

# Correlation between Serum 25-Hydroxyvitamin D Levels with Keloid Severity

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## Abstract

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**BACKGROUND:** Keloids are dermal fibroproliferative tumours characterised by excessive deposition of extra cellular matrix components. The active form of vitamin D is known to inhibit the proliferation of keloid fibroblasts by inhibiting extracellular matrix production induced by transforming growth factor  $\beta$  (TGF- $\beta$ ) and increasing matrix metalloproteinase (MMP) activity. Vitamin D derivatives are thought to be an early preventive treatment strategy for keloid.

**AIM:** To determine the correlation between serum 25-hydroxyvitamin D level with keloid severity.

**METHODS:** This is a cross-sectional analytic study involving 32 keloid patients. Keloid patients were diagnosed by history and clinical examinations. Then an assessment of the severity was conducted using the Vancouver Scar Scale (VSS). We conducted blood sampling and measurement of serum 25-hydroxyvitamin D level to the patients. This study has been approved by the Health Research Ethics Commission of the Faculty of Medicine, Universitas Sumatera Utara, H. Adam Malik General Hospital Medan.

**RESULTS:** There is negative correlation between serum 25-hydroxyvitamin D level with severity in keloid patients ( $p = 0.0001$ ;  $r = -0.737$ ). There is no significant correlation between serum 25-hydroxyvitamin D level with gender ( $p = 0.271$ ), age ( $p = 0.201$ ;  $r = -0.232$ ), duration of keloid ( $p = 0.505$ ;  $r = -0.122$ ) and family history ( $p = 0.262$ ).

**CONCLUSION:** Lower level of plasma 25-hydroxyvitamin D, the severity of keloid became an increasingly heavy. There is no significant difference between serum 25-hydroxyvitamin D level with gender, age, duration of keloid and family history in keloid patients.

## Introduction

Keloid is dense fibrous tumours that develop from abnormal responses to skin injuries restoration. Keloid is a pathologic scar that extends beyond the boundary of the wound, benign and has no potential for malignancy [1], [2]. Keloid is dermal fibroproliferative tumours characterised by excessive deposition of extracellular matrix components [2].

The 25-hydroxyvitamin D level which is the main form of vitamin D in the circulation and this molecule is a measure for assessing vitamin D status in the body [3]. It is known that vitamin D has a

beneficial role in slowing the progression of tissue fibrosis [4], [5], [6]. The active form of vitamin D is known to inhibit the proliferation of keloid fibroblasts by inhibiting extracellular matrix production induced by TGF- $\beta$  and increasing MMP activity and acting as an anti-inflammatory mediator [7].

Vancouver Scar Scale is one of the most widely used scarring scoring systems in clinical research. This scale assesses four variables: vascularisation, pigmentation, consistency, and height/thickness [8], [9]. It is known that each of this variable is relevant to untreated keloid scar [9].

## Methods

This study was conducted from January 2018 to September 2018. This study was a cross-sectional analytical study involving 32 keloid patients who had been diagnosed with keloid by history and clinical examination at the Universitas Sumatera Utara, Medan, Indonesia, with an age of 16-40 years. Every subject who had signed informed consent was included in this study. Exclusion criteria were pregnancy, hormonal disorders including thyroid and parathyroid disease; kidney and liver disease, systemic diseases including cardiovascular disease, diabetes mellitus, and tuberculosis and malignancy; autoimmune diseases including psoriasis, systemic lupus erythematosus, and scleroderma; long-term history of anti-seizure medication, antibiotic and antiviral drugs such as phenobarbital, phenytoin, carbamazepine, rifampicin, and antiretroviral; there is a history of conventional treatment for keloids such as triamcinolone acetonide injection, topical corticosteroids, cryosurgery, radiation, laser, occlusive dressings, compression therapy and interferon in the past two months; and consuming any vitamin D supplementation in the past 1 month. This study has been approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara. In all study subjects, we assessed the severity of keloid using VSS and blood samples were taken for measurement of serum 25-hydroxyvitamin D level.

The results were analysed statistically by the Spearman correlation test. This test was used to investigate the relationship between the level of serum 25-hydroxyvitamin D with keloid severity.

## Results

Most of the subjects involved in this study were women, aged 21-25 years, suffered from keloid for 1-5 years, had no family history of keloid, and moderate keloid severity (Table 1).

**Table 1: Subjects and characteristic**

Variable	n	%
Gender		
Male	8	25.0
Female	24	75.0
Age		
16-20 years	6	18.8
21-25 years	13	40.6
26-30 years	2	6.3
31-35 years	3	9.4
36-40 years	8	25.0
Duration of disease		
1-5 years	23	71.9
6-10 years	4	12.5
11-15 years	1	3.1
16-20 years	4	12.5
Family history		
Father	1	3.1
Mother	2	6.3
Sibling	9	28.1
None	20	62.5
Severity		
Mild	2	6.3
Moderate	16	50.0
Severe	14	43.8

Statistically, there was a negative correlation between serum 25-hydroxyvitamin D level, and keloid severity ( $p = 0.0001$ ,  $r = -0.737$ ), the lowest level of serum 25-hydroxyvitamin D in this study subject was in severe-degree (VSS 10-14) is  $12.34 \pm 2.61$  ng/mL (Table 2).

**Table 2: Serum 25-hydroxyvitamin D level based on the severity**

Severity	Serum 25-hydroxyvitamin D level (ng/mL)				
	n	Mean	SD	Min	Max
Mild	2	26.95	0.78	26.40	27.50
Moderate	16	20.98	5.19	6.90	27.40
Severe	14	12.34	2.61	6.60	16.60

In Table 3, there was no significant relationship between serum 25-hydroxyvitamin D level with gender ( $p = 0.271$ ), age ( $p = 0.201$ ;  $r = -0.232$ ), duration ( $p = 0.505$ ;  $r = -0.122$ ), and family history ( $p = 0.262$ ).

**Table 3: Relationship between serum 25-hydroxyvitamin D level with gender**

	Serum 25-hydroxyvitamin D level (ng/dL)			
	n	Mean	SD	p
Gender				
Male	8	19.73	4.73	0.271
Female	24	16.85	6.70	
Family history				
Present	12	19.22	6.83	0.262
None	20	16.60	5.95	

## Discussion

The active form of vitamin D is known to inhibit the proliferation of keloid fibroblasts by inhibiting extracellular matrix production induced by transforming TGF- $\beta$  and increasing MMP activity [7].

In this study, there was a negative correlation between serum 25-hydroxyvitamin D level with keloid severity. The negative correlation indicates that the lower the serum 25-hydroxyvitamin D level, the more severe the degree of the keloid. The results of this study are by the research conducted by Medikawati et al., which found a negative correlation between plasma 25-hydroxyvitamin D level and the severity in keloid subjects ( $r = -0.584$ ;  $p < 0.001$ ) [10]. Study on the correlation of serum 25-hydroxyvitamin D level in keloid is still scarce, but in the study by Zhang et al., found the presence of VDR in keloid fibroblasts culture and incubation of keloid fibroblasts with 1.25-dihydroxy vitamin D suppresses TGF- $\beta$ 1 which induces type I collagen, fibronectin, and  $\alpha$ -SMA expression [11]. Also, several studies have shown that the Nuclear Transcription Factor-kB (NF-kB) signalling pathway is activated in keloid fibroblasts, whereas it is known that vitamin D has a role in regulating inflammation through inhibition of NF-kB. This contributes to the idea that vitamin D can inhibit the inflammatory process as occurs in keloid [12].

There was no significant relationship between serum 25-hydroxyvitamin D level and the gender of keloid patients in this study. The authors have not found a study discussing the relationship between serum 25-hydroxyvitamin D level with gender in keloid patients, but in a study by Yu et al., it was found that gene polymorphisms from vitamin D receptors affected the level of serum 1.25-hydroxyvitamin D and on stratification analysis based on gender found that this tendency only exists in the female subject but not in the male subject [4].

In this study, there was no significant relationship between serum 25-hydroxyvitamin D level and the age of keloid patients. According to Hagenau et al., study of the global serum 25-hydroxyvitamin D status in the general population, it was found that the lowest serum 25-hydroxyvitamin D level was at an age group of  $\leq 15$ , and the highest was at the age group of 66-75 years, but there was no significant relationship between the level 25-hydroxyvitamin D with age [13].

In this study, there was no significant relationship between the level of serum 25-hydroxyvitamin D and the duration of the keloid. It is known that there is a role for vitamin D in the pathogenesis of keloid, but the authors have not found literature discussing the relationship between the level of serum 25-hydroxyvitamin D and the duration of the keloid. To determine whether there is a role for vitamin D in the course of the duration of the disease requires further research.

This study also found no relationship between the level of serum 25-hydroxyvitamin D with a family history. In a study by Lu et al., which analysed the role of family history of keloid, the highest keloid severity was observed in subjects with a positive family history, and the risk for the occurrence of keloid in the first-degree relative was 72.45%. These results indicate that genetic factors play an important role in the occurrence of the keloid [14].

In conclusion, the lower level of serum 25-hydroxyvitamin D, the greater the severity of keloid, there was no correlation between serum 25-hydroxyvitamin D level with gender, age, duration, and family history of the keloid. Further studies are needed to determine the benefits of vitamin D derivatives administration to keloid patients, as a basis for consideration of additional therapy in the management of keloid in health services.

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