein binding rate is 86.2%. Half-life elimination is 12.4 hours. Its metabolism occurs primarily via glucuronidation by UGT2B7, UGT1A3, UGT1A8, and UGT1A9. The time to reach the peak level in plasma is 1.5 hours. Its excretion is via urine (54.4%) and feces (41.2%) [54].

Androgen therapy like testosterone may result in changes in insulin sensitivity and glycemic control. In diabetic patients, androgens may reduce blood glucose levels, therefore, the dosage of antidiabetic agents should be reduced. If coadministration occurs, blood glucose and HbA1C levels should be monitored. Hence, empagliflozin-testosterone interaction poses a moderate risk [46–51]. Empagliflozin did not alter fertility in male rats at dose levels up to 700 mg/kg/day, about 155 times the human dose [55, 56].

1.15 Ertugliflozin (moderate)

Ertugliflozin is an antidiabetic agent, acts as a sodium-glucose cotransporter 2 inhibitor.

Its protein binding rate is 93.6%. Half-life elimination is 16.6 hours. The volume of distribution is 85.5 L. Its metabolism occurs primarily via UGT1A9 and UGT2B7-mediated O-glucuronidation. CYP-mediated metabolism is minimal. Its bioavailability is almost 100%. The time to reach the peak level in plasma is 1 hour. Its excretion is via urine (50.2%) and feces (40.9%) [57].

Androgen therapy like testosterone may alter insulin sensitivity or glycemic control. In diabetic patients, androgens may reduce blood glucose levels, hence, antidiabetic agent dosage should be reduced. If coadministration occurs, blood glucose and HbA1C levels should be monitored. Hence, ertugliflozin-testosterone interaction poses a moderate risk [46–51].

2. Conclusions

Patients receiving testosterone therapy and healthcare professionals prescribing testosterone-based drugs should pay attention to drug-drug interactions. Cardiovascular diseases are frequently seen today and therefore the use of drugs related to the cardiovascular system is common. Hence, before initiating the testosterone treatment, the concomitant drugs should be questioned and the possible interaction status should be checked. Otherwise, unwanted negative side effects may be encountered that disrupt body systems and increase morbidity.

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Conflict of interest

There is no conflict of interest to be declared.

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