Short review (expert opinion)

Transdermal delivery of testosterone

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ABSTRACT

Male hypogonadism has been treated with exogenous testosterone since the 1930s. The early transdermal patches of testosterone became available in the 1980s with gel and solution preparations following subsequent decades. This review focuses on the skin permeation characteristics of testosterone, pharmacokinetics following application of transdermal formulations and formulations currently available. At present, gels dominate the market for transdermal testosterone replacement therapy, presumably because of their greater patient acceptability and non-occlusive nature compared with patches. However, specific incidences of secondary transfer of gels to children with consequent unwanted effects such as precocious puberty have been reported. A regulatory review of all testosterone replacement therapies is currently underway which may have implications for future prescribing practices of transdermal testosterone products.

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1. Introduction

Testosterone (Fig. 1) is an androgenic steroid hormone which regulates a number of important functions in males including sperm production, sex drive, fat distribution, muscle mass, bone density and red blood cell production. Production of testosterone in the testes is regulated by luteinizing hormone (LH) in the pituitary gland. Puberty starts with the production of LH and follicle-stimulating hormone (FSH), the latter hormone being critical for spermatogenesis. The action of testosterone is via the androgen receptor, located in the nucleus and cytoplasm of target cells. Deficiency or absence of testosterone in men is defined as hypogonadism which is further classified as either primary (originating in the testes) or secondary (resulting from a problem in the hypothalamus or pituitary gland). Testosterone deficiency may result from autoimmune conditions (Addison’s disease or hypoparathyroidism), genetic disorders (Klinefelter’s or Turner’s syndrome) or may result for other reasons including accidents, infection, excessive exposure to heavy metals or alcohol, radiation, chemotherapy and tumours. With age, males experience declining testosterone levels and loss of the normal diurnal rhythm of testosterone which may also result in clinical hypogonadism [1].

The symptoms of hypogonadism include impaired libido, loss of sexual function, regression of secondary sex characteristics, low muscle mass and decreased bone density [2,3]. The primary approach for management of this condition is testosterone replacement therapy. Testosterone is currently administered to hypogonadal patients using various routes including oral, parental (injection or implant) and transdermal delivery. Although transdermal testosterone delivery devices first became available in the 1980s, percutaneous administration of testosterone for treatment of hypogonadism was reported as early as the 1930s [4]. Transdermal delivery of testosterone offers a number of advantages compared with other routes of delivery including improved patient compliance, ease of administration and/or cessation of therapy and the achievement of sustained drug plasma levels. The goal of effective transdermal testosterone delivery is to achieve plasma levels in the range of normal endogenous production of 3–10 mg over 24 h and in a time dependent manner thus mimicking the circadian profiles of healthy males [5,6]. In this article the historical development of transdermal testosterone formulations is reviewed as well as the various formulations currently are available. Emerging technologies are also considered as well as safety considerations for steroidal hormone formulations.
2. Physicochemical properties, pharmacokinetics and metabolism

The physicochemical properties and pharmacokinetics of testosterone are summarised in Table 1.

When administered orally, testosterone is subject to significant metabolism in the gastrointestinal tract [13] and in the liver [14]. Following intravenous injection, the half-life of testosterone in blood has been reported to vary from 10 to 100 min [9,10]. Testosterone is metabolised to several keto derivatives via oxidation at the 17-OH group as well as to dihydrotestosterone (DHT) and estradiol. Metabolites are excreted as glucuronide or sulphate conjugates [9] with about 6% of drug being excreted unchanged [11]. In the systemic circulation testosterone is bound to sex hormone binding globulin (SHBG) tightly, and loosely to albumin with a small amount (~2%) of the free molecule [15,16]. Total testosterone measurement is accepted for evaluation of most patients; however, free testosterone is determined in some cases because of changes in SHBG concentration with health status, age or drug therapy [17].

Testosterone is metabolised in adipose tissue and skin by 5α reductase and aromatase to DHT and estradiol, respectively [18]. Higher levels of reductase are found in perianal skin areas e.g. the scrotum [19] explaining the elevated levels of DHT observed in studies with scrotal patches [20,21]. Long term exposure to testosterone has also been suggested to increase 5α reductase levels in hypogonadal men [22]. The potential long term effects of elevated DHT associated with scrotal patches raised concerns as elevated DHT levels had earlier been reported in prostate hyperplasia [23].

3. Testosterone skin permeation

Christophers and Kligman [24] reported the measurement of testosterone absorption in vivo using a residual analysis technique in 10 young (19–30 years) and 10 old (71–82 years) subjects. The site on the back was first cleansed with ether followed by application of 0.02 ml of a 1% solution of 14C testosterone in ethylene glycol monomethyl ether over an area of ~1.8 cm². Silicone vacuum grease was used to ensure no spreading of the solutions and initial counts were taken after drying of the application. Following occlusion of the site with Saran Wrap for 24 h final radioactivity was measured. The difference between the initial and final counts indicated 38% absorption for younger subjects and 13% absorption for older subjects. However it should be noted that this study does not necessarily show that this high amount was absorbed into the circulation; there may be some remaining in the stratum corneum. In a later study by Roskos et al. [25], where direct measurement of testosterone was conducted, no significant differences in testosterone absorption for younger and older subjects were observed.

Radionlabelled testosterone was applied to the forearm in an acetone vehicle at a dose of 4 μg/cm². Urinary testosterone measurements indicated that the percentage dose absorbed for the young group (22–40 years) was 19.0 ± 4.4% and for the old group the value was 16.6 ± 2.5%. Measurement of testosterone from the human forearm was also reported by Feldman and Maibach in a number of earlier studies [26,27]. Radionlabelled testosterone was dosed at 0.06 mg/13 cm² in an acetone vehicle containing 25% of either dimethyl formamide (DMF), dimethyl acetamide (DMAC), dimethyl sulphoxide (DMSO), mineral oil (MO) or propylene glycol (PG). Treated sites were not protected in any way and subjects were requested not to wash the areas for one day. The urine of subjects was collected for five days and analysed with 11.8% of the radiolabel being excreted for the control vehicle (acetone alone). DMSO and DMF increased the penetration of testosterone by four and two-fold, respectively. DMAC and PG also increased testosterone permeation but to a lesser extent and MO had no effect compared with the control. In a later study, conducted under similar condition, the amount of testosterone absorbed from an acetone vehicle was reported as 13% of the applied dose [28]. Schaefer et al. [29] estimated the flux of testosterone through skin as 0.05 nmol/cm²/h over a 12–24 h period, based on the earlier work of Maibach and colleagues. The authors also determined a flux value for testosterone of 1 × nmol/cm²/h for a 0.1% preparation based on in vivo experiments over 100 min; as this is a relatively short time, steady state is not likely to have been achieved.

Bucks et al. [30] reported values of ~20% of testosterone absorbed for a repeated application study in five healthy male volunteers. Testosterone was applied in an acetone vehicle over a 28 cm² area of the forearm at a dose of 4 μg/cm²; radiolabelled compound was applied on days 1 and 8 while unlabelled material was applied for days 2–7 and days 9–14. The application site was washed every day prior to application of the next dose and urine was collected daily for 14C analysis. In a later study [31], testosterone absorption in vivo was studied for occluded versus “protected” (covered but not occlusive) conditions. Following a single doseapplication the percentage of drug absorbed for the occluded studies was higher (46%) compared with the protected conditions (18%). For multiple doses applied at the same site (daily application at the same skin site for 14 days) drug absorption at day 8 was not significantly different compared with the single dose occluded study (~50%).

4. Transdermal testosterone patch formulations

4.1. Scrotal patches

Most of the matrix scrotal patches developed by Alza which were evaluated in the early clinical studies were available in three strengths: 20 cm², 40 cm² or 60 cm² with respective drug content being 5 mg, 10 mg and 15 mg. Approximately one-third of the drug content was delivered from the patches. Elevated levels of DHT and high ratios of DHT to testosterone, associated with the elevated
reductase enzyme activity, were observed after 2–4 weeks con- tinuous use of the patches [21,22,32].

Trans-scrotal patches achieved testosterone levels of 400 ng/ml or greater, in hypogonadal subjects, in less than 4 h [33], with dose dependent increases depending on patch size. Six patients under- went five one-week treatments with patches being applied for 22 h daily. Subjects wore a placebo patch for the first week and then were treated with 20, 40 or 60 cm² patches containing 5, 10 or 15 mg of testosterone, respectively. Mean average testosterone serum levels for placebo and for the patches were 135 ± 38 ng/dl, 348 ± 66 ng/dl, 455 ± 77 ng/dl and 624 ± 65 ng/dl. Korenman et al. [22] reported the results of short and long-term treatment with trans-scrotal patches for three patients. For the former, patches with varying drug content were applied daily for periods of four days in randomised order five weeks after treatment by injection of testosterone enanthate. One treatment involved application of patches to the inner thigh, which necessitated an additional tape overlay. Following this study, patches were re-designed for the long-term study to be larger and to improve adhesiveness. Analysis of patch residual content indicated 30% absorption trans-scrotally and patients achieved normal testosterone levels over the one year treatment period. When applied to the thigh, no increases in serum testosterone were observed.

Subjective increases in sexual function were reported in a four- week study conducted with 5 subjects using 40 cm² and 60 cm² patches [21]. McClure et al. [34] evaluated both 40 cm² and 60 cm² patches in a 12-week study on four subjects and reported restoration of normal sexual function with positive effects on mood and energy. The incidence of irritation with the scrotal patch was reported to be lower compared with the non-scrotal patches which were subsequently developed. However some patients did not have an adequate scrotal area to accommodate the patch; problems with adhesion of patches were also reported [35].

4.2. Non-scrotal patches

Reservoir type patches for application to non-scrotal skin were subsequently developed and evaluated in vitro and in vivo [36,37]. The reservoir consisted of testosterone, penetration enhancers and glycine in a gelled vehicle. Patches were adhered to skin with a peripheral adhesive and a microporous membrane (not rate-limiting) separated the reservoir from the adhesive. The active area of drug delivery of the patch was 7.5 cm² and the testosterone loading of patches was 12.5 mg. In vitro permeation studies suggested ~3.4 mg of testosterone would be delivered over 24 h in vivo. For clinical studies two patches were applied nightly to various sites on the torso. In vivo studies were conducted both for a single patch application and for a four-week period of application. Physiological levels of DHT as well as testosterone were achieved, thus avoiding the first-pass metabolic effects of the scrotal patches. Non-scrotal patches were evaluated for a single application (two patches applied to the mid-back at night) and following a four-week period of application of two patches nightly to various parts of the upper body [37]. For the single application patches were removed after 24 h and measurements were conducted over 48 h. An increase in baseline testosterone levels of 5.8 ± 0.9 nmol/l to an average peak value of 44.1 ± 4.8 nmol/l at 5.7 ± 0.6 h was observed; values subsequently decreased to 17 nmol/l for the remaining 12 h. After removal of the patches the elimination half-life was 116 ± 17 min. For the four week study the average peak testosterone concentra- tion was 33.5 ± 4.3 nmol/l, which was achieved after ~6 h applica- tion of the patches. A time-averaged testosterone level of 21.8 ± 4.3 nmol/l was also attained after this period of application. Steady state profiles of both testosterone and DHT mimicked nor- mal daily variation. Residual content analysis of the patches indi- cated that drug input ranged from 3 to 7 mg/day. Patches were well tolerated with the exception of one subject who developed an allergy to one of the patch excipients. Subjective improvements were reported for sexual function and well-being for patients who were treated with trans-scrotal patches for 7 months [36].

Arver et al. reported the pharmacokinetics of testosterone deliver- y from these patches as part of a multicentre, open-label study in 34 patients over a 12-month period [38]. Testosterone levels were measured 12 h after patch application in the morning. Mean testosterone levels were 522.6–642.1 ng/dl, and were within the normal range. The average testosterone level, based on assessment from months 3 to 12, was 599.8 ± 199.6 mg/dl. Normal circadian testosterone levels were observed with a morning peak of 740.9 ± 278.2 mg/dl and a night-time trough of 213.3 ± 80.0 mg/dl. The DHT to testosterone ratio was within the normal range for healthy men. Sexual function was reported to improve significantly which was subjectively assessed using structured questionnaires and daily logs. 10 Patients reported skin irritation and subsequent- ly three patients withdrew from the study because of this side effect. The most common adverse events were pruritus, mild or moderate erythema (15 subjects) and application site itch (15 sub- jects). Blister reactions were also reported where patches were applied to bony prominences (6 patients).

As part of the 12-month study reported by Arver et al. [38] the same authors also examined the influence of site of application of the patch on testosterone pharmacokinetics and metabolism [39]. In a sequential crossover design study two patches were applied for 24 h to the back, abdomen, upper arm, chest, shin or thigh. Sequential applications were separated by a minimum of 2 days (24 h after the previous patches were applied). Time averaged steady state testosterone concentrations (Css) for bioavailable testosterone (non-SHBG bound testosterone) for the sites were ranked as follows: back > thigh > upper arm > abdomen > chest > shin. To optimise testosterone delivery the authors suggested that the preferred sites for applying the patches should be the back, thigh, upper arm and abdomen. In addition, it was noted that no significant dermal metabolism of testosterone was evident at any of the sites tested.

Yu et al. [40] conducted an open-label, randomised, crossover study to evaluate dose proportionality of non-scrotal patches (D-TRANS, Alza Corp). 19 Hypogonadal men were recruited and either one or two patches were applied daily for 7 days to the upper buttocks. Patches were 60 cm² in dimension with an estimated drug delivery of 5 mg per day. As a positive control scrotal patches with the same dimensions and with a nominal delivery of 6 mg/day were also used. Plasma testosterone levels were simi- lar for all treatments and mirrored normal testosterone levels. Average serum concentrations for placebo, scrotal patch, application of one patch and application of two patches were respectively 157 ± 172, 403 ± 255, 570 ± 225 and 941 ± 382 ng/dl. Analysis of the log-transformed normalised increased area under the curve (AUC) data indicated that serum levels of testosterone were pro- portional to patch surface area. All three treatments produced an early increase in plasma testosterone with maximal concentrations observed 2–4 h after patch application. Testosterone levels remained relatively stable over 24 h and on removal of patches, testosterone levels declined rapidly to near baseline. There were no statistically significant increases in the ratio of testosterone to DHT for the non-scrotal patches.

5. Transdermal gel formulations

5.1. AndrogeT™

There are several currently marketed transdermal testosterone gel formulations (Table 2). AndrogeT™ was the first preparation to
become available (in June 2000) and within one year of launch supplanted patches as the preferred transdermal testosterone preparation of choice in the United States [41]. This is a hydro-alcoholic gel formulation containing isopropyl myristate which the patient applies evenly to the shoulders/upper arms and/or abdomen area. The original Androgel™ preparation contained 1% w/w testosterone and more recently a formulation containing 1.62% w/w of drug has become available (Table 2). For the recommended starting dose of 50 mg testosterone for Androgel™ 1%, and assuming an applied dose of 2 mg/cm² the approximate area of application is ~2500 cm². Androgel™ 1.62 has a starting dose of 40.5 mg testosterone with an estimated area of application of ~1250 cm².

A crossover study conducted by Wang et al. [42] in 9 subjects over 14 days indicated that steady state testosterone levels were achieved between 48 and 72 h after first application of the gel. Patients applied one metered dose (25 mg) either at the same site (left arm/shoulder) four times or at four separate sites (left and right arms/shoulders and left/right abdomen). Within 4 days of stopping the treatment testosterone serum levels returned to baseline. Mean AUC values were not significantly different (p > 0.05) for gel applied at multiple sites versus gel applied repeatedly at one site. Based on mean serum testosterone concentration after gel application the authors also estimated the bioavailability of testosterone from the formulation was 9–14%.

The efficacy of the gel compared with Androderm™ patches was evaluated by Swerdloff et al. [43] after 1, 30, 90 and 180 days of application. Both the pharmacokinetics and tolerability of 50 and 100 mg testosterone daily were evaluated in a randomised, multi-centre parallel study involving 227 subjects. Serum testosterone levels reached normal values within 1 day of treatment with either gel or patch. Average steady state levels of testosterone remained stable for the duration of treatment with the gel. Proportionality in serum testosterone levels was demonstrated for the different doses of gel. Although ratios of DHT to testosterone were raised following application of the gel, values remained within the normal range. Discontinuation rates indicated that the gel was significantly (p = 0.0002) better tolerated by patients than the patch. Treatment with the gel also improved sexual mood and function, increased muscle mass and strength and decreased fat mass [44]. Longer term studies confirmed these beneficial effects with no clinically significant changes in biochemistry or blood counts [45,46].

### 5.2. Testim™

Testim™ was the second testosterone gel to become available (in February 2003) and it contains the penetration enhancer pentadecalactone in addition to a number of other components (Table 2). The gel is applied to the shoulders and upper arms; the area of application is ~2500 cm² for a 50 mg testosterone starting dose. Marbury and co-workers [47] conducted a randomised crossover to compare the pharmacokinetics of Androgel™ versus Testim™. Formulations (50 mg testosterone) were applied to subjects with a 7-day interval between applications of the different preparations. Estimates of the maximum plasma concentration (Cmax) for total testosterone, free testosterone and DHT and AUC0–24 values were higher for Testim™ compared with Androgel™; the authors concluded that the preparations were not bioequivalent. A randomised multi-centre study conducted by McNicholas et al. [48] over 90 days compared Testim™ with a patch formulation. Two doses of the gel (50 and 100 mg testosterone) were investigated and compared with a patch (Andropatch™, 2 × 12.2 mg testosterone). The gel formulation resulted in more favourable pharmacokinetic profiles than the patch which were also dose dependent. Testim™ also produced a significant decrease in body fat and improved sexual function compared with the patch. Patients tolerated the gel formulation better than the patch with higher rates of skin reactions and study withdrawal resulting from patch treatment. This is probably related to the non-occlusive nature of the gels used. Improved delivery of testosterone from Testim™ compared with Androderm™ was also reported by Steidle et al. [49]. This randomised, multicentre study involved 406 subjects and compared Testim™ (50 or 100 mg of testosterone) with a patch (Androderm™, 2 × 12.2 mg testosterone) formulation and placebo gel. Average testosterone plasma concentrations at day 90 were 7.3, 11.9, 13.8 and 17.1 nmol/l for placebo, patch, 50 mg of gel and 100 mg of gel, respectively. Significant improvements in body mass and fat as well as sexual function were observed for the 100 mg gel treatment compared with the patch and placebo. The results of two long term multicentre studies were later reported by Dean et al. [50] with the data supporting the results of the 90 day studies.

### 5.3. Fortesta™

A third gel, Fortesta™, was approved by the FDA in 2010. This 2% testosterone formulation contains oleic acid (a known penetration

### Table 2

Examples of commercial transdermal testosterone preparations.

<table>
<thead>
<tr>
<th>Brand name (Watson Laboratories)</th>
<th>Formulation</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androderm™ 2 mg/day, 32 cm²</td>
<td>Patch</td>
<td>Testosterone, alcohol, glycerine, glycerol monooleate, methyl laurate, sodium hydroxide, purified water, Carbomer Copolymer Type B</td>
</tr>
<tr>
<td>Testoderm TTS™</td>
<td>Patch</td>
<td>Testosterone, alcohol, hydroxypropyl cellulose</td>
</tr>
<tr>
<td>Testoderm Formulation</td>
<td>Scrotal Patch</td>
<td>Testosterone, ethylene-vinyl acetate co-polymer membrane with polysobutylgraye coating</td>
</tr>
<tr>
<td>Androgel™ (AbbVie)</td>
<td>Gel</td>
<td>Testosterone, alcohol, isopropyl myristate, purified water, sodium hydroxide</td>
</tr>
<tr>
<td>Androge 1.62™ (AbbVie)</td>
<td>Gel</td>
<td>Testosterone, Carbopol 980, ethyl alcohol, isopropyl myristate, purified water, sodium hydroxide</td>
</tr>
<tr>
<td>Testim™ (Auxilium Pharmaceuticals)</td>
<td>Gel</td>
<td>Testosterone, acylate, Carbopol, ethanol, glycerine, pentadecalactone, polyethylene glycol, propylene glycol, purified water, tromethamine</td>
</tr>
<tr>
<td>Fortesta™ (Endo Pharmaceuticals)</td>
<td>Gel</td>
<td>Testosterone, butylated hydroxytoluene, Carbomer 1382, ethanol, oleic acid, propanol, purified water, 2-propanol, triethanolamine</td>
</tr>
<tr>
<td>Vogelox™ (Upsher-Smith Laboratories)</td>
<td>Gel</td>
<td>Testosterone, Carbomer copolymer Type B, Carbomer homopolymer Type C, diisopropyl adipate, ethyl alcohol, glycerine, methyl laurate, oleyl alcohol, polyethylene glycol, propylene glycol, purified water, tromethamine</td>
</tr>
<tr>
<td>Axirom (Licensed in the US to Eli Lilly)</td>
<td>Solution</td>
<td>Testosterone, ethanol, isopropyl alcohol, octyl salicylate, povidone</td>
</tr>
</tbody>
</table>

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enhancer) and is applied by the patient to the front and inner thighs rather than the upper body. For a 40 mg testosterone starting dose the estimated area of application is ~1000 cm². A multicentre open label clinical study conducted by Dobs et al. [51] over 90 days evaluated the efficacy, pharmacokinetics and safety of a 2% gel formulation in 129 patients. Patients were supplied with a metered dosage pump with each actuation delivering 10 mg of testosterone per 0.5 ml of gel. The starting dosage was 40 mg of testosterone with dose adjustment occurring depending on total serum testosterone levels at defined study intervals. At the end of the study period more than 75% of patients achieved normal testosterone levels; skin reactions were reported in 16% of patients. More recently Mornet al. [52] reported the results of a 14 day study conducted in 34 patients. Patients applied the gel (40 mg testosterone) once daily to the inner thighs. Normal testosterone levels were achieved within 3 h with steady state serum testosterone levels being achieved at a median time of 1.1 days. The median drying time of the gel was also reported as 2.4 min. Treatment related side effects were reported for 3 patients and included skin dryness, application site rash and diarrhea.

5.4. Vogelxo™

The most recent transdermal testosterone gel formulation to be launched (July, 2014) is Vogelxo™. This formulation contains a number of penetration enhancers including diisopropyl adipate, methyl laurate and oleyl alcohol. Patients apply the gel to the shoulders and arms with a starting dose of 50 mg of testosterone. FDA approval was based on a multidose (50 or 100 mg of testosterone), multicentre clinical trial conducted over 90 days; 74% of patients (192 subjects) achieved normal testosterone levels by the end of the study. Skin irritation is listed as a potential side effect of the product [53].

5.5. Secondary exposure to testosterone from gel formulations

From 2000 to 2009 the FDA received a number of reports of inadvertent transfer of testosterone gels to children from patients. One or more of the following adverse events was reported in these children: advanced bone age, enlargement of sex organs, premature development of pubic hair, erections, increased self-stimulation, libido, and aggressive behaviour. In order to prevent inadvertent exposure of women and children to testosterone gels patients are instructed to wash their hands after using the product, to ensure treated sites are covered with clothing once the gel has dried and to wash treated skin sites if skin-to-skin contact is anticipated [54]. The potential unwanted exposure to others, prompted the issuance of a draft guidance in 2013 in relation to applications for approval of generic testosterone gels. These will only be received if the proposed gel formulation is qualitatively and quantitatively the same as the reference listed drug [55].

6. Transdermal testosterone liquid formulation – Axiron™

A transdermal testosterone formulation for application to the axillae, using an applicator rather than the hands, was approved in 2010. This product is a solution and it contains the penetration enhancer octyl salicylate as well as ethanol, isopropanol and povidone. In pilot studies application of the formulation to the axillary region resulted in higher serum testosterone concentrations compared with application to the inner forearm. An open label study conducted over 120 days evaluated the pharmacokinetics and efficacy of the formulation [56]. Patients used a pump-actuated device to apply the formulation (30 mg testosterone per 1.5 ml) with a starting dose of 60 mg of drug. Where necessary, dosage was adjusted to maintain testosterone levels within the normal range. More than 80% of patients achieved normal testosterone levels with significant improvements also reported in sexual function and general physical and mental health. The adverse events reported included application site irritation, application site erythema, headache, increased haematocrit, nasopharyngitis, diarrhoea and vomiting. An extension to this primary study to 180 days was used to analyse further the type and/or severity of skin reactions observed [57]. Application site irritation and erythema were the most common problems but were classified as mild in severity. Although application to the axillae should reduce the risk of inadvertent transfer of the product to others patients are instructed to follow similar precautions as for gel preparations to prevent secondary testosterone exposure.

7. Safety concerns related to transdermal testosterone therapy

An increased incidence of prostate events and haematocrit values >50% was flagged in a meta-analysis of intramuscular, oral and transdermal delivery; there was no evidence that testosterone therapy increases prostate cancer [58]. A number of recent publications reporting respectively on a clinical trial, an observational study and a meta-analysis have raised concerns about cardiovascular risks associated with testosterone replacement therapy [59–62]. However Corona et al. [63] reported no evidence of cardiovascular risk based on a meta-analysis of 75 studies. An alert that this issue was being investigated by the FDA was issued by the agency in January 2014. The influence of route of testosterone administration on adverse events was recently evaluated by Borst et al. [64] who conducted two meta-analyses of 67 clinical studies. Oral administration of testosterone was associated with a significant increase in cardiovascular risk; no significant increase was noted for transdermal or injectable testosterone. In addition, the authors suggested that further research was necessary to determine whether administration by the latter two routes was protective or detrimental. Transdermal testosterone was also noted to result in significantly raised DHT levels compared with intramuscular administration.

8. Alternative uses of transdermal testosterone

The application of androgens for male contraception was initially evaluated in the 1970s [65,66]. Male hormonal contraception requires the delivery of either exogenous testosterone alone or in combination with a progestogen in order to suppress LH and FSH secretion from the pituitary. A combination of testosterone gel and injections of depomedroxyprogesterone acetate was studied in 38 men over 24 weeks [67]. Levels of spermatogenesis achieved were comparable with implantable and injectable combinations of testosterone and progesterone. The ability of testosterone and nesterone gels to suppress LH and FSH levels was evaluated by Mahabadi et al. [68]. Although nesterone alone demonstrated gonadotrophin suppression, significant effects were observed for combination of the gels. In a later study in 56 males the combination regimen was shown to suppress spermatogenesis to levels consistent with infertility in 88.5% of subjects [69].

9. Summary and outlook

The delivery of drugs transdermally was pioneered by Alza in the late 70s and early 80s but some 30 years later; it is evident that very few of the many actives on the market have appropriate properties to be delivered by this route. Transdermal testosterone replacement therapy has come of age with a variety of technologies currently available compared with other actives delivered via the
 skin. The transdermal route is appropriate for testosterone because of its physicochemical and pharmacological properties. Despite the success of the delivery of testosterone, there is still a need to produce formulations, which minimise irritation, are cosmetically acceptable and have good patient compliance. Although gel and roll-on formulations address some of these requirements, they have introduced the added risk of unwanted exposure to others; similar safety issues will be pertinent for spray formulations. Safety concerns in relation to cardiovascular risks of testosterone replacement therapy also remain controversial and the outcome of an ongoing regulatory review should provide some clarification. The potential of transdermal testosterone for contraception is actively being investigated but longer term studies are needed.

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