Testosterone Therapy: Transdermal Androgens

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Introduction

Transdermal administration of a medication is a method for delivering prescribed doses of drug through the intact skin. The drug can be introduced through an attached patch with a drug reservoir, through a permeable membrane, or directly applied to the skin in the form of a gel or lotion. The subcutaneous tissues serve as a depot as small doses are being constantly released into systemic circulation, thus achieving sustained serum levels. There may be a small peak of testosterone within the first few hours after application and then the transdermal testosterone preparation usually maintains serum testosterone within the adult male range for 24 h. Transdermal delivery systems have been available as patches or spray for estrogen replacement in women and as patches, gels, or lotions for androgen replacement in men [1, 2]. Transdermal testosterone gels are the most commonly used formulation to treat hypogonadism in the US and several other countries [3, 4], while long-acting injectables are more widely used in European countries. Some acceptability studies have shown that men of different ages prefer topical gel products due to ease of use and avoidance of the more severe skin irritation seen with reservoir-based

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"patch" delivery systems [5]. Currently available topical products vary by their application methods and dosage adjustment strategies, and are generally expensive. Growing availability of generic agents may lead to decreased cost and improve affordability. This chapter describes advantages and disadvantages of currently available transdermal testosterone preparations, as well as recommendations for treatment and dosing strategy for hypogonadal men.

Advantages and Disadvantages of Transdermal Testosterone Compared With Other Delivery Systems

Table 11.1 shows the advantages and disadvantages of transdermal testosterone preparations. Transdermal testosterone preparations usually result in less fluctuation of serum testosterone levels compared with oral preparations [6, 7]. However, recent studies suggest that serum testosterone varied with fluctuations within a day in older men after testosterone gel application [8]. Furthermore, increases in serum testosterone levels may occur independently of time-related pharmacokinetics in individual patients: these seemingly random measures may be related to changes in blood flow due to exercise and skin temperature. For some transdermal testosterone preparations, depending on the time of gel application, serum testosterone profile mimics normal circadian variation observed in healthy young men [9]. Additionally, transdermal administration helps to avoid first-pass liver metabolism and has less effect on liver secreted proteins such as lipoproteins. Slow-sustained delivery of testosterone may help to avoid adverse effects related to peaks and troughs of testosterone concentrations commonly seen with injectables or oral administration, which may result in adverse effects such as acne, mood swings, and erythrocytosis [6, 10]. It has also been suggested that transdermal preparations may have a better cardiovascular safety profile than injectables [11]. Discussion on testosterone replacement therapy and cardiovascular disease risk is found in Chap. 17.

Table 11.1 Advantages and disadvantages of transdermal testosterone for replacement in hypogonadal men

Advantages	Disadvantages
1. Ease of application	1. Possibility of skin to skin transfer with gels and lotion on close skin contact
2. Availability of large skin surface area for application	2. Local site irritation mainly with patches compared with gels
3. Provides steadier and more sustained release of testosterone into the circulatory system	3. Elevation of DHT due to high 5-alpha reductase expression in skin (most pronounced when applied on scrotal skin)
4. No hepatic first pass results in higher bioavailability and less changes in liver dependent proteins	4. Variable rate of absorption
5. Mimics physiologic testosterone secretion with some preparations	5. Expensive

DHT - 5α Dihydrotestosterone

Preliminary data also show lower levels of spermatogenesis suppression in comparison with injectable treatment [12], but these findings need to be validated in larger cohorts.

Skin irritation is a common side effect with all transdermal preparations but is much more pronounced with testosterone patches. Additionally, as the pricing level of these transdermal preparations is generally higher than commonly available short-acting injectables (i.e., testosterone enanthate and cypionate), this makes these user friendly methods less affordable to many hypogonadal men. Specific shortcomings for the different types of transdermal preparations will be discussed in detail in respective sections.

Transdermal Patches

Scrotal patches were the first commercially available transdermal formulation, but have since been phased out in the US as newer more convenient alternatives became available. Thin, flexible, and self-adherent scrotal patches contain polymeric membranes impregnated with testosterone. When applied daily on the scrotal skin, the scrotal patch can consistently maintain testosterone level in the mid normal range. Testosterone levels peak at 2–4 h and remain within the reference range of adult men for 24 h after the application of the scrotal patch. Application of the scrotal patch requires the clipping of scrotal hair and the large area of the patch does not allow application in hypogonadal men with small scrotum [13, 14]. Scrotal skin has high 5α-reductase activity which results in serum 5α dihydrotestosterone (DHT) levels in the high upper or above the reference range of adult men [15]. Although serum levels of DHT do not correlate with intra-prostatic DHT levels and on long-term follow up there is no known increase in incidence of prostatic cancer [16], there remain concerns in the minds of some clinicians or regulatory agencies with regard to slightly higher DHT levels [17]. Scrotal patches are rarely used by patients mainly because of inconvenience of poor adherence to skin.

Non-scrotal patches (Androderm®) deliver 2 or 4 mg of testosterone. The usual starting dose is one 4 mg patch applied daily before bed time. Testosterone is continuously released for 24 h with maximum concentration ranging within 4–12 h after application of the patch. After removal of the patch, serum testosterone decreases with an apparent half-life of approximately 70 min [9, 18]. Dosing should be adjusted based on morning testosterone levels after 2 weeks of usage. Values outside the adult male reference range require a dose decrease to 2 mg/day (one 2 mg patch) or increase to a maximum recommended dose of 6 mg/day (4 and 2 mg patches applied simultaneously).

Testosterone patches can be applied to healthy and clean skin on the back, abdomen, thighs, or upper arms but not the scrotal skin or bony prominence. Application sites should be rotated and the same site should be avoided for 7 days. The patch consists of a drug reservoir and a multilayer drug delivery system. In order to transport the required amount of testosterone through the skin, these systems are equipped with an enhancer which may lead to skin allergic contact dermatitis [19]. Mild

allergic skin irritation is noted in up to two thirds of patients, while up to 10–15 % of patients have been reported to discontinue the treatment. Topical corticosteroids have been suggested to decrease the discontinuation rate of the skin patches [19, 20]. More serious skin reactions are rare, however, localized skin necrosis has been reported [21]. It is recommended that prior to a magnetic resonance imaging procedure a patch is removed because it may cause skin burns because the patch contains aluminum. Another larger non-scrotal matrix patch without enhancer was developed (Testoderm TTS®). Although this patch has caused less skin irritation than the reservoir patches, the problem of adherence to skin and frequent dislodgement led to discontinuation of marketing of this non-scrotal testosterone patch.

Certain precautions are recommended to ensure the maximum effect of patches, such as avoiding water contact for at least 3 h after application. Excessive sweating or physical activity may lead to non-adherence of the patch. If the patch becomes dislodged, it is recommended to reapply it by rubbing the finger around the edges. In case the patch falls off completely, it is advised to apply a new patch if this occurred before noon, otherwise waiting until regular evening application.

Transdermal Gels

Transdermal gels are becoming increasingly popular and have surpassed injectable preparations as the most common form of testosterone replacement in the US and United Kingdom over the past decade [3].

Testosterone gel is applied directly to the skin avoiding the requirement of a patch or a membrane and resulting in less skin irritation than that observed with transdermal patches. Testosterone gel is available as prepackaged single dose packets or multi-dose pumps. Some manufacturers provide both options (Table 11.2). Most testosterone gel preparations are formulated as hydroalcoholic gel, others use other enhancers in lotions. When applied to the skin, testosterone is absorbed into the stratum corneum over time, which serves as a reservoir. Testosterone is slowly released into the circulatory system over several hours resulting in steady state serum levels of the hormone [22]. The release of testosterone from the reservoir continues for about 24 h. Only approximately 10 % of the testosterone applied on the skin surface is absorbed into the circulatory system during a 24-h period.

The gel is applied to a large area of the skin, usually on the arms and shoulders, and the area of application may affect the absorption of testosterone [23]. Long-term studies with testosterone gel have shown that steady and relatively consistent serum levels of testosterone levels are attained [7], which results in significant improvement of sexual and body composition parameters [24–26].

Several formulations of testosterone gels are available on the market [1, 2, 27]. Currently available gels vary in testosterone concentration and are usually applied once a day. Their pharmacokinetic profiles are also similar: Androgel 1 %®/ Testogel 1 %® [7], Testim® 1 % [28], Axiron®2 % [29] Fortesta Gel® 2 %/Tostran® 2 % [30], and Androgel 1.62 %® [31]. These transdermal preparations have been proven to be efficient in normalizing serum levels, as well as reversal of androgen

Table 11.2 Characteristics of some testosterone gels (based on manufacturer's label)

Name, strength, (Manufacturer)	Packaging	Dosage	Time of testing	Application site	Sites to be avoided	Swim/shower after
Androgel 1 % (AbbVie Inc.)/Testogel 1 % (Besins Healthcare)	25 or 50 mg packet, multi-dose pump (12.5 mg/actuation)	50–75–100 mg Once daily	Not provided	Shoulders, upper arms, abdomen (coverable by short sleeve T-shirt)	Elsewhere (eg, genitals, chest, back, abdomen, axillae, or knees)	5 h
Androgel 1.62 % (AbbVie Inc.)	40.5 or 20.25 mg packet Multi-dose pump (20.25 mg/actuation)	40.5 mg (20.25–81) Once daily	AM pre-dose morning blood draw ~14 and 28 days after start	Shoulders and upper arms bilat. (area covered by short sleeve T-shirt)	Elsewhere (eg, genitals, chest, abdomen, axillae, or knees)	2 h
Axiron 2 % (Eli Lilly and Co.)	Multi-dose pump (30 mg/actuation)	60 mg (30–120) Once daily	2–8 h post application at least 14 days of constant use	Axillae bilaterally	Other parts of body	2 h
Fortesta 2 % (Endo Pharmaceuticals Inc.)/ Tostran 2 % (ProStrakan)	Multi-dose pump (10 mg/actuation)	40 mg (10–70) Once daily	2 h post application 14 and 35 days after start	Use one finger on front and inner thighs (not near scrotum) bilat.	Genitals or other parts of body	2 h
Testim 1 % (Auxilium Pharmaceuticals Inc)	50 mg in tube with emollient	50–100 mg Once daily	AM pre-dose T concentration 14 days after start	Upper arm, shoulder (coverable by T-shirt)	Abdomen, scrotum, penis	2 h
Vogelxo 1 % (Upsher-Smith Laboratories, Inc.)	50 mg tube or packet Multi-dose pump (12.5 mg/actuation)	50–100 mg Once daily	AM pre-dose T concentration ~14 days after start	Upper arm, shoulder	Abdomen, genitals	2 h

deficiency symptoms for long periods of treatment [24] and have been considered an acceptable form of testosterone substitution by users [5]. The maximum concentration of testosterone achieved is variable depending on the preparation but usually within 2–5 h of application and is maintained for 24 h. When applied in the morning, a profile somewhat similar to circadian rhythm in healthy men is maintained. Recent studies in older hypogonadal men have shown that after testosterone gel application there were large fluctuations in serum testosterone concentration both within and between patients [8]. Skin structural differences may be one of the causes of these significant variations in the bioavailability of the drug, which poses challenges in predicting effectiveness of medication and determining an adequate dose, as well as appropriate time for testing serum testosterone levels [8, 32]. Non-time-dependent pulses of serum testosterone also occur in relation to exercise and skin temperature. Both factors may be mediated through changes in dermal blood flow. Another important issue is a possibility of blood sample contamination when it is drawn at the gel application site, which has led to spurious increase in measured testosterone levels [33]. Sampling of blood after testosterone gel applications should be away from the application sites.

Different sites for drug application have been studied with various degrees of success. Scrotal skin is thin and highly vascular hence it leads to better and sustained absorption of testosterone, which made it one of the early targets in the development of transdermal patch preparations. Scrotal application is not used for the gels because of the relatively small area where the gel can be applied. Application on the axillary region may enhance absorption and may cause less skin transfer, and has been shown to be beneficial to patients who failed other transdermal preparations in a single study [34]. However, because the skin is sensitive in the area, skin irritation, edema, and erythema have been observed as in other transdermal preparations [35]. On the other hand, even though application of 1.62 % testosterone gel on abdominal skin led to 30–40 % lower availability than on the upper arms and shoulders, application on all of these sites resulted in eugonadal testosterone levels [36]. While selection of an application site may not be an issue for most patients, those failing to achieve sufficient systemic levels may benefit from a change of site.

Additionally, some gels include emollients that prevent skin drying and ensure better testosterone absorption. There are data to suggest that this may help achieve better bioavailability and higher serum concentrations [37]. Differences in gel formulations and their pharmacokinetic profiles are a reason why gels cannot be used and dosed interchangeably. Therefore, it is recommended to follow specific instructions on sites for application and dosing of the drug provided in the labeling. Dosing information and recommendations for some of the preparations are presented in Table 11.2. It should be noted that some gels are marketed in various countries under different names but are in fact produced by the same manufacturer.

As most of the gels contain alcohol, they are flammable, therefore precautionary measures are required. More importantly, there is a risk of skin to skin transfer of the gel to other persons on close contact. This is particularly important in women and children whose endogenous testosterone levels are low. To avoid this risk, hands

must be washed with soap and water after application of the gel. Once applied, the gel on the application site dries within several minutes and should be kept covered with clothes at all times or washed thoroughly with soap and water to remove any residue of gel if close skin to skin contact is anticipated [38]. However, showering within a short period of time (15–30 min) after application of the gel may result in lower serum testosterone levels [39] and should be avoided. Manufacturer recommendations for minimum time before washing after application vary from 2 to 5 h among different formulations (Table 11.2). It must be noted that washing within that time resulted in approximately 30 % decreased bioavailability of testosterone, however, serum testosterone levels within normal range were sustained. Even with these precautionary recommendations in place, skin to skin transfer continues to pose challenges including reports of virilization of prepubertal children [40–43]. Therefore, physicians prescribing the use of transdermal testosterone gels or lotions must discuss with the participants the risks of transfer and the measures to prevent transfer, as well as other potential adverse events of testosterone discussed in Chaps. 14, 16, 17.

Elevation of DHT has been found to be more pronounced in transdermal gels compared to other formulations possibly due to high 5-α reductase expression in skin (especially when applied on scrotal skin) [7]. In contrast to transdermal patches, a much larger area of skin is exposed to testosterone, thus leading to an increase in systemic DHT concentration. Because DHT is the main androgen in the prostate, it may have more stimulating effects on prostate growth. While serum DHT to testosterone ratio is increased after transdermal testosterone application, there are no data showing the association between higher DHT levels and adverse effects on prostatic hyperplasia or cancer of the prostate [17]. Elevation of DHT has been associated with a higher risk of cardiovascular events in observational studies [44] but needs to be systematically assessed in large scale long-term studies. On the other hand, this moderate increase in DHT levels that is seen in transdermal gel users usually remains within the reference range limits in healthy adult men and has not been related to adverse effects on primary DHT targets, such as the prostate.

Another important drawback of currently available testosterone gels is their cost. Compounded testosterone may be one of the alternatives but is not recommended as there is no quality control standard for compounded medications. A recent study from Canada reported large variations of testosterone levels in these preparations [45] and standardization strategies have been suggested [46]. Increasing availability of generic testosterone gels may lead to decreased costs and improve affordability in the near future.

As discussed above, there are distinct differences among the various transdermal preparations. Decision on the most appropriate treatment strategy should be based on an individual patient profile and personal preferences after all available strategies are discussed. It is of utmost importance that the patient is comfortable with the selected treatment as compliance is one of the major challenges with long-term treatment of chronic asymptomatic conditions [47].

Other Topical Testosterone Delivery Systems

Similar strategies to those used in transdermal testosterone delivery systems have been used in developing trans-mucosal preparations. Currently available systems include the trans-buccal system and intranasal gel. The mucous membrane of the nose is more permeable than skin, and therefore because of a higher level of absorption, lower doses of testosterone are required. On the other hand, nasal application of testosterone results in quick onset and short duration of action, which leads to fluctuation of systemic testosterone levels and requires multiple daily applications (two or three times per day for intranasal gel) [48]. The trans-buccal system involves application of a tablet to the buccal mucosa, where the tablet forms a gel and delivers steady levels of testosterone for about 8–12 h [49]. Although there is no significant irritation to the gums, the tablet can be dislodged and some patients did not like to have a gel tablet in their mouth. There is also no dosing flexibility as all patients are required to apply one tablet twice a day and discontinue use if systemic testosterone level is outside normal range. A report of the safety and efficacy after 2 years of continuous use of this buccal delivery system [50] showed that up to 62 % of subjects had at least 80 % of their testosterone measurements within reference range of adult men and the safety profile was generally favorable with local adverse effects (gum edema, blistering, and gingivitis) being mostly mild, leading to discontinuation in 4.3 % of patients.

Conclusion

Transdermal testosterone delivery by applying gels or lotions onto the skin is the preferred method of many men. This delivery method does not require invasive injections or implants and can be administered in the patient's home environment. Significant skin irritation is not a common problem with gels and dose titration can be achieved by adjusting the number of actuations of a canister or a number of sachets or tubes. The main issue with transdermal testosterone for replacement therapy is the potential of skin to skin transfer of medication upon close skin contact. This can be largely avoided by showering or wearing protective clothing when skin contact is anticipated. The choice of which testosterone replacement treatment is optimal for the patient depends on the patient's preference and whether there are contraindications to other therapies. In older men with comorbidities, it may be prudent to commence treatment with lower doses of transdermal testosterone. If adverse effects develop, the application of the gels or lotions can be stopped and the patient's testosterone will return to the prior levels within a period of several days. With the emergence of more transdermal testosterone preparation options, the cost may be reduced making this delivery system more affordable for hypogonadal men.

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