



ROLE OF VITAMIN D IN THE TREATMENT OF ATOPIC DERMATITIS

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ABSTRACT

Atopic dermatitis (AD) is a chronic and recurrent inflammatory condition that affects patients' quality of life. One alternative that has an anti-inflammatory effect on AD is vitamin D (25-hydroxyvitamin D (25(OH)D). Although the main treatment for AD uses drugs such as corticosteroids or immunosuppressants, the side effects caused are quite high. Therefore, the aim of this review This literature aims to find out more about the effectiveness of vitamin D against AD, so that it can be an alternative treatment option. Objective: To determine the role of vitamin D in the treatment of atopic dermatitis. Method: The research took database sources from Pubmed, Google Scholar, Science Direct, and Cochrane from 2014-2023 which were then selected based on the inclusion and exclusion criteria that had been created. A total of 17972 articles were found using the keywords ("Vitamin D" OR "Calciferol" OR "Calcitriol") AND "Atopic Dermatitis" AND ("Role" OR "Function") which then after screening, 16 articles were taken for this literature review. Results: AD is an inflammatory condition that is influenced by various factors. The severity of this disease can be assessed using SCORAD or EASI. AD patients generally have lower serum vitamin D levels and decreased SCORAD index. However, vitamin D supplementation in AD treatment varies according to each country and geographic region. Conclusions: Various studies have been conducted to review the effects of vitamin D supplementation on AD, but not all of them show significant effects. This is influenced by many factors, especially age, dosage, preparation, country and geographical area. So more in-depth research is needed on this matter.

Keywords: atopic dermatitis; calciferol; calcitriol; vitamin D

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INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin condition with clinical presentations of dry, itchy, and inflamed skin (Kim et al., 2016). AD is caused by multifactorial factors (genetic, environmental, immunological, and barrier dysfunction). Vitamin D plays a crucial role not only in maintaining bone health, but also in supporting immune function in inflammatory disorders, including AD or eczema. Vitamin D has therapeutic effects on treatment of AD, such as maintaining the immune system by modulating T cells, B cells, and dendritic cells, reducing production of pro-inflammatory cytokines such as interleukin-17 (IL-

17) and interleukin-22 (IL-22), and promoting production of anti-inflammatory cytokines such as interleukin-10 (IL-10). In addition, vitamin D promotes keratinocyte differentiation and enhances protein expression involved in skin barrier formation. This suggests that supplementation of vitamin D decreases transepidermal water loss and increases filaggrin levels that are substantial in skin barrier restoration in AD patients. Clinical trials investigating the effects of vitamin D supplementation on AD have shown mixed results. Some studies suggest that vitamin D may lead to improvements in AD symptoms and severity while others do not find significant benefits. Therefore, an elaboration on this topic is necessary (Kim & Bae., 2016).

AD severity is evaluated through clinical tools known as SCORing Atopic Dermatitis (SCORAD) and Eczema Area and Severity Index (EASI) (Eichenfield et al., 2014; Chrichton et al., 2021). SCORAD takes into account objective signs, subjective symptoms, and the extent of affected areas of AD and converts it to a numerical score. AD severity is then categorized as mild, moderate, and severe based on this total score (Eichenfield et al., 2014). Another standardized way to measure disease severity and track treatment progress is EASI. EASI measures the extent and intensity of AD lesions in four different regions by observing four specific eczema signs and scoring them on a scale of 0 to 3 (none, mild, moderate, severe) for each body region. Higher EASI score indicates more severe AD (Chrichton et al., 2021). The main treatment for AD uses drugs such as corticosteroids or immunosuppressants, the side effects caused are quite high. Therefore, the aim of this literature review is to further determine the efficacy of vitamin D as an alternative in AD treatment.

METHOD

The search strategy used the keywords (“Vitamin D” OR “Calciferol” OR “Calcitriol”) AND “Atopic Dermatitis” AND (“Role” OR “Function”) on various electronic databases such as Pubmed, Google Scholar, Science Direct, and Cochrane with a total of 17972 articles. Then articles were screened using inclusion and exclusion criteria. Inclusion criteria include articles with publication years 2014-2023, articles published in English, and articles in the form of meta-analyses, systematic reviews, cohort studies, case reports, and literature reviews. Exclusion criteria included articles published in books, websites, and articles with only abstracts, not open access, and without full text articles. There were 16 articles used in this literature review.

RESULTS

Scoring of Atopic Dermatitis (SCORAD) Index and Eczema Area and Severity Index (EASI) Score

Scoring of Atopic Dermatitis (SCORAD) index, developed in 1993 by the European Task Force of Atopic Dermatitis (ETFAD) is a scoring method to assess severity of AD. SCORAD evaluates the extent of AD (A: according to rule of nine; 20% of the score), intensity (B: erythema, oedema/papules, effect of scratching, crust formation, lichenification, and dryness; 60% of the score; four grades for each item: 0,1,2,3), and subjective symptoms (C: itch, sleeplessness; 20% of the score) of the most representative lesion rather than the most severe or mildest lesion. Severity of AD is divided into mild (score below 25), moderate (score between 25-50), and severe (score beyond 50) (Figure 1). This evaluation can be completed between 7-10 minutes according to investigators' experience (Severity Scoring of Atopic Dermatitis: The SCORAD Index., 1993; Oranje et al., 2007).

SCORAD INDEX
EUROPEAN TASK FORCE
ON ATOPIC DERMATITIS

Last Name: _____ First Name: _____
Date of Birth: _____ DD/MM/YY
Date of Visit: _____

Figures in parenthesis for children under two years

A: EXTENT Please indicate the area involved _____
B: INTENSITY _____
C: SUBJECTIVE SYMPTOMS PRURITUS + SLEEP LOSS _____

A/5 + 7B/2 + C

CRITERIA	INTENSITY
Erythema	
Oedema/Papulation	
Oozing/crust	
Excoriation	
Lichenification	
Dryness*	

* Dryness is evaluated on uninvolved areas

MEANS OF CALCULATION
INTENSITY ITEMS (average representative area)
0 = absence
1 = mild
2 = moderate
3 = severe

Visual analog scale (average for the last 3 days or nights)
PRURITUS (0 to 10) _____ 0 _____ 10
SLEEP LOSS (0 to 10) _____ 0 _____ 10

Figure 1. SCORAD index (Severity Scoring of Atopic Dermatitis: The SCORAD Index., 1993; Oranje et al., 2007).

Eczema Area and Severity Index (EASI) was developed in 1998 and validated in order to meet the standard as an AD severity evaluation tool. According to Harmonizing Outcome Measures in Eczema (HOME), EASI is a recommended core instrument for measuring signs in all AD clinical trials (Hanifin et al., 2022).

Severity Score	Area Score							
Grade each sign on a scale: 0=clear/none 1=mild 2=moderate 3=severe	% Involvement	0	1-9%	10-29%	30-49%	50-69%	70-89%	90-100%
	Area Score	0	1	2	3	4	5	6

EASI Calculator (Adults)

Body Region	Erythema (0-3)	Edema/Papulation (0-3)	Excoriation (0-3)	Lichenification (0-3)	Area Score (0-6)	Multiplier	Score
Head/Neck	(+)	(+)	(+)	()	x	x 0.1	
Trunk	(+)	(+)	(+)	()	x	x 0.3	
Upper Extremities	(+)	(+)	(+)	()	x	x 0.2	
Lower Extremities	(+)	(+)	(+)	()	x	x 0.4	
The final EASI score is the sum of the 4 region scores (0-72):							_____

EASI Calculator (Pediatrics < 8 years old)

Body Region	Erythema (0-3)	Edema/Papulation (0-3)	Excoriation (0-3)	Lichenification (0-3)	Area Score (0-6)	Multiplier	Score
Head/Neck	(+)	(+)	(+)	()	x	x 0.2	
Trunk	(+)	(+)	(+)	()	x	x 0.3	
Upper Extremities	(+)	(+)	(+)	()	x	x 0.2	
Lower Extremities	(+)	(+)	(+)	()	x	x 0.3	
The final EASI score is the sum of the 4 region scores (0-72):							_____

EASI Score Interpretation

Clear	Almost Clear	Mild	Moderate	Severe	Very Severe
0	0.1-1.0	1.1-7.0	7.1-21.0	21.1-50.0	50.1-72.0

Figure 2. EASI score assessment and calculation (Hanifin et al., 2022).

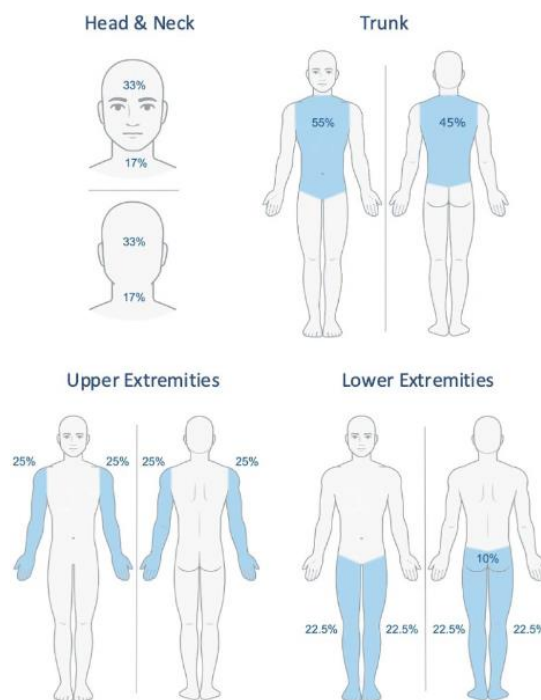


Figure 3. Area of involvement (Hanifin et al., 2022).

Vitamin D: Mechanism of Action in AD Treatment

The effects of vitamin D supplementation can be observed in Table 1 and Figure 4 :

Table 1.
Vitamin D Supplementation Effects in AD Severity

No	Author name, year	Participants	Dose of Vitamin D	Duration of Treatment	Results
Vitamin D administered in human (supporting study)					
1.	Vestita <i>et al.</i> , 2015; Hattangdi-Haridas <i>et al.</i> , 2019; Kim G <i>et al.</i> , 2016	Children with AD	1000-1600 IU	1-3 months	AD severity improvement (a decrease of 7-10 in SCORAD index) ^{2,18,19,}
2.	Fu <i>et al.</i> , 2022	AD patients		1-3 months	AD severity improvement (a decrease of 11-19 in SCORAD index) ²¹
3.	Ghanem <i>et al.</i> , 2017	Children with AD	500 IU (5 drops daily)	1 month	AD severity improvement (a decrease of 10 in SCORAD index) ²²
4.	Raj <i>et al.</i> , 2022	AD patients	1000 IU	3 months	AD severity improvement (a maximum decrease of 41 in SCORAD index (severe AD) and a decrease of 2 in SCORAD index (mild AD)) ²³
5.	Bothou <i>et al.</i> , 2018	8-year-old girl with AD lesions in all region	Oral calcitriol of 0.5 mcg (3 times daily) and oral cholecalciferol (4000 IU)	6 months	AD severity improvement (a decrease of SCORAD index from 70 to 10) ²⁴

6.	Sánchez-Armendáriz <i>et al.</i> , 2018	AD patients	5000 IU	1-3 months	AD patients with serum levels >30 ng/mL are more responsive compared to AD patients with serum levels ≤30 ng/mL. ²⁵
7.	Camargo <i>et al.</i> , 2014	AD children with the average of 9 years old	Oral drop of Vitamin D supplementation (1000 IU)	1 month	A decrease of EASI score of 6.5; a decrease of IGA of 1 in AD children. ²⁶
Vitamin D administered in human (opposing study)					
1.	Park <i>et al.</i> , 2023	AD patients	2000 IU		Vitamin D supplementation does not significantly decrease SCORAD Index compared to placebo. ²⁷
2.	Lara-Corrales <i>et al.</i> , 2019	Children with AD	Oral drop of Vitamin D supplementation (2000 IU)	3 months	No significant difference on SCORAD Index. ²⁸
Vitamin D administered in animals					
1.	Umehara <i>et al.</i> , 2023	NC/Nga mice (Nishiki-nezumi Cinnamon/Nag oya mice)	Topical Vitamin D	4 days	Significant decrease of dermatitis score and TEWL (1 nmol topically compared to 0.1 nmol); increase of epidermal thickness (0.1 nmol topically); decrease of epidermal thickness (1 nmol topically) ²⁹

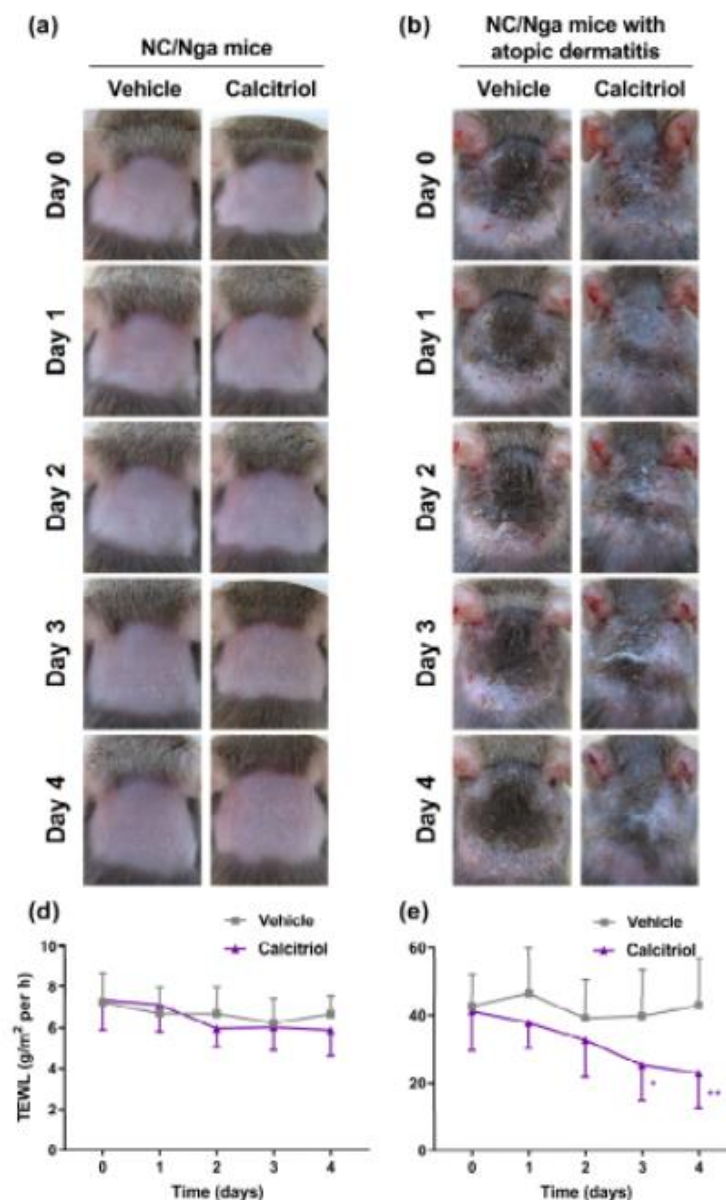


Figure 4. The effects of a daily topical application of calcitriol for 4 days on the condition of the skin in NC/Nga mice without atopic dermatitis (a) and NC/Nga mice with atopic dermatitis (b) (Umehara et al., 2023).

Vitamin D Status in Atopic Dermatitis Patients

Vitamin D status and serum level in AD patients can be observed in Table 2 and Table 3.

Table 2.
Vitamin D Status in AD Patients

No	Authors name, year	Participants	Mean of Vitamin D serum levels
1.	Vestita <i>et al.</i> , 2015; Hattangdi-Haridas <i>et al.</i> , 2019; Fu <i>et al.</i> , 2022	All Ages with AD	Decrease about 2.0-13.63 ng/mL at baseline
		Children with AD	5.2-23.2 ng/mL (Decrease about 3.0-6.4 ng/mL at baseline)
		Adults with AD	10.2-28.9 ng/mL (Decrease about 0.1-.0.9 ng/mL at baseline; not statistically significant)

2.	Vestita <i>et al.</i> , 2015	Mild AD	21.2 ng/mL
		Moderate AD	17.8 ng/mL
		Severe AD	13.3 ng/mL
3.	Dogru., 2018	Children with severe AD compared to children with moderate and mild AD	< 20 ng/mL
4.	Hata <i>et al.</i> , 2014	Children with AD and darker skin color (Fitzpatrick V and VI)	Type V/VI skin had a lower mean level of 18.8 ng/mL in comparison to Type III/IV with a mean level of 28.7 ng/mL (P = 0.04)

Table 3.
Vitamin D Supplementation to Improve Serum Level in AD Patients

No	Author name, year	Participants	Dose of Vitamin D	Duration of Treatment	Improvement of Vitamin D serum levels
1.	Lara-Corrales <i>et al.</i> , 2019	Children with AD	2000 IU	3 months	18.8 ng/mL to 32.6 ng/mL (improvement of 13.8 ng/ mL)
2.	Hata <i>et al.</i> , 2014	Adults with AD	4000 IU	3 weeks	28.4 ng/mL to 37.8 ng/mL (improvement of 9.4 ng/ mL)
3.	Sánchez-Armendáriz <i>et al.</i> , 2018	Children and Adults with AD	5000 IU	3 months	Improvement of 18.8 ng/ mL

DISCUSSION

Atopic Dermatitis

Atopic dermatitis (AD) is a chronic and recurring inflammatory cutaneous condition characterized by pruritus, eczematous plaques, and impaired epidermal barrier (Mansour & Salah., 2020). AD significantly impacts quality of life in both infants and adults. AD mainly affects young children under the age of seven years old with predilection areas in the face, scalp, and extensor surfaces. However, AD is also frequent among adults with epidemiology of 7-10% and predilection area mainly in flexural surfaces (Aldaghi et al., 2022; Weidinger et al., 2018). AD is caused by both genetic and environmental factors. Patients with a family history of atopic diseases (eczema, asthma, and allergic rhinitis) often have impaired skin barrier function due to genes mutation such as filaggrin (FLG) that leads to reduced water retention and increased susceptibility to irritants and allergens which can trigger further immune responses (O'Regan et al., 2009; Margolis et al., 2012). The immune system in AD is skewed towards a Th2-dominant response, leading to an increased production of pro-inflammatory cytokines such as interleukin-4 (IL-4), interleukin-13 (IL-13), interleukin-31 (IL-31) that induces inflammation and itching. AD patients also have elevated levels of Immunoglobulin E (IgE) that binds mast cells which release histamines and other inflammatory mediators, leading to itching and inflammation (Gittler et al., 2012). Exacerbation of AD is also caused by environmental factors such as limited exposure to ultraviolet light, living in dry climatic conditions, and consuming a diet high in sugars and polyunsaturated fatty acids (O'Regan et al., 2009; Flohr & Mann., 2014).

Previous Treatment of Atopic Dermatitis

1. Methotrexate (MTX)

Methotrexate (MTX) is an immunosuppressant commonly used in psoriasis. MTX is administered orally, intravenously, and subcutaneously. Randomized trials using MTX and Azathioprine showed a good outcome on severe ADs and a decrease of mean SCORAD in week 12. However, MTX often causes liver toxicity. MTX is also teratogenic, therefore women of child bearing potential must use effective contraception during therapy (Wollenberg et al., 2019).

2. Mycophenolate Mofetil (MMF)

Mycophenolate Mofetil (MMF) is an immunosuppressant drug commonly used in treatment of systemic lupus erythematosus and prevention of transplant rejection. According to several case reports and uncontrolled clinical trials, MMF is considered effective in AD treatment. However, MMF has some side effects including gastrointestinal problems (nausea and diarrhea; only at the start of treatment), leukopenia, and thrombocytopenia. MMF should also be discontinued 6 weeks before starting pregnancy (Wollenberg et al., 2019).

Vitamin D: Mechanism of Action in AD Treatment

Antimicrobial peptides (AMPs), filaggrin, and involucrin also enhance epidermal barrier health (Mutgi & Ko., 2012). Vitamin D supports immune system and decreases local and systemic inflammation by modulating cytokine production, inhibiting T-helper cell (Th-1 and Th-17) proliferation, and decreasing IL-2, IFN- γ , and IL-4 secretion (Di Filippo et al., 2015). AD is a condition where skin barrier function is deficient and cathelicidin levels are altered. An altered cytokine microenvironment suppresses AMPs expression, specifically Th2 cytokines (IL-4 and IL-13) (Di Filippo et al., 2015). Vitamin D promotes toll-like receptor and antimicrobial peptides (cathelicidin, B defensin), improves external tolerability to pathogens by inducing LL-37, and reduces cytokine release, inflammation, and angiogenesis (Vestita et al., 2015). Vitamin D also suppresses pro-inflammatory cytokines (IL-12, IFN- γ), inhibits IgE release, and stimulates IL-4, IL-5, IL-10 production in order to inhibit dendritic cell activity and mast cell release (Kim et al., 2016; Hattangdi-Haridas et al., 2019). However, vitamin D supplementation in infants during breast-feeding is not recommended due to an increase risk of allergen penetration through the skin (Kim et al., 2016; Vestita et al., 2015).

The effect of vitamin D supplementation on AD still has pros and cons as seen in Table 1. Most studies show a decrease in the SCORAD index. Even research conducted by Bothou et al. showed quite significant results, namely a decrease in the SCORAD index from 70 to 10 using oral calcitriol and cholecalciferol. However, the other 2 articles showed no significant results. This can be influenced by various factors, such as dose, age, and geographic location. However, vitamin D supplementation in AD treatment differs according to each country and geographical regions. SCORAD Index in AD patients receiving vitamin D supplementation decrease significantly in Iran and Mexico but increase significantly in Italy. According to WHO, there is no significant difference in SCORAD Index in America (Park et al., 2023). Meanwhile, research on NC/Nga mice using topical calcitriol for 4 days showed a significant reduction in dermatitis and TEWL scores (1 nmol topical compared to 0.1 nmol); increased epidermal thickness (0.1 nmol topical); decreased epidermal thickness (1 nmol topical). This supports the beneficial effects of vitamin D (Umehara et al., 2023).

Vitamin D Status in Atopic Dermatitis Patients

AD patients generally has lower vitamin D serum levels and a decrease in SCORAD index (Ghanem et al., 2017; Raj et al., 2022; Sanchez-Armendariz et al., 2018; Hata et al., 2014). Serum vitamin D levels in AD patients are influenced by various factors, namely age, severity, and race. In several studies in Table 2, it can be seen that serum vitamin D levels increase with age, decrease with increasing AD severity, and are higher in whites than blacks. Vitamin D supplementation can help increase serum vitamin D levels as shown in Table 3. However, According to Endocrine Society Clinical Practice guideline, vitamin D supplementation will increase the risk of persistent AD especially after long treatment periods as shown in a cross-sectional study in AD children after four years of therapy. Therefore, it is necessary for clinicians to be concerned (Hata et al., 2014)

Vitamin D Supplementation for Babies Below 1 Year Old

Drug administration, especially vitamin D supplementation in babies is noted based on body weight to reach maximum effect. Vitamin D supplementation with a daily dose of 1000 IU for 2 months has shown a decrease in SCORAD index with an average of 12 in babies below 1 year old. In addition, there is a percentage shrinkage from 59.2% to 14.8% in babies with moderate AD (Aldaghi et al., 2022).

Early Vitamin D Supplementation in AD Prevention

Allergic diseases, including atopic dermatitis are common in newborn babies with vitamin D deficiency, therefore early supplementation may be necessary. However, according to an RCT conducted by Rosendahl et al., there are no shown differences in the application of high dose vitamin D to babies aged 2 weeks to 24 months old neither with daily dose of 400 IU or 2000 IU for 12 months (Rosendahl et al., 2019).

Topical Vitamin D Application in Atopic Dermatitis

Currently, there are no clear studies nor consensus discussing about topical vitamin D application in AD treatment. However, a case report of a 36-year-old man with AD reported a positive effect when a low dose of calcitriol cream (0.6 ug/g) was applied twice daily for 10 days to his upper and lower eyelid. Therefore, it could be concluded that low dose of topical calcitriol application restores a normal cytokine balance resulting in the improvement of skin lesions (Mirzakhani et al., 2015).

CONCLUSION

Several trials using vitamin D to relieve AD symptoms have shown satisfactory results. These beneficial effects may be due to the induction of endogenous AMPs in AD skin via oral vitamin D supplementation. Differences in research results regarding vitamin D supplementation for DA can be influenced by various factors such as age, dose, preparation, country and geographical area. Therefore, it is recommended to conduct further research on the effectiveness of vitamin D, especially in the treatment of AD for further clinical implementation.

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