

## **Transdermal Testosterone Treatments**

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### **Abstract**

Transdermal testosterone treatments have been available for over 60 years, but only recently have they been widely accepted following evaluation in controlled clinical trials. The benefits of androgen treatment via this route have been shown to include relief of androgen deficiency symptoms, including low libido and depression in both sexes, erectile dysfunction, osteoporosis, as well as improvement in many of the features of metabolic syndrome.

Comparison of the creams, patches and gels now on the market show widely different patterns of absorption according to the type of preparation and site of application. Scrotal skin gives forty times the absorption achieved by application of testosterone creams to the forearm, shoulders, abdomen or chest. This makes safe, effective, physiological, acceptable, and above all economic, testosterone treatment available to many more patients than could otherwise be helped, providing the basic safety guidelines such as those provided by ISSAM are followed by competent physicians applying this form of hormonal treatment.

### **Development**

Attempts at transdermal administration of testosterone began in the 1940's with the work of Dr Jayle, a French physician, who in 1942 prepared a cream containing testosterone which claimed some clinical success<sup>1</sup>. From the outset, this cream raised the problem faced by

subsequent cream and gel preparations, that of transfer to female partners. Though this was infrequent, and usually only followed injudicious application to the lower abdomen by the patient immediately prior to intercourse, it was reported as occasionally being a cause of hirsutism of the face and thighs in the wives of men using medroxyprogesterone acetate and large amounts of testosterone cream, in research on male contraception<sup>2</sup>.

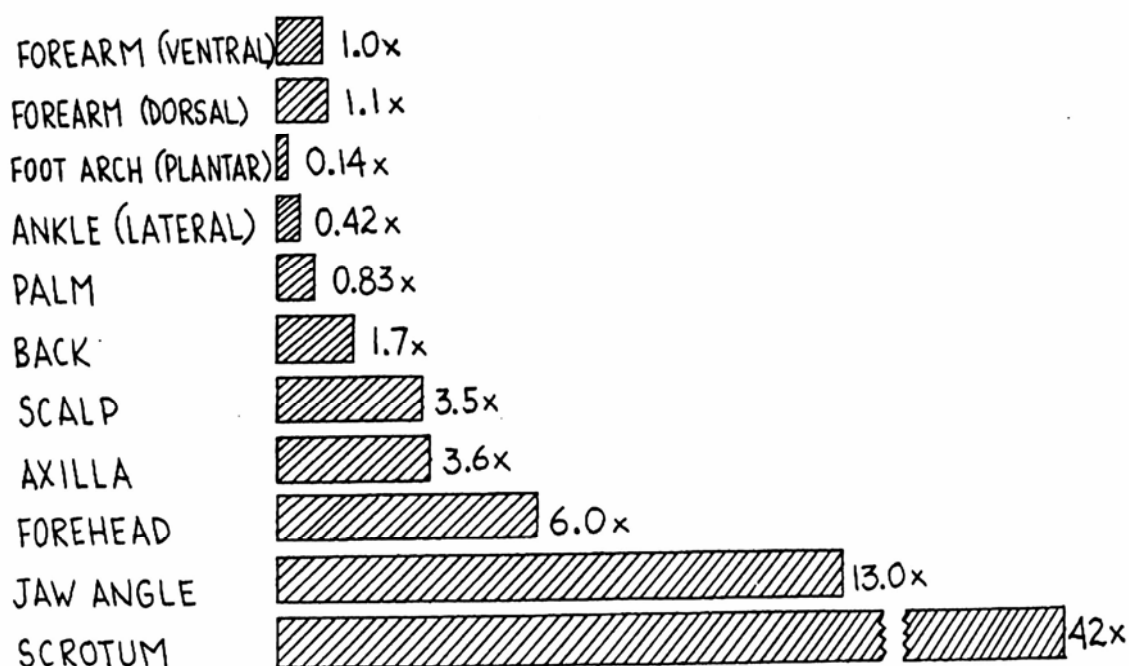
This was followed, also in France, by a cream containing dihydrotestosterone, called Andractim. However, though this was absorbed more rapidly, the somewhat impractical advice of showering a minimum of ten minutes after application, and prior to intercourse, was still recommended to prevent transfer. Another disadvantage was that it only raised blood levels of DHT, which though theoretically a more potent androgen, in practice has more limited range of clinical actions than testosterone, and cannot be aromatised to estrogen. It was shown to be less efficient than testosterone in preventing bone loss in androgen deficient men, and the conclusion was that 'transdermal preparations of testosterone are more advisable than percutaneous DHT' for obtaining normal physiological levels of sex steroids<sup>3</sup>.

As with all transdermal treatments, one of the chief limitations is the transport of steroids through the thick stratum corneum barrier. This is less of a problem in relation to estrogen treatment in women, where an amount an order of magnitude lower is sufficient to give adequate levels in the pico-molar region. Here one patch impregnated with 50-100 micrograms of estradiol is sufficient to maintain adequate blood levels for 3-4 days. The daily dose of testosterone needed to provide adequate supplementation with around 5mg absorbed, is however of the order of 10-25mg as a patch, even with their special delivery systems, or 50-100 mg in a cream or gel applied to the chest or abdomen. Interestingly, this

corresponds closely to the 50-100mg given daily as testosterone undecanoate (2-4 of the 40mg capsules, each containing the equivalent of 25mg testosterone). This low uptake through the dermis and the gut mucosa, results in the wastage of 50-95% of the manufactured dose of testosterone, which makes it correspondingly expensive via either route especially if an expensive delivery system is needed for each daily dose.

Testosterone creams have been produced for many years by compounding pharmacies throughout the world, but have never been extensively researched or taken up. This has partly been because of a low level of clinical interest, and corresponding investment by the major pharmaceutical companies, but also because of poor quality control by the small-scale producers. However this seems set to change with a range of creams being produced by an Australian company, Lawley Pharmaceuticals in Perth. They have recently produced a range of creams including ANDROMEN® Forte and ANDROMEN® for men, containing 50mg and 20mg per gram testosterone respectively, and ANDRO-FEME® for women containing 10mg per gram. This latter preparation has already undergone a clinical trial in the treatment of desire disorders, and proved to be well absorbed and tolerated, and highly effective in improving well-being, mood and sexual function in premenopausal women<sup>4</sup>.

Clinical studies are being undertaken in several countries to explore the use of these testosterone creams via the scrotal and labial/vaginal routes (the female equivalent of the scrotum). The original work on the absorption of steroid creams on different areas of the body showing high levels of absorption of corticosteroids through the sponge-like scrotal skin had been reported by Feldmann and Mailbach in 1967<sup>5</sup> (Fig 1).



**Fig 1.** Total absorption of corticosteroid cream from different areas.

The much greater absorption of testosterone through scrotal skin has been confirmed by the extensive research<sup>6</sup> undertaken on scrotal patches (see below) and is due to enhanced uptake through the thinner stratum corneum and better blood supply of the skin in these areas. This makes it possible to reduce the dosage and hence the cost of testosterone treatment given by this route as compared to other forms of treatment (Table I).

Testosterone Preparation	Cost (£)	% Abs.	Theory	Practice
Testosterone Pellet Implants	20	100 *	***	
Injected T-Esters (Sustenon)	5	100 *	*	
Injected T-Undecanoate (Nebido)	22	100 **	****	
Oral T-Undecanoate (Andriol)	27	10 **	**	
T-Gel (Testogel)	33	15 ***	***	
Scrotal T-Cream (Andromen)	8	70 ****	***	

**Table I :** Costs of Treatment/Month (Medication only – other costs to medical system and patients not included), % of products absorbed, their

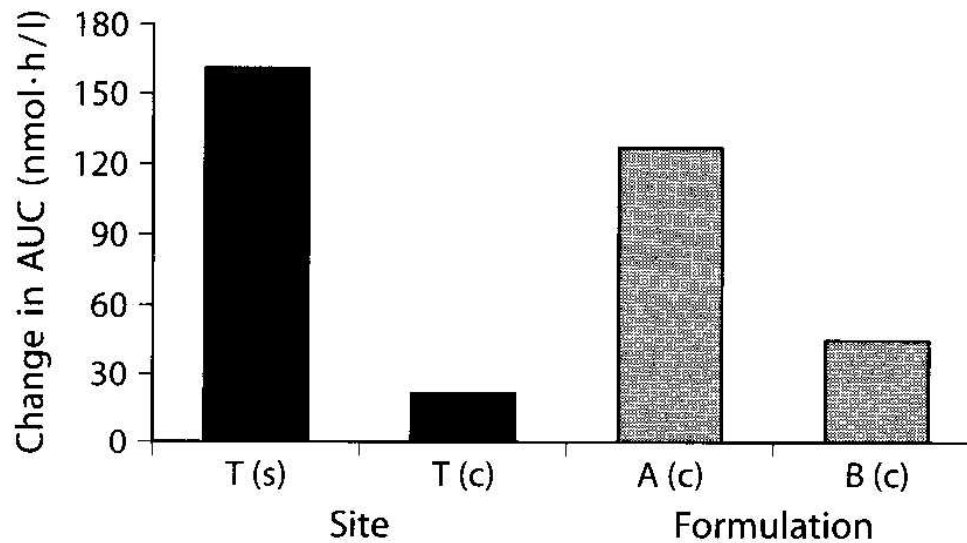
theoretical advantages in providing physiological replacement, and practical acceptability to the patients.

If these studies fulfil their early promise, the implications in terms of making low-cost androgen therapy available in an economic, physiological, safe, and easy to administer form are extensive.

### **Scrotal Patches (Testoderm)**

Attempts to improve absorption by using a patch applied to the thinner scrotal skin were encouraging, but never became more than an experimental method. A scrotal patch called Testoderm was developed by Alza Research in the USA, and tested in Germany by Bals-Pratche et al<sup>7</sup> and America<sup>8</sup>. The former group showed that over nearly 24 hours, serum testosterone levels in normal men were moderately increased, with concentration curves almost parallel to basal levels. Seven hypogonadal patients also responded to this 'Transdermal Testosterone System (TTS)', and serum testosterone levels were in the normal range during a 12-week treatment period. There were no side-effects, and a low incidence of skin reactions.

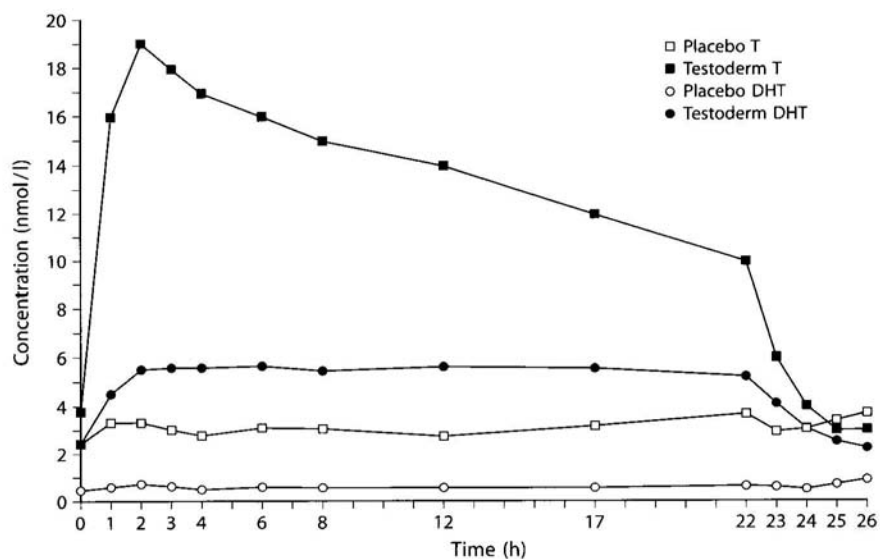
Subsequent research<sup>6</sup> confirmed the safety and clinical efficacy of this preparation for periods up to 8 years, and that there was much greater absorption of the testosterone through the scrotal skin than elsewhere in the body<sup>1</sup>.



**Fig 2** Skin site and formulations affects testosterone concentrations. Baseline corrected mean Area-Under-the-Curve (AUC) figures: T(s) - Testoderm applied to scrotal skin; T(c) – Testoderm applied to chest; A(c) – Formulation A, containing skin permeation enhancer applied to scrotal skin; B(c) - Formulation A applied to chest<sup>6</sup>.

As shown in 12 healthy men, these features resulted in a forty times greater absorption from this site than from chest skin, though this gradient was halved by the addition of permeation enhancers (Fig 2).

Further, this method of application appeared to give more rapid absorption, reaching a maximum after 3 hours, than testosterone gels or creams, which are normally applied to the trunks or arms. This results in a more physiological pattern of diurnal variation, and potentially less suppression of nocturnal endogenous synthesis of testosterone (Fig 3).



**Fig 3** Effects of a Testoderm scrotal patch applied at time zero and removed at 22hours, on total testosterone and DHT compared to placebo<sup>9</sup>.

The extensive clinical experience with the scrotal testosterone patch showed both good a good safety profile and a wide range of clinical benefits. Compared to testosterone injections it maintained total testosterone levels in the normal range, unlike the saw-tooth effect of short-acting testosterone injections and consequent weekly fluctuations in emotional state.

Apart from maintaining testosterone levels within the physiological range, the Testoderm system avoided the increases in estrogen levels seen with injections and implants, as well as the polycythemia which is a common problem when either of these routes is used. However, because of the high level of 5 $\alpha$ -reductase in the scrotal skin. there is a 2-3 times increase in blood DHT levels with Testoderm. This did not appear to have any adverse effects however on the prostate, skin or any other organ in this or other studies<sup>6</sup>.

The clinical benefits associated with treatment with Testoderm were wide-ranging. It was shown to maintain bone mineral density in cortical bone and increased it rapidly in vertebral bone. In men with low

testosterone levels, an increase in lean body mass and decrease in abdominal fat, together with a slight increase in strength was seen in the first 6 months of treatment, and did not improve further at a one year follow-up.

### **Skin Patches**

Another approach to the general safety principle in androgen therapy of mimicking the normal concentration of testosterone and its active metabolites<sup>10</sup> was the development of non-scrotal transdermal patches. These had the advantage that there was no need to shave the scrotal skin, but the disadvantages that they were conspicuous and often caused loss of hair and irritant reactions in the areas of the back, upper arm, abdomen and thigh, where they were applied. Though these reactions could be reduced by pretreatment of the application site with corticosteroid cream, the systems never achieved wide acceptance and have largely been abandoned. They did however provide a large amount of data on their clinical effectiveness in a wide range of conditions, as well as safety of long-term application<sup>3;11;12</sup>. Though provided in 2.5 and 5.0mg dose systems, to achieve levels in the upper part of the physiological range, 2 or even 3 units might need to be applied, and again expense was a limiting factor.

### **Skin Gels (Testogel®, Androgel®, Testim® and Androlone®)**

These are the latest development in transdermal testosterone treatment, and again have undergone extensive research showing good physiological androgen replacement patterns, excellent safety, and a wide range of clinical benefits.

Testosterone and other steroids when applied to the skin in alcoholic gels, dry rapidly, leaving the hormone to be slowly absorbed through the

stratum corneum, which serves as a reservoir. The very detailed studies of Swerdloff et al<sup>11</sup> have shown that this reservoir in the skin releases testosterone into the circulation gradually over several hours. On single dose application peak levels are reached after 18-24 hours, while with once daily application, steady state levels are only reached 7-14 days later. Absorption was found to be 23% greater if the gel was applied at four sites rather than one. However, only 9-14% of the 50-100mg testosterone applied as a daily dose was absorbed. The present formulation of the gel cannot be applied to the genitalia because the alcohol it contains causes pain in the delicate skin of these areas, and the amount absorbed from the scrotum would be excessive if applied in these relatively large amounts.

Though the gel system of transdermal testosterone treatment is rapidly gaining acceptance in America and Europe, its pharmacokinetics do raise certain problems in relation to its long-term use which have to be weighed up against the benefits. The gel is highly acceptable to the patients as it is convenient, painless, and promotes the macho image that it is not really a medication, but a natural supplement to be applied as part of their regular morning toilet.

It does however take 5-10 minutes for one 5 gram sachet dose to dry, while 10grams takes even longer. Also it constrains the daily showering, bathing or swimming routine. It may even limit the timing of intercourse, because of the possibilities of transfer to a female partner from the quite large areas of skin to which it needs to be applied, particularly in the higher dosage. Also the cost of gels, which are often needed in 10gram doses daily, can be more than twice that given by injection, implantation, orally or with scrotal creams (Table I).

The slow absorption pattern of the gel means that although physiological levels can be maintained, there is abolition of the normal diurnal variation

and hence a truly physiological pattern of androgen metabolism. This is also more likely to suppress the usual gonadotrophin surge which occurs during sleep, and result in a greater decrease in endogenous synthesis than short-acting preparations such as testosterone undecanoate, those administered via the scrotum, or even skin patches.

Similarly, because of the slower absorption of the gel, there are greater rises in estradiol and particularly DHT than with other preparations, including the patch.

### **Conclusions**

From this review of the development, advantages and disadvantages of different form of transdermal testosterone treatment, it can be seen that the skin can provide a safe, physiologic, economic and highly acceptable and effective route of administering androgens in both men and women. With the availability of these transdermal preparations, what is needed is greater medical and lay acceptance of testosterone treatment both in treating the symptoms of androgen deficiency, together with the many disease processes in which it plays an important part, and its key role in the preventive medicine of the future.

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This research was supported by Lawley Pharmacy  
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