Review Article

Local and Systemic Complications of Local Testosterone Patches and Gels

Abstract

In recent decades, testosterone therapy has gained the attention of many researchers due to the increased demand for this modality worldwide, the increased average age of the different populations, and increased awareness of the potential uses of the modality in clinical settings. Using testosterone therapy aims to treat erectile dysfunction, libido disorders, and potentially enhance physical strength and general body functions. It should be noted that the administration of this treatment modality has been reported with various adverse outcomes despite the remarkable efficacy and wide rates of administration among the different populations. In the present literature review, we have discussed the potential local and systemic complications of applying local testosterone patches and gel. The main advesre events that were reported for both formulas have been skin reactions at the site of application. However, these reactions are not usually serious, and only a few patients discontinued the therapy due to these reactions. In general, evidence indicates that the exogenous administration of testosterone has been associated with many systemic complications as cardiovascular diseases, prostate cancer, obstructive sleep apnea, and elevated hematocrite value. However, evidence regarding this association is still controversial, and additional studies are needed for verfication.

Keywords: Testosterone; transdermal; patches; gel; treatment; hypogondism; complications; adverse events.

Introduction

In recent decades, testosterone therapy has gained the attention of many researchers due to the increased demand for this modality worldwide, the increased average age of the different populations, and increased awareness of the potential uses of the modality in clinical settings. Using testosterone therapy aims to treat erectile dysfunction, libido disorders, and potentially enhance physical strength and general body functions [1-3]. A previous report in the United States estimated that the prescription and administration of testosterone therapy has significantly increased between 2001 and 2011, from 0.81 to 2.91%, respectively [3].

The routes of administration of testosterone therapy are various, including subdermal, oral, transdermal, buccal, oral, nasal, and intramuscular. Besides, two different formulas have been reported for the transdermal route, including gels and patches and both of which have been reported with favorable efficacies and different dosages. However, it should be noted that the administration of this treatment modality has been reported with various adverse outcomes despite the remarkable efficacy and wide rates of administration among the different populations. In the present literature review, we aim to discuss the complications that have been reported with the administration of local testosterone patches and gels among the different studies in the literature.

Methods

This literature review is based on an extensive literature search in Medline, Cochrane, and EMBASE databases which was performed on 26th September 2021 using the medical subject headings (MeSH) or a combination of all possible related terms, according to the database. To avoid missing poetential studies, a further manual search for papers was done through Google Scholar, while the reference lists of the initially included papers. All relevant papers were

screened for useful information, with no limitations placed on date, language, age of participants, or publication type.

Discussion

Among the different approaches that have been proposed for testosterone administration, local patches that are applied to the scrotal skin have been the first modalities developed for testosterone administration clinically [4, 5]. However, it has been reported that the application of these modalities did not last for a long period [6]. Therefore, researchers exerted efforts and developed more routes, although it has been demonstrated that the application of testosterone patches to scrotal skin was associated with favorable physiological levels. In 1995, the U.S. Food and Drug Administration approved the use and administration of non-scrotal transdermal patches that provided in 2 and 4 mg/day formats. It has been recommended that the starting dose should be 4 mg/day and nightly applied and rotated over the abdomen, back, thighs, and upper limbs [7]. It should also be noted that these patches should not be used for continuous seven days. Different local and systemic complications have been reported secondary to the administration of local testosterone transdermal patches. In a previous multicenter investigation, the authors demonstrated that 60% of the included patients that applied transdermal testosterone patches developed pruritis and/or mild-to-moderate skin erythematous changes locally at the site where the patch was applied. However, it has been estimated that only 9% of the same population discontinued the application of the treatment modality because of these adverse events. It has been further demonstrated that hematocrit values elevation was significantly more apparent among patients treated with the intramuscular route than others treated with the transdermal testosterone patch [8]. As a result of the reported skin adverse events, evidence indicates that many patients do not adequately comply with the treatment modality which might affect the

treatment outcomes. Such adverse events have been attributed to involving permeation enhancers within the formula to enhance the absorption of testosterone through the skin [9]. The intrusive nature and size of the patch were also reported to be of concern for applying these patches. In Europe, evidence shows that the patch is no longer used despite the implications that demonstrated that limited risk of transference when using transdermal testosterone patches. Some of the reported advantages of using this patch include the induction of a normal circadian rhythm of testosterone, quick reversal after removing the patch, and is easily applicable and non-invasive.

In the last two decades, different studies have demonstrated the efficacy of different transdermal testosterone liquids and gels. However, there have been some concerns about the potentiality of the modality to be transferred to children and females that come in contact with the patient that applies it. Unlike the transdermal patches, evidence indicates that applying transdermal gels is less likely to induce skin irritation, and was also reported to be more efficacious than other routes of administration, including the intramuscular one [10]. In previous multicenter investigations, it has been reported that the reaction sites of administration were rarely reported among the included patients, and only a few discontinued treatment application at 12 months during a 48 follow-up period among adult patients aged 19-68 years old [11, 12]. However, it should also be noted that one patient discontinued the treatment plan because of the punctate rash and erythema. Furthermore, the other three patients also discontinued the treatment plan due to the significant elevation of the prostate-specific antigen during the treatment period above the allowed limits. It has also been estimated that 4.9% of the included patients developed gynecomastia, and 7.4% developed acne. It should be noted that these adverse events were reported among patients that only received the 1% testosterone gel. Other concentrations were also investigated in the

literature. For 2% testosterone gel, estimates show that skin reactions were prevalent in 16.1% of the included participants with hypogonadism in a multicenter investigation [13]. Among the affected patients, it has been demonstrated that most of them (79%) had mild reactions while the rest had moderate ones. Among the whole population, it has been demonstrated that only 2 patients discontinued administration because of drug reactions. Similar findings were also reported in a previous randomized controlled trial [14]. A 2% of testosterone was also proposed efficacious as a solution, and evidence shows that erythema, headache, local site irritation, and elevated hematocrit values were the most prevalent adverse events in 5%, 5%, 7%, 4% among the included population in a previous investigation [15]. According to this evidence, it could be concluded that the transdermal administration of testosterone is efficacious and is associated with a minimal number of adverse events. The testosterone administration can also be associated with a risk of cardiovascular events, although the risk has not been significantly indicated. In the following section, we will discuss some of these events.

Many adverse events have been reported for prolonged testosterone therapy when administered through any of the reported routes. However, estimates regarding the true prevalence rates of these complications are still inconsistent, and no apparent recommendations were provided in the literature about the timing when testosterone therapy should be discontinued. Evidence indicates a significant association between testosterone deficiency and cardiovascular diseases [16, 17]. However, evidence regarding whether testosterone replacement can have a beneficial effect on reducing this risk is still controversial among studies and is only based on single reports. In this context, two previous meta-analyses concluded that the risk of cardiovascular diseases was not significantly reduced following the administration of testosterone therapy [18, 19].

On the other hand, a more recent meta-analysis that was conducted by Xu et al. [20] reported that the risk of developing cardiovascular events significantly increased following the administration of testosterone therapy, Nevertheless, it should be noted that the findings of the different included trials might have been influenced by the source of funding. Even though, the authors still confirmed that the reported risk was significant among the different trials that were not subjected to funding bias. In another retrospective investigation, Vigen et al. [21] reported that the administration of testosterone therapy was significantly associated with the development of ischemic stroke, myocardial infarction, and mortality irrespective of coronary artery diseases were present before treatment initiation or not. Muraleedharan et al. [22] also conducted a prospective cohort investigation to study the impact of testosterone supplementation on mortality for patients with diabetes. The authors demonstrated that the mortality rates were significantly higher among patients within the low testosterone group. Furthermore, the authors concluded that no significant association was found among patients that received testosterone and mortality from cardiovascular events, and the association was only reported among patients that had lower testosterone endogenous levels at baseline. Another cohort investigation by Finkle et al. [23] reported that the estimated relative risk for ≥65 years old was 2.19, which was higher than the 1.15 risk that was reported for other patients that received phosphodiesterase type 5 inhibitors for developing non-fatal myocardial infarction events. Basaria et al. [24] also demonstrated that the risk of cardiovascular events was significantly associated with the changing levels of serum testosterone in their logistic regression model. In a previous double-blind randomized-controlled trial that was conducted by Basaria et al. [25] in 2010, the study reported that the study was discontinued because of the high incidence rates of cardiovascular events among patients that received testosterone therapy.

Another adverse event that has been reported includes the elevation of the prostate-specific antigen. This has been reported by many investigations in the literature following the administration of exogenous testosterone through different routes. In a previous European trial that included 200 men with hypogonadism and was treated with transdermal testosterone administration, it has been reported that among the patients that completed the intended follow-up period of this investigation, only 7 developed higher prostate-specific antigen >4.0 ng/ml. Nontheless, it should be noted that 6 of these patients were treated for suspected prostatitis, which was associated with a significant reduction in the assessed antigen levels. Finally, at the end of the investigation, the authors indicated that no cases of cancer prostate were observed in this investigation [26]. Although the current guidelines indicate that the associated elevation in the prostate-specific antigen following the administration of testosterone is safe and lies within the normal range, a previous investigation by Bhasin et al. [27] indicated that it can be associated with an increased risk of developing cancer prostate. In this context, various investigations have assessed the association between the administration of testosterone supplementation and the risk of prostate cancer. Evidence regarding this association has been very controversial among these studies. Some evidence supports that testosterone significantly elevates the prostate-specific antigen levels, however, it was reported that androgen deprivation treatment can be used to treat prostate cancer. The previous meta-analysis by Calof et al. [19] demonstrated that patients that administer testosterone therapeutic modalities have 11 times an increase in the risk of undergoing a biopsy more than the placebo group, nevertheless, no significant difference was noticed between the two groups in terms of the rate of diagnosed prostate cancer. In a retrospective investigation, Kaplan and Hu also demonstrated that no significant differences were noticed between patients that received testosterone replacement therapy and others that did not in

terms of overall survival, disease-specific survival, and need for androgen deprivation treatment [28]. Lower urinary tract symptoms were also reported to be associated with some patients that received testosterone supplementation. The findings from previous investigations do not significantly support any potential association between worsening symptoms and prostate volume and the administration of testosterone. Furthermore, some studies have even demonstrated that patients' symptoms might significantly improve following the administration of the treatment modalities. Increased prostate volume might be an adverse event as reported by previous investigations [29, 30]. Therefore, more clinical trials are needed for further validation and demonstration of the current evidence. Furthermore, many studies have evaluated the association between testosterone administration and obstructive sleep apnea, however, only a few of them indicated that the therapy can worsen the impact on developing the condition [31-35]. In a randomized controlled trial, Hoyos et al. [33] reported that obstructive sleep apnea worsended following the administration of testosterone at 7 weeks following the administration, however, the observed outcomes were reported to be mild and the impact was reserved after 18 weeks since the administration of testosterone.

Conclusion

The main adverse events that were reported for both formulas have been skin reactions at the site of application. However, these reactions are not usually serious, and only a few patients discontinued the therapy as a result of these reactions. In general, evidence indicates that the exogenous administration of testosterone has been associated with many systemic complications as cardiovascular diseases, prostate cancer, obstructive sleep apnea, and elevated hematocrite value. However, evidence regarding this association is still controversial and additional studies are needed for verfication.

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