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Genital Lichen Sclerosus – Has There Been any Progress in Treatment?

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Abstract

Lichen sclerosus (LS) is a chronic inflammatory dermatosis localized mainly in the anogenital region, accompanied by itching, atrophy and sclerosis. Progressive destructive scarring in genital lichen sclerosus (GLS) may result in burying of the clitoris in females and phimosis in males. Affected persons have an increased risk of genital cancers. It is often unrecognized in everyday clinical practice due to undiagnosed squamous cell carcinoma at the site of lesions. Remissions are rare and the estimated remission rate is only 16%. GLS is a lifelong, incurable condition, but significant improvement can be achieved. Numerous therapeutic modalities have been used in GLS; unfortunately, the number of controlled studies is small and the results are mostly related to the management of symptoms, not the progression of the disease and destructive scarring. A systemic meta analysis of seven randomized controlled trials on local therapy of GLS was performed. It included a total of 249 patients treated with six topical agents: clobetasol propionate, mometasone furoate, testosterone, dihydrotestosterone, progesterone and pimecrolimus. Topical corticosteroids, clobetasol propionate 0.05% (highly potent) and mometasone furoate 0.05% (potent), showed to be significantly more efficient compared to placebo. Pimecrolimus 1% cream and clobetasol propionate 0.05% showed similar efficacy. Both agents have proven effective in the treatment of GLS: there was no statistically significant difference in relieving symptoms of pruritus and burning/pain. Tacrolimus 0.1% ointment also proved to be effective in the treatment of GLS. Topical androgens and progesterone did not show significant efficacy. Topical tretinoin and calcipotriol have been used with limited success, but they may induce irritation, so they are rarely used in the treatment of GLS.
Other therapeutic options for GLS include ultraviolet A1 (UVA-1) phototherapy, methotrexate, retinoids, cyclosporine, stanozolol, hydroxychloroquine, calcitriol, laser and photodynamic therapy, but the number of patients is small to allow for conclusive assessment. Surgery is not a standard therapeutic option for GLS.
In conclusion, treatment of GLS should be carried out in two phases: introduction of remission and maintenance of remission; topical therapy should include highly potent corticosteroids once daily during three months, followed by twice per week, or twice daily during 4 to 6 weeks, and then twice per week. There are different opinions regarding maintenance therapy: application of super potent or potent topical corticosteroids; these patients need long-term, several-year follow-up, although there is no agreement what parameters should be assessed; treatment efficacy is often reduced to monitoring GLS symptoms.

Key words

Lichen Sclerosus et Atrophicus; Meta-Analysis; Administration, Topical; Review; Dermatologi Agents; Clobetasol; Tacrolimus

Lichen sclerosus (LS) is a chronic inflammatory dermatosis, which primarily affects the anogenital region, and manifests with extensive sclerosis, atrophy and itching. Extragenital LS has milder symptoms; it is most common on the thighs, neck and trunk, and oral mucosa is rarely involved.

Genital lichen sclerosus

Women and girls with genital lichen sclerosus (GLS) present with postinflammatory scarring which may cause fusion of the labia minora, narrowing of the vaginal introitus, and burying of the clitoris, resulting in dyspareunia, sexual dysfunction, and anal or genital bleeding (Figures 1, 2, 3a-b) (1).

GLS in children is uncommon, so differential diagnosis in any pre-pubertal child presenting with chronic vulval symptoms is of great importance. The long-term prognosis is unknown, but assumptions that the condition will resolve at puberty may be incorrect (2).

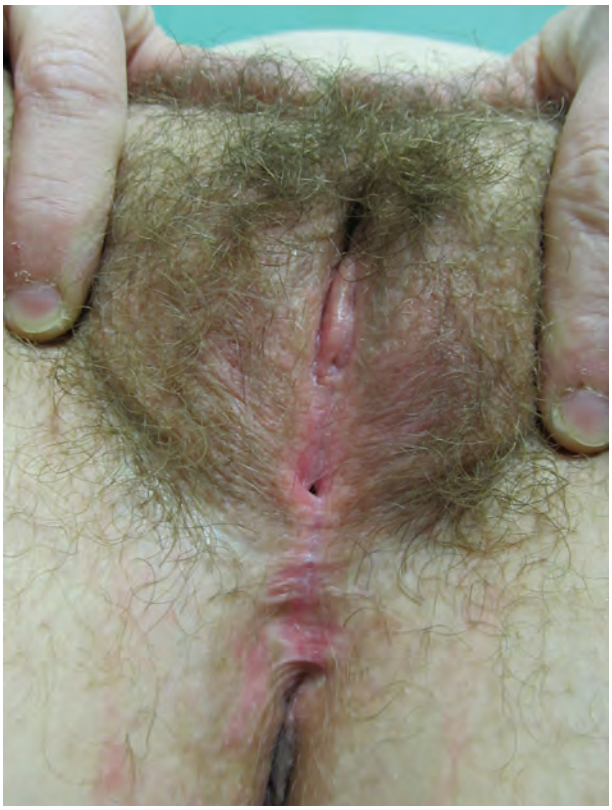

Figure 1. Vulval lichen sclerosus

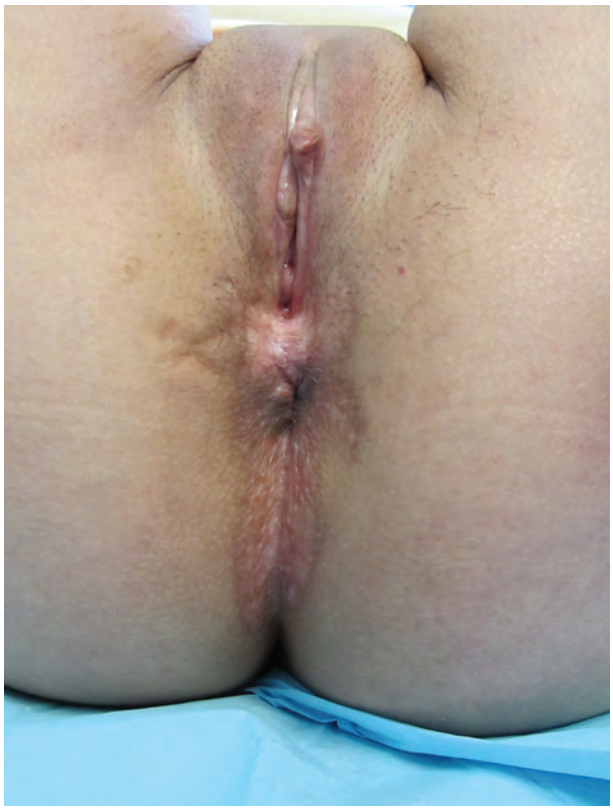

Figure 2. Vulval atresia

Vulval lichen sclerosus is associated with a significant risk for squamous cell carcinoma (SCC) of the vulva (3).

In men and boys, GLS is most common on the glans penis and prepuce (Figure 4), which may cause phimosis, paraphimosis, painful erection, and urethral meatal stenosis. The dermatological aspects of male genital lichen sclerosus (MGLS) have not received much prominence in the literature. Sexual morbidity appears under-appreciated: the relative places of topical treatment and circumcision are not established (4). Occluded contact with urine in males and reduced estrogen levels in females, are imortant factors in the etiopathogenesis of MGLS and VLS, respectively.

Prognosis in terms of sexual function, urination difficulties and penile cancer is uncertain (Figure 4).

The cause of LS is unknown, but there is strong association with autoimmune diseases, thyroid disease, pernicious anemia, diabetes mellitus, alopecia areata, vitiligo, and mucous membrane pemphigoid (5). Approximately 74% of patients with LS have an increased titer of circulating antibodies in the serum (6), and in 42% the titer is over 1:20 (5). The increased incidence of autoantibodies to extracellular matrix protein 1 (ECM-1) may point to its autoimmune pathogenesis (7).

Treatment

GLS requires long-term management; there is no cure, but significant improvement can be achieved. Unfortunately, the number of controlled studies is small and the results are mostly related to the management of symptoms, not the progression of the disease and destructive scarring (3).

Before starting treatment of LS, Bradford and Fischer (3) consider it necessary to answer a few questions:

1. Are there valid alternations to intermittent potent corticosteroids?
2. Should treatment be standardized or individualized?
3. Does treatment modify scarring, loss of vulval substance and risk of SCC?

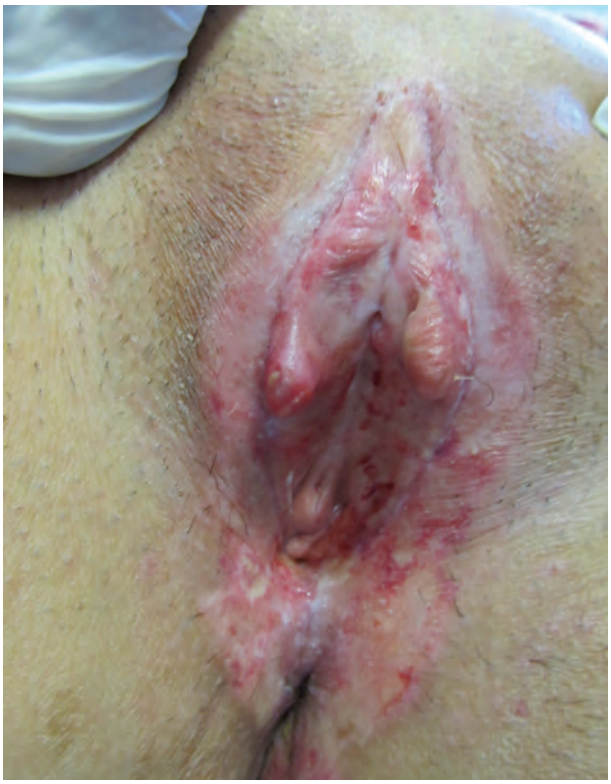

Figure 3a. Vulval lichen sclerosus with genital bleeding

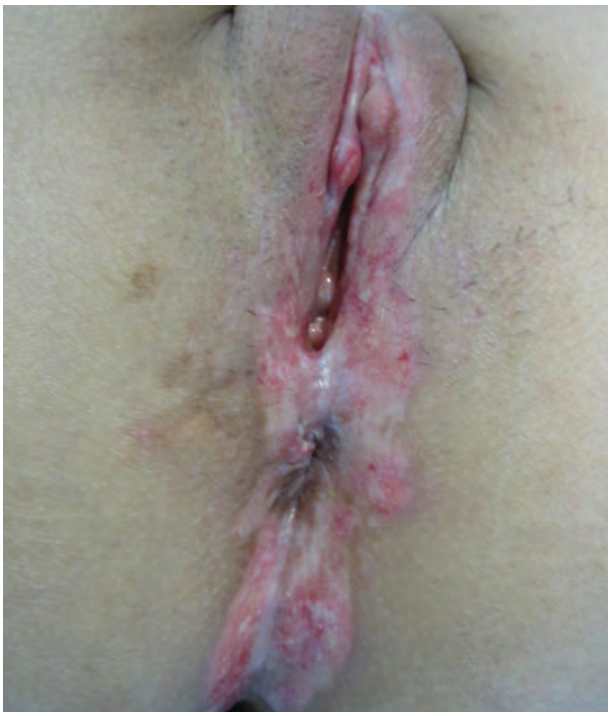

Figure 3b. Vulval lichen sclerosus with anal bleeding

Figure 4. Male genital lichen sclerosus

4. Are there risks of long-term potent corticosteroids on the vulva?
5. What should be the purpose and length of follow-up?

There are multiple treatment modalities for GLS, including topical and systemic agents (Table 1). Most authors agree that treatment of GLS should be carried out in two phases: introduction of remission and maintenance of remission.

Despite the use of numerous medications and topical agents in the treatment of GLS, there are few comparative studies of their effectiveness.

The Cochrane Library published a very good meta-analysis of randomized controlled trials on topical interventions for GLS by Ching-Chi and associates. It included 7 randomized controlled trials with a total of 249 participants covering 6 treatments (Table 2).

The aforementioned meta-analysis clearly shows the lack of standardized therapeutic procedures for the management of GLS, mostly due to the small number of respondents with a small number of studies meeting the inclusion criteria for meta-analysis (1).

Table 1. Treatment of genital lichen sclerosus (1)

Modality	Agent
Topical	Ultrapotent steroids (eg., clobetasol propionate 0.05%)
	Potent steroids (eg., mometasone furoate 0.05%)
	Calcineurin inhibitors (pimecrolimus tacrolimus)
Systemic	Retinoids (isotretinoin, acitretin, etretinate)
	Calcineurin inhibitors (cyclosporine)
	Androgens (stanazolol)
	Antimalarials (hydroxychloroquine)
	Corticosteroids (pulsed doses of methylprednisolone + methotrexate)
	Cytostatic drugs (methotrexate)
	Calcitriol
Surgical	Vulvectomy
	Circumcision
	Surgical dilatation + methotrexate
Light therapy	Phototherapy (UVA 1)
	Photodynamic therapy
	Laser (Carbon dioxide)

The lack of standardized protocols for the treatment of GLS may be partly explained by differences in the length of treatment, whereas in some studies the length of treatment was not indicated. However, in most studies the length of treatment was three months (Table 3).

Nevertheless, few studies compare the efficacy of several drugs, but rather their efficacy with placebo, which was also seen in Cochrane Library meta-analysis (1). However, this analysis provided significantly better insight into the effectiveness of drugs used in

Table 2. Cochrane library meta-analysis of randomized controlled trials on topical interventions for genital lichen sclerosus (Ching-Chi and associates) (1)*

Meta-analysis	Treatment options
	Clobestasol propionate
	Mometasone furoate
	Testosterone
	Dihydrotestosterone
	Progesterone
	Pimecrolimus

*, 249 participants covering 6 treatments

the treatment of local GLS. Cochrane Library meta-analysis clearly reported different effectiveness of drugs used in the treatment of genital lichen sclerosus (1).

Topical corticosteroids

A critical evaluation of clinical and histologic effects of topical, 3-months' treatment of VLS with clobetasol propionate versus placebo, showed that clobetasol was significantly more effective than placebo: participant-rated improvement/remission of symptoms: risk ratio 2.85 (95% confidence interval (CI) 1.45 - 5.61); investigator-rated global degree of improvement: standardized mean difference (SMD) 5.74 (95% CI 4.26 – 7.23) (1, 8).

When response of balanitis xerotica obliterans to mometasone furoate versus placebo in children with lichen sclerosus was assessed, after 5 weeks of therapy, the investigator-rated mean clinical grade of phimosis improved in the mometasone furoate group, but worsened in the placebo group (9). Potent topical steroids proved to be safe and effective in the treatment of childhood GLS (1), whereas early aggressive treatment gives the best therapeutic response (10).

Table 3. The length of treatment of genital lichen sclerosus

Trial	Duration
Clobetasol propionate versus placebo	3 months
Mometasone furoate versus placebo	5 weeks
Testosterone versus placebo	3 months; 1 year
Testosterone versus clobetasol propionate	3 months
Testosterone versus placebo as maintenance therapy after initial 24 week-treatment with clobetasol propionate 0.05% cream	Maintenance therapy

Topical androgens and progesterone

Topical androgens, testosterone propionate 2% cream and dihydrotestosterone 2% cream, were studied in five randomized clinical controlled trials on topical interventions for GLS (8, 11, 12, 13, 14). After 3 months of application (8) as well as after one year of aplication (11), there were no significant differences in therapeutic effects between testosterone and placebo in topical therapy of VLS (1, 8, 11). After 3 month of application, testosterone was significantly less effective than clobetasole propionate (1, 8).

No woman with VLS showed a significant improvement after a 3 month trial with dihydrotestosterone versus placebo (12). When comparing effects of topical testosterone to dihydrotestosterone in VLS, during 3 months without a washout period, there were no significant differences in efficacy between the two androgens (1, 13). When testosterone maintenance therapy effects on VLS treated with 0,05% clobetasole propionate were compared to placebo, testosterone worsened the symptoms, whereas placebo caused no change in symptoms or gross appearance (1, 14).

After 3 months of application, topical progesterone cream 2% showed no difference in efficacy compared to placebo in the treatment of of VLS (1, 8).

Topical calcineurine inhibitors

A double-blind randomized contolled trial tested effects of clobetasol versus pimecrolimus in patients with VLS: both pimecrolimus 1% cream and clobetasol propionate 0.05% cream were effective in relieving pruritus and burning pain after 3 months of application, there were no significant differences between pimecrolimus and clobetasol propionate relieving pruritus and burning pain; investigator global assessment showed both preparations were effective; clobetasol propionate was more effective than pimecrolimus in improving inflammation (15). Thus, investigator-rated global degree of improvement, measured by SMD, showed that pimecrolimus was less effective than clobetasol in improving gross appearance (1). Oskay et al. reported good effects of pimecrolimus 1% cream in the treatment of VLS in postmenopausal women (16). Kim et al. performed a prospective study investigating the efficacy of topical tacrolimus ointment in 16 patients with active lichen sclerosus. They found that tacrolimus ointment was a safe and effective treatment for GLS and that it should be used for long-term duration to prevent relapse (17). Similar findings were reported by Virgili et al. who treated VLS in 11 women with tacrolimus 0.1% ointment (18). However, there are authors who believe that topical corticosteroids may increase the risk for human papillomavirus (HPV) infection in men, and that they should not be treated by calcineurin inhibitors, except in resistant cases.

Others

Edmonds and associates estimated that circumcision is effective in 75% of men, and that it appears to abrogate the risk of squamous cell carcinoma; nevertheless, there are conflicting opinions.

Apart from topical tretinoin 0.025 and calcipotriol, which may induce improvement, but also irritation, thus they are rarely used in the treatment of GLS, other forms of LS treatment have shown benefits only in the open-label series or in individual cases: oral retinoids, methotrexate, cyclosporin, surgical therapy, cryotherapy, vulvectomy, carbon dioxide laser vaporisation, pulsed dye laser therapy, photodynamic therapy (19, 20).

Conclusions

In conclusion, we can say that: 1) topical clobetasol propionate, as well as other ultrapotent and potent steroids, such as mometasone furoate, are effective in treating vulval and penile GLS; 2) there is no consensus on how long treatment should last, but most authors agree that treatment of GLS should include highly potent topical corticosteroids once daily during 3 months, followed by twice per week, or twice daily during 4 to 6 weeks, and then, “if necessary” (a common term used in research), twice a week; 3) circumcision is effective in males; 4) topical pimecrolimus and tacrolimus are effective in eliminating subjective complaints of patients and lead to objective improvement; 5) there is no evidence supporting the use of topical androgens and progesterone; 6) long-term multi-year follow-up of patients is necessary, although there is no agreement on which parameters should be assessed; treatment efficacy is often reduced to monitoring GLS symptoms; 7) it still remains unknown wether effective

treatment can reduce the risk of genital squamous cell carcinoma.

Abbreviations

LS - lichen sclerosus
GLS – genital lichen sclerosus
UVA – ultra violet
VLS – vulval lichen sclerosus
SCC – squamous cell carcinoma
MGLS – male genital lichen sclerosus
ECM-1 – extracellular matrix protein-1
CI – confidental interval
SMD - standardized mean difference
HPV – human papillomavirus

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Genitalni lihen sklerozus – Ima li pomaka u terapiji?

Sažetak

Lichen sclerosus (LS) je hronična upalna dermatoza, lokalizovana uglavnom u anogenitalnoj regiji, praćena svrabom, atrofijom i sklerozom. Progresivno destruktivno ožiljavanje u genitanom lihenu sklerozus (GLS) može dovesti do prekrivanja klitorisa kod žena i fimoze kod muškaraca. Postoji povećan rizik za genitalni kancer. U praksi se dešavaju previdi zbog nedijagnostikovanja spinocelularng karcinoma na mestu lezija. Remisije su retke, kod lečenih do 16%. Lečenje GLS je dugotrajno, nema izlečenja, ali je moguće postići značajno poboljšanje. Brojna terapijska sredstva primijenjuju su za lečenje GLS, nažalost, broj kontrolisanih studija je mali a dobijeni rezultati se odnose na kontrolu simptoma, ali ne i na progresiju bolesti i pojavu ožiljavanja. Urađena je metaanaliza na sedam randomizovanih kontrolnih studija koje su se

odnosile na lokalnu terapiju GLS. Analiza je obuhvatila ukupno 249 lečenih pacijenata i šest lokalnih preparata: klobetazol propionat, mometazon furoat, testosteron, dihidrotestosteron, progesteron i pimekrolimus. Topijski kortikosteroidi, klobetazol propionat 0,05% (jako potentan) i mometazon furoat 0,05% (potentan), u odnosu na placebo pokazali su se značajno efikasnijim. Pimekrolimus 1% krem u komparaciji sa klobetazol propionatom 0,05%, pokazao je sličnu efikasnost. Oba preparata su se pokazala efikasnim u lečenju GLS: nije utvrđena statistički značajna razlika u njihovoj efikasnosti kada su kupiranje pruritusa i pečenja/bola u pitanju. Efikasnim u lečenju GLS pokazao se i takrolimus u obliku 0,1% masti. Topijski androgeni i progesteron nisu ispoljili značajnu efikasnost. Topijski tretinoin i kalcipotriol mogu dati poboljšanje, ali i iritaciju, pa se retko primenjuju u lečenju GLS. Druga terapijska sredstva koja se primenjuju u GLS su fototerapija (*UVA-1 rays*), metotreksat, retinoidi, ciklosporin, stanazolol, hidroksihlorokvin, kalcitriol, laseri i fotodinamička terapija, ali je broj lečenih ovim preparatima mali da bi se donosili temeljni zaključci. Hirurška intervencija kao primarni oblik lečenja GLS nije indikovana.

Zaključak. Lečenje GLS treba sprovoditi kroz dve faze, uvođenjem u remisiju i održavanjem postignutog efekta; u lokalnoj terapiji treba koristiti jako potentne kortikosteroide jedanput dnevno tokom tri meseca, zatim dvaput nedjeljno, ili dvaput dnevno 4 do 6 nedelja, a potom dvaput nedeljno. Da li u održavanju postignutog učinka treba primenjivati superpotentne ili potentne topijske kortikosteroide mišljenja su različita; potrebno je dugotrajno praćenje ovih bolesnika, više godina, mada ne postoji saglasnost koje parametre treba procenjivati; najčešće se procena efikasnosti leka svodi na praćenje simptoma.

Ključne reči

Lichen sclerosus et atrophicus; Meta analiza; Topijska primena; Pregled; Dermatološki preparati; Clobetasol; Tacrolimus