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Original Articles

Efficiency of 7-dehydrocholesterol vitamin-D3 complex cream for xerosis and pruritus in elderly women

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Abstract

Background: Xerosis and pruritus (XP) are the most common skin conditions in the elderly, manifesting clinically as roughness, scales, fissures, and mild-to-severe itching. Vitamin D improves skin hydration, transepidermal water loss (TEWL), and regulates the immune system. We aimed to determine the efficiency of topical 7-dehydrocholesterol (DHC)-vitamin D3 complex cream in elderly patients with XP.
Methods: An experimental phase III study was performed on elderly women with XP from December 2021 to March 2022 at the Geriatric Dermatology Clinic of Dr. Mohammad Hoesin General Hospital, Palembang. Inclusion criteria were age older than 55 years, healthy or with comorbidity. The exclusion criteria include the use of moisturizer within two weeks before the study. DHC-vitamin D3 cream was applied on subject's volar arms once a day. Overall dry skin score (ODSS), visual analog scale (VAS) for pruritus and adverse effects, skin hydration, TEWL, sebum level, serum vitamin D level, and dermatology life quality index (DLQI) were assessed at baseline and after 4 weeks. Statistical analysis was done with Wilcoxon and paired T-test.
Results: Eighteen elderly women were included. Most subjects were 60 to 74 years old (83,3%). Half the subjects (50%) had comorbidity. There was a significant difference in skin hydration ($p<0.001$), TEWL ($p<0.001$), serum vitamin D levels ($p<0.001$), and DLQI score ($p<0.001$) after treatment. The cream was well-tolerated with no adverse effects.
Conclusion: Topical 7-DHC vitamin D3 complex cream is proven to improve skin barriers, increase serum vitamin D levels, well-tolerated, and provided satisfaction and comfort in elderly women with XP.

Keywords: *7-DHC vitamin D3, complex cream, elderly women, skin barriers, xerosis and pruritus*

Background

Xerosis cutis, also known as dry skin, xerosis, or xeroderma, accompanied by pruritus in the elderly is a complex biological process influenced by both intrinsic (genetics, cellular metabolism, hormones, and metabolic processes) and extrinsic factors (sun exposure, pollution, radiation, chemicals, and comorbidities such as diabetes mellitus, heart or kidney problems, dementia, and cerebral infarction). The accumulation of these factors changes the structure and function of the skin, resulting in a slowed-down cell cycle and turnover of the epidermis, leading to skin homeostasis disruption. The incidence and severity of xerosis and pruritus (XP) increase with age.[1,2] In the elderly, the clinical manifestations of XP typically include scaly skin, atrophy, roughness, dryness, fissures or cracks, thickened epidermis, uneven skin color, deep wrinkles, as well as dull and vulnerable skin, accompanied by mild-to-severe

pruritus, which causes a scratch-pruritus-scratch reaction. The severity of XP results in complications, such as secondary infections, ulcerations, and chronic wounds.[1] XP also decreases quality of life, causing anxiety, insomnia, and depression. A study done by Yahya et al. in 2020 showed that XP is among the most common skin disorders in the elderly, accompanied by mild-to-severe pruritus.[3] Mekic, et al. in 2019 conducted a cross-sectional study and found a 60% incidence of older people with XP.[4]

The predilection sites of XP include extremities, and both lower legs and arms, but it can also affect the trunk and face.[4] According to the Endocrine Society, serum vitamin D levels in the elderly can be classified into sufficient (≥30 ng/mL), insufficient (21–29 ng/mL), and deficient (≤20 ng/mL). The prevalence of vitamin D3 deficiency is known to have been increased by an average of 96%.[5] Overall, vitamin D3 positively impacts skin aging through a comprehensive inflammatory response mechanism, improving epidermal barrier function, preventing DNA damage, and repairing DNA. It also has antioxidant and photoprotective properties.[6] An *in vivo* study proved that keratinocytes contained vitamin D3, which controls the differentiation process and monitors skin barrier function.[7] An epidemiological study in the elderly demonstrated the relationship between vitamin D3 deficiency and the severity of chronic skin diseases, such as infections, psoriasis, and atopic dermatitis. It also increases the risks of osteoporosis and osteomalacia, which results in falls and fractures.[8] Another study showed that vitamin D3 deficiency in elderly patients with psoriasis poses a higher risk for cardiovascular disorders and is associated with carcinogenic effects and increased mortality.[9] A review by Knox and O'Boyle in 2021 showed that skin lipids have an important role in the skin's structure and function, starting from the inner layer (hypodermis), which is rich in ceramide, to the lipids (ceramide, cholesterol, and triglycerides) in the epidermal surface.[10]

In the elderly, the management of XP consists of the application of moisturizer with occlusive, humectant, and emollient properties to improve skin hydration and prevent transepidermal water loss (TEWL), facilitating the skin's barrier functions. Adding topical vitamin D in the treatment regimen for elderly patients is necessary to reduce TEWL, improve elasticity and flexibility, and prevent the degradation of skin structures, such as collagen and elastin, which can reduce the formation of wrinkles and improve chronic wounds. Vitamin D3 plays a role in keratinocyte differentiation and in improving the body's innate and adaptive immunity. Vitamin D3 improves skin homeostasis, reduces inflammatory processes, protects the skin from sun exposure, and accelerates wound healing.[11] The current study aimed to determine the efficiency of topical 7-dehydrocholesterol (DHC)-vitamin D3 complex cream in elderly patients with XP.

Methods

A prospective experimental phase III study was performed from December 2021 to March 2022. The study used consecutive sampling of elderly women patients with XP. The sample size was calculated using Pocock's formula. The study was performed in the Dr Mohammad Hoesin Central General Hospital, Palembang with ethical clearance number 247/keprsmh/2021. Inclusion criteria were age older than 55 years, diagnosed with XP, healthy or with comorbidity, and signed an informed consent form. The exclusion criterion was the use of another moisturizer within two weeks prior to the study.

The subjects received 7-dehydrocholesterol (DHC)-vitamin D3 complex cream, applied on the volar arms once a day. Comorbidity data were obtained from the medical records. Clinical manifestations of XP were assessed using the overall dry skin score (ODSS), serum vitamin D levels, dermatology life quality index (DLQI), as well as skin hydration, TEWL, and sebum levels assessed using Corneometer, Tewameter, and Sebumeter, respectively, with Multi Probe Adapter 6 (Courage+Khazaka=CK, Köln, Germany). The severity of pruritus and side effects were assessed with a visual analog scale (VAS). The assessment was performed at baseline and after 4 weeks of treatment. Statistical analysis was performed with the Wilcoxon test and paired T-test. A p-value of <0.05 indicates significance.

Results

The characteristics of the study subjects are presented in Table 1. Of the 18 elderly women with XP, most were aged 61–74 years (83.3%), with the rest being 55–60 years (16.7%), averaging at 62.50 years. The study also showed that half of the subjects (50%) had comorbidities consisting of six subjects with hypertension (33.3%), two subjects with diabetes mellitus (11.1%), and one subject with hypothyroidism (5.6%). Normality test revealed a non-normal data distribution. Clinical manifestations assessed using ODSS had a p-value of 0.317 ($p>0.05$) on the Wilcoxon test,

indicating the lack of statistically significant difference (Table 2). The severity of pruritus and side effects assessed using VAS had a p-value of 0.034 (p<0.05) according to the Wilcoxon test, indicating a statistically significant difference (Table 2). Skin sebum levels were assessed using the Sebumeter with a p-value of 0.440 (p> 0.05) according to the paired T-test, indicating no statistically significant difference (Table 2). Skin hydration was tested using a Corneometer and the Wilcoxon test showed a statistically significant difference (p <0.001) (Table 2). TEWL was tested using a Tewameter and the paired T-test showed a p-value of <0.001 (p<0.05), indicating a statistically significant difference (Table 2). Serum vitamin D3 level was analyzed using a paired T-test, showing a p-value of <0.001 (p<0.05), indicating a statistically significant difference (Table 3). The DLQI showed an eight-fold increase in satisfaction rate and the Wilcoxon test showed a p-value of <0.001, indicating a statistically significant difference (Table 3).

Discussion

Moisturizer is one of the main skin care treatments for elderly patients with XP and involves the following four-step process: 1) repairing skin barrier; 2) increasing skin hydration; 3) reducing TEWL; and 4) restoring skin lipid function by attracting, retaining, and redistributing water into the skin layer. Additionally, moisturizer must be cosmetically elegant, acceptable for sensitive skin (hypoallergenic, non-sensitizing, fragrance-free, and non-comedogenic), affordable, long-lasting, quickly absorbed, and able to accelerate hydration repair to prevent or reduce skin TEWL.[13]

Table 1. Characteristics of the Study Subjects

Characteristics	Number of Subjects (n=18)	%
Age (mean ± standard deviation)	62.50 ± 5.74	
55-60 years	3	16.7
61-75 years	15	83.3
Comorbidity		
None	9	50%
Hypertension	6	33.3%
Diabetes mellitus	2	11.1%
Hypothyroidism	1	5.6%

Table 2. Assessment of Clinical Manifestations, Sebum Level, Skin Hydration, and Transepidermal Water Loss (n=18)

Assessment	Tools	Treatment		p
Clinical manifestation	ODSS	Before After	0.0 (0.0-1.0) 0.0 (0.0-0.0)	0.317
Pruritus	VAS	Before After	0.0 (0.0-1.0) 0.0 (0.0-1.0)	0.034*
Sebum level	Sebumeter	Before After	57.7 ± 10.3 55.2 ± 11.9	0.440
Skin hydration	Corneometer	Before After	8.5 (4.0-13.0) 21.0 (12.0-27.0)	<0.001*
TEWL	Tewameter	Before After	21.0 (17.0- 25.0) 8.5 (6.0-9.0)	<0.001**

ODSS: overall dry skin score; TEWL: transepidermal water loss; VAS: visual analog scale; *Wilcoxon, p<0.05; **paired T test, p<0.05

Table 3. Assessment of Serum Vitamin D Levels and Level of Satisfaction (n=18)

Assessment	Tools	Treatment		p*
Serum Vitamin D levels	Blood chemistry	Before After	17,7 ± 10,3 55,2 ± 11,9	<0,001
Level of Satisfaction	DLQI	Before After	2,0 (2,0-3,0) 16,0 (12,0-18,0)	<0,001

DLQI: dermatology life quality index; *paired T test, p<0.05

Based on the results above, XP was found in elderly women aged 60-74 years. Half of the subjects had comorbidity, including hypertension in six subjects (33.3%), diabetes mellitus in two subjects (11.1%), and hypothyroidism in one subject (5.6%). The Indonesian Ministry of Health defines elderly patients as men and women aged 60 years and above.[14] Normal physiological changes in the elderly affects skin structure and decreases its ability to regenerate. These are also influenced by extrinsic cumulative factors, such as air/weather, sun exposure, nutrition, irritants and allergens passing through the skin, inflammatory reactions, and pruritus.[15] Additionally, the body's declining immune system in the elderly affects the sensitivity of the nervous system, leading to more severe pruritus. Polypharmacy and comorbidities, such as diabetes mellitus and hypertension are often observed in elderly patients, increasing the severity of pruritus.[16] A review by Rebelos, et al. showed that the administration of pro-vitamin D3 supplements improved the functions of the immune system and bone cells in people with vitamin D deficiency.[17] According to another review by Augustin, et al. XP generally manifested as xerosis cutis and pruritus in elderly people aged ≥ 60 years old with comorbidities, such as diabetes mellitus, heart disorders, cerebral infarction, and dementia.[18] Aboeldahab, et al. conducted a cross-sectional study on elderly patients aged ≥60 years (n=225). The study showed that XP was found in 73.8% of patients with the most prevalent comorbidity being kidney disorders (46.2%).[19] In the current study, the study subjects were all women, and the number of subjects without comorbidity was the same as the number of subjects with comorbidity.

Vitamin D biologically functions to (1) regulate keratinocyte proliferation, differentiation, and apoptosis; (2) act as the skin's immune system [inhibits T-cell proliferation and regulatory T (Treg) cells induction]; (3) downregulate pro-inflammatory cytokines; (4) stimulate expression of antimicrobial peptides (AMPs); and (5) regulate skin barrier integrity and permeability.[20] Moisturizers serve as occluder, humectant, and emollient that could improve skin hydration and reduce TEWL to protect the skin. The lipid component supplied to epidermal keratinocytes rearranges intercellular lipids, restoring the skin's normal physiological function.[21] Consumption of vitamin D supplements can reduce autoimmune diseases and activate vitamin D receptor (VDR) so that it can inhibit the differentiation and proliferation of B lymphocytes to T-helper (Th), reduce inflammatory process, make the immune system more tolerant, and inhibit pro-inflammatory production. Th1 cytokine activity stimulates Th2 and T-reg cells.[17] In this study, there are no statistically significant difference in terms of clinical manifestation (p=0,317).

Vitamin D3 affects the innate and adaptive immune system by inducing the expression of AMPs, such as cathelicidin, which modulates immune and inflammatory cell responses, acting as an immune system barrier against microbes.[22] Guttmenn-Guber, et al. conducted a randomized controlled clinical study by applying a topical low-dose vitamin D3 analog (calcipotriol ointment) in dystrophic epidermolysis bullosa (DEB) patients. The study showed a significant reduction in pruritus and accelerated wound healing. The ointment could be applied safely as daily wound care.[23] Rasool, et al. did a randomized controlled clinical study on chronic urticaria (CU) subjects by giving vitamin D3 supplementation. The treatment group had significantly reduced pruritus compared to the controls.[24] This study also found a statistically significant difference in the severity of pruritus (p=0.034).

With increasing age, the elderly are influenced by extrinsic and intrinsic factors that cause skin disorders such as xerosis cutis and pruritus, especially in developing countries like Indonesia.[25] Physiologically, the elderly experiences increase in TEWL and disturbances in hydration of the stratum corneum and skin pH.[26,27,28] A review of molecular biology done by Howard et al. in 2022 on elderly patients showed that there were changes in the skin microbiome composition, which resulted in dry skin, pruritus, eczema, and many complications.[29,30] According to Choi, et al., elderly women are physiologically characterized by a decrease in estrogen, structural degeneration, and slow progressive skin functional changes, making them susceptible to skin diseases, including eczema, asteatotic dermatitis, contact and allergic dermatitis, seborrheic dermatitis, and autoimmune diseases, which can be fatal.[31]

According to Lynde, et al. moisturizer ingredients and additional active complex (containing free fatty acids [FFA], ceramide, and cholesterol) can improve skin barrier function and decrease the incidence of contact and allergic dermatitis, seborrheic dermatitis, as well as autoimmune diseases.[31,32] Kang, et al. did a review on maintaining moisture content in the epidermis and improving the function of the skin barrier.[21] The study found that the difference in skin sebum levels based on the Sebumeter was not statistically significant (p=0.440), and concluded that moisturizers do not work directly on sebaceous glands to increase sebum levels.

A study done by Li on Asian populations, the clinical manifestation of photoaging shows that pigmented lesions are more dominant in Asian population than in Caucasians.[33] Skin lipids have an important role in the structure and function of the skin, starting from the ceramide-rich inner layer (hypodermis), to the epidermal surface containing ceramide, cholesterol, and triglycerides.[10] According to Tollenaera, et al. the main role of the stratum corneum lipids is to maintain skin hydration and reduce TEWL, thus administering moisturizers rich in lipids is beneficial for the skin of elderly people with XP.[34]

Studies by Kahraman, et al. and Kang, et al. showed that moisturizers containing ceramide are effective and safe for the treatment of inflammatory skin disorders.[21,35] In this study, skin hydration, as assessed using Corneometer, was observed to be increased significantly ($p<0.001$). There was an eight-fold increase after 4 weeks of treatment. This moisturizer combination contains ceramide, FFA, cholesterol, and squalene which act as occluder, humectant, and emollient. The ointment also contains supplemental vitamin D3, which is beneficial in maintaining skin hydration and improving TEWL for the elderly.

In elderly skin, molecular biological changes, specifically the loss of protein structure, occur in the complex corneum layer, resulting in impaired skin hydration. Additionally, TEWL also affects skin barrier function. Providing topical moisturizers with emollient, humectant, and occlusive properties improves skin hydration and pH, and reduces TEWL. Administering moisturizers is beneficial for elderly patients and/or patients contraindicated for systemic treatments, since moisturizers act as both treatment and prevention.[36,37,38] In this study, there was a statistically significant difference in TEWL with an 8-fold increase in skin hydration ($p <0.001$), indicating that this moisturizer complex combined with vitamin D3 can repair skin hydration and TEWL, leading to improvements in the skin barrier.

A review by Daryabor showed that having normal vitamin D level improves the innate and adaptive immune system, leading to the production of antimicrobial substances and chemotaxis to improve skin barrier function.[39] A study by Zou reported that vitamin D3 works directly on keratinocyte differentiation[40] while Bikle reported that there are vitamin D3 receptors in keratinocytes that physiologically activate vitamin D3, which functions to regulate the differentiation and permeability of skin barrier, prevent proliferation, promote innate immunity, and suppress tumor formation.[41]

According to White, vitamin D3 supplementation plays a crucial role in cathelicidin expression, which has a molecular biological positive impact on increasing innate and adaptive immunomodulation through the regulation of AMPs for treating skin inflammation.[8] Zhang, et al. conducted a study on diabetic foot patients, and reported an increase in gram-negative bacteria causing inflammatory reactions on the skin surface, worsening skin disorders.[42] Amin, et al. conducted a study in elderly patients with XP. Empirically, there was a relationship between the decrease in total free fatty acids, ceramide, triglyceride, and free amino acids with an increased incidence of XP.[43]

A study by Russell-Goldman found a statistically significant relationship between vitamin D3 supplementation and the improvement of skin hydration.[11] Ceolin, et al. conducted cross-sectional a study in Brazil in 2020 on 557 elderly. The study showed that 7-DHC vitamin D3 deficiency in the blood was associated with depressive symptoms, which improved after the administration of vitamin D supplementation.[5] A 2024 study by Janjetovic showed that topical vitamin D3 as a sunscreen can prevent photoaging caused by extrinsic risk factors, such as sun exposure.[44] In this study, serum vitamin D levels differed significantly ($p<0.001$). Further research is needed to determine whether providing a moisturizer complex combined with vitamin D3 increases vitamin D in the blood, particularly in the elderly with comorbidities, low vitamin D levels, and polypharmacy.

According to Danimayostu, et al. vitamin D supplementation has a positive impact on the elderly through a comprehensive inflammatory response mechanism, improvement of skin barrier function, prevention of DNA damage, DNA repair, and antioxidant and photoprotective properties.[45] According to several researchers, policies on the provision of vitamin D3 (polymorphisms, analogs, and metabolites) as anti-aging supplementation is necessary to improve elderly health.[44,46] Augustin conducted a double-blind clinical trial, applying water-in-oil moisturizer to the subjects, which led to improved skin hydration and reduced TEWL. The treatment can be used long-term and effective.[18] Administering moisturizers with emollient, humectant, and occlusive properties is safe for elderly skin.[47]

Ikoma, et al. conducted a study on 60 elderly patients with XP who received moisturizers containing ceramide. The study showed significant satisfaction.[48] Shim, et al. did a double-blind randomized clinical trial on repeated applications of

moisturizer. The study showed a significant hydrating effect on the skin.[49] Finch, et al. did a study on 184 elderly patients with abrasions on their extremities. The twice-daily application of moisturizers reduced the effects of abrasions, thereby reducing costs and improving wound care.[50]

Akpinar and Karadağ did a review in 2022 and concluded that vitamin D has antioxidant properties and activity in brain tissue, which can prevent mood disorders. Vitamin D supplementations are needed so that sufficient vitamin D levels can be maintained.[51] Alavi, et al. did a randomized clinical trial on elderly patients aged ≥ 60 years old (n=78), and vitamin D supplementation was proven to improve depression in the elderly.[52] In the current study, there was a statistically significant difference in DLQI scores ($p<0.001$). Regular application of moisturizer complex combined with vitamin D3 provided satisfaction and comfort for elderly women. This study is consistent with a previous study, in which the effects of topical vitamin D were better than oral vitamin D after 4 weeks of application. However, this study has some limitations owing to the fact that only elderly women were included. The small number of subjects (n = 18) is another limitation that should be considered. Further study with larger sample size should recruit elderly men and women, and categorize them according to XP severity.

Conclusion

Topical 7-DHC vitamin D3 complex cream showed good results, was significantly well-tolerated, and had no side effects. In patients with xerosis cutis, especially in the elderly with low serum vitamin D3 levels, it is recommended to give topical 7-DHC vitamin D3 complex cream as an XP prevention or treatment.

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Author Contributions

All authors act as the guarantor of the manuscript. YFY is the conceptor and main investigator of this study. MR, PHJ, DABN, and MABE participated in data acquisition and interpretation. YK, TLT, and NR participated in writing of the study, data analysis, and statistical analysis of the study.

Conflict of interest

No conflict of interest.

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