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Association of Vitamin D Deficiency and Diabetic Foot Ulcer Patients in Dr Mohammad Hoesin General Hospital Palembang

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ABSTRACT

Vitamin D plays a role in the healing process of diabetic foot ulcers (DFU); it can improve the immune system, regulate inflammation function, and regulate growth factors in diabetes mellitus (DM). The immunomodulatory effects of vitamin D include reduced production of IL-2, IL-6, and TNF-alpha and increased production of IL-10. It also increases the activity of antimicrobial peptides (AMP) such as cathelicidin, and it promotes the differentiation of monocytes into macrophages, phagocytosis, and the production of lysosomal enzymes. Furthermore, vitamin D stimulates growth factors including vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF-β). In this study, the incidence of DM and DFU in DM patients at RSUP Dr. Mohammad Hoesin Palembang will be compared to serum vitamin D levels. This research uses quantitative methods with an analytical observational design. The Mean vitamin D serum level was 11,727 ng/mL, and there was a significant association between serum vitamin D deficiency and DFU (p-value; 0.036 < 0.05). There was a significant association between serum vitamin D deficiency and DFU occurrence (p-value; 0.036 < 0.05) in Mohammad Hoesin General Hospital Palembang. Based on the results of this study, we proposed that patients with diabetic foot ulcers should have their serum vitamin D levels checked, and that vitamin D should be given to them as part of their therapy.

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Introduction

One chronic consequence of diabetes mellitus (DM) is diabetic foot ulcers (DFU). The prevalence rate of DFU in the DM population is quite high, about 4-15% and (Harrisa et al., 2020; Ji et al., 2021; Yunir et al., 2022). The immune system and growth factors, which are crucial to the healing of wounds, perform less well in people with diabetes. In hyperglycemic conditions, proinflammatory mediators increase, leading to chronic inflammation and delayed wound healing time in DM patients (Cimmino et al., 2013). As an inflammatory marker, fibrinogen promotes the expression of some protease enzymes such as matrix metalloproteinases-9 (MMP-9) (Giatsidis et al., 2018).

DFU patients had higher blood sedimentation rate (ESR) and C-reactive protein (CRP) levels. Elevation of CRP and ESR in DFU can be used as indicators of wound severity (Muller et al., 2008). The higher the CRP or ESR of DFU patients, the worse the wound. Defense systems are unable to create an initial response to damage as a result of decreased immune function, growth factor, and inflammatory system activity. Formation of granulation tissue will be delayed in DFU (Lobmann et al., 2002).

MMP-9 plays a role in the degradation of the extracellular matrix in the wound-healing process. TIMP-1 is an inhibitor of several protease enzymes including MMP-9. High levels of MMP-9 and low TIMP-1 are predictors of obstacles to DFU healing in DM patients (Caley et al., 2015; López-López et al., 2014; Shin et al., 2019). Based on research conducted by Lopez et al. (2014), vitamin D3 could regulate MMP gene expression from keratinocyte cells in DFU patients (Ross et al., 2011).

In addition to controlling calcium metabolism to preserve bone health, vitamin D can help diabetic foot ulcers (DFU) heal more quickly because it strengthens the immune system, controls inflammatory cytokines, and modifies the activity of growth factors, proteolytic enzymes like MMPs, and their inhibitors in diabetic mellitus (DM) (Dai et al., 2019; Ghezel et al., 2019; Kamble & Swarnkar, 2019; Kinesya et al., 2023; Ross et al., 2011; Yammine et al., 2020).

By boosting the action of antimicrobial peptides (AMP) like cathelicidin, stimulating monocyte differentiation into macrophages, enhancing phagocytosis function, and elevating lysosomal enzyme synthesis, vitamin D modulates the immune system. Vitamin D also affects the action of the inflammation system for several interleukins and growth factors by reducing the production of IL-2, IL-6, and TNF-α and increasing the production of IL-10. TGF-β and VEGF are two examples of growth factors that are activated by vitamin D (Kamble & Swarnkar, 2019).

Numerous MMP genes that are generated by keratinocyte cells are influenced by vitamin D. Furthermore, increased blood vitamin D levels have been demonstrated in recent research to upregulate MMP-1 expression, which is considered a trustworthy marker of DFU wound healing [8, 10].

Sunlight's ultraviolet B rays cause the skin to spontaneously create the prohormone vitamin D. The activation of vitamin D's effect in the skin is attributed to vitamin D receptors (VDR) in the skin. The relationship between vitamin D and VDR affects the control of basal cell keratinocyte growth, which acts as a physical barrier. Vitamin D also helps to regulate cell differentiation in the skin, which in turn helps to synthesise keratin, involucrin, transglutaminase, loricrin, and filaggrin (Tiwari et al., 2014).

By affecting the function of the Matrix Metalloproteinase (MMPs) enzymes and the activity of the Tissue Inhibitor Matrix Metalloproteinase (TIMP), vitamin D also plays a part in the proteolysis of the extracellular matrix (ECM), which is generated during the remodeling phase of DFU wound healing. In DM patients, there are high glucose levels in blood serum; this condition increases macrophage infiltration, increasing TNF-α in the wound. Increased levels of TNF-α cause more expression of MMP produced by keratinocyte cells and delay wound healing in DFU patients, as in invitro research conducted by Huang et al. (2019), Elevated glucose levels trigger M-1 macrophage polarization, which hinders keratinocyte migration through TNF-α. This is a crucial mechanism that postpones the healing of diabetic wounds. For DFU among other disorders, vitamin D supplementation treatment is an option (Dadaei et al., 2015; Holick et al., 2011).

A level of vitamin D less than 50 nmol/mL (<20 ng/mL) is considered a deficiency of vitamin D. Serum Vitamin D level more than 50 nmol/L (20 ng/mL) is recommended. In healthy

people, daily requirement for vitamin D is 15 mcg (600 IU) (Masood et al., 2015; Rastogi et al., 2022). The Endocrine Society states that people need a daily vitamin D supplement of at least 37.5 to 50 mcg (1,500–2,000 IU) in order to maintain blood 25(OH)D levels above 75 nmol/L (30 ng/mL). High-dose vitamin D is more effective in promoting wound healing in DFU (Marcinowska-Suchowierska et al., 2018; Rastogi et al., 2022).

Based on other studies, it has also been proven that low levels of Vitamin D3 have a close relationship with the occurrence of LKD due to prolonged inflammation and infection processes 28–30. Studies such as the Randomized Double-blinded Clinical Trial by Halschou-Jensen et al. in Denmark in 2021 and the study by Razzaghi et al. in Iran in 2017 have demonstrated that administering additional high-dose vitamin D3 therapy to patients with LKD improves the wound healing process more than administering low doses.

Further research is required to determine the relationship between serum vitamin D levels and the incidence of diabetes mellitus and DFU, as there is still a dearth of information in Indonesia, particularly in South Sumatra, regarding vitamin D levels and the degree of DFU and the high risk of disability due to DFU.

Research Methods

This study used quantitative methods with an analytical observational design to determine the relationship between serum vitamin D levels in DM patients with DFU. The research was conducted at the Mohammad Hoesin Palembang General Hospital (RSMH) from January to September 2023. The study population included all patients at RSMH who underwent blood sampling to examine serum vitamin D levels. Retrieving, inputting, and collecting data were carried out using medical record data stored in e-Medical Records (EMR). The data collection period that satisfied the inclusion and exclusion criteria was used for data collection. Data recorded included the subject's identity, serum vitamin D levels, current blood sugar values, and whether the patient had diabetes mellitus with diabetic foot ulcers (DFU) or not.

Before analyzing research data, determine the data type to be processed based on each research variable. In each study, the data obtained were converted into ordinal form before bivariate analysis. All calculations of the results of this research were done using SPSS software. This research was conducted with approval from the Dr. Mohammad Hoesin General Hospital Health Research Ethics Committee No. DP.04.03/ D.XVIII.6.11/ ETIK/ 99/ 2023.

Results and Discussion

Result

The connection between blood vitamin D levels and DFU patients at Mohammad Hoesin General Hospital Palembang was investigated using a retrospective analytical observational design from January to September 2023. 658 patients satisfied the inclusion criteria.

Table 1 Patient Demographic Characteristics and Health Status

Variable	n	%
Gender		
Man	166	25.2
Woman	492	74.8
Age		
≥ 60 Years	302	45.9
50 – 59 Years	275	41.8
≤ 49 Years	81	12.3

Vitamin D levels		
Deficiency	555	84.3
Insufficiency	84	12.8
Sufficient	19	2.9
Diabetes Mellitus Status		
DM + DFU	30	4.6
DM	111	16.9
Non-DM	517	78.6

In this study, 658 samples of patients were treated at RSUP Dr. Mohammad Hoesin Palembang. 166 (25.2%) samples were male and 492 (74.8%) were female. The highest age group of the sample was in the group aged more than 60 years with 302 (45.9%) samples. In this study, there were 555 (84.3%) samples who had Vitamin D deficiency, there were 111 (16.9%) samples suffering from DM, and there were 30 (4.6%) samples with DFU (Table 1).

Table 2 Serum Vitamin D Levels of Patients at RSMH (ng/mL) (n=658)

	Mean	**Min**	**Max**
DM + DFU	11.727	5.5	23.3
DM	24.736	4.9	156
Non-DM	22.849	5.1	151.3
All Patients	22.660	4.9	156

DM= Diabetes Mellitus, DFU= Diabetic Foot Ulcer

The average vitamin D level across all patients in this research is 22,66 ng/mL; in the DM group, it is 24,736 ng/mL; and in patients with DFU (30), the average blood vitamin D level is around 11,727 ng/mL (Table 2).

Table 3 Association Between Serum Vitamin D Concentration and Diabetes Mellitus Patients in Mohammad Hoesin Hospital Palembang (n=658)

Variable	**Deficiency**		**Insufficiency**		**Sufficient**		**Total**		**P-Value**
	N	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
DM + DFU	30	100%	0	0%	0	0%	30	100%	
DM	90	81.1%	14	12.6%	7	6.3%	111	100%	0,026
Non-DM	435	84.1%	70	13.5%	12	2.3%	517	100%	
Total	555	84,3%	84	12,8%	19	2,9%	658	100%	

DM= Diabetes Mellitus, DFU= Diabetic Foot Ulcer

The association between each hospital patient's vitamin D level and the Chi-Square test was examined. The study demonstrated a strong connection (p-value of 0.026) between the occurrence of diabetes mellitus (DM) in patients at Mohammad Hoesin General Hospital in Palembang and serum vitamin D deficiency (Table 3).

Table 4 Association Between Serum Vitamin D Concentration and DFU Patients in Mohammad Hoesin Hospital Palembang (n=120)

Variable	Deficiency		Insufficiency		Sufficient		Total		P-Value
	n	%	n	%	n	%	n	%	
DM + DFU	30	100%	0	0%	0	0%	30	100%	0,036
DM	90	81.1%	14	12.6%	7	6.3%	111	100%	
Total	120	85,1%	14	0,9%	7	0,5%	141	100%	

DM= Diabetes Mellitus, DFU= Diabetic Foot Ulcer

The chi-square test was used to look at the connection between vitamin D levels and diabetes mellitus with DFU. The Chi-Square test produced a p-value of 0.036 <0.05, indicating a possible correlation between the frequency of DFU patients in RSMH and the blood vitamin D level (Table 4).

Discussion

In this study, we analyzed 658 samples. The samples were divided into two groups DM and Non-DM. The samples consisted of 492 (74.8%) females and 166 (25.2%) males; in this study, we found females more than males. The largest sample age in the age group is over 60 years, with a total of 302 (45.9%) samples. A complication of DM is more frequently found in elderly patients because in the elderly group, there is more atherosclerosis of the vessels, especially in the lower extremity, and the immune system's capacity is declining, along with the body's resistance to infection and the inflammatory response.

From all of the 658 samples in this study, there were 517 (78.6%) samples without DM, 111 (16.9%) samples with DM, and 30 (4.6%) samples DM with DFU. Out of all the samples, we discovered that 555 (84.3%) had inadequate levels of vitamin D, 84 (12.8%) had inadequate levels, and 19 (2.9%) had appropriate levels. Many samples had vitamin D deficiency, both from patients. Diabetes Mellitus patients and patients who do not suffer from Diabetes Mellitus. It is well recognized that type 2 diabetic mellitus (T2DM) and vitamin D insufficiency have combined to become a contemporary epidemic (Vijay et al., 2023). A growing amount of evidence suggests that vitamin D deficiency may contribute to the onset and consequences of diabetes. Numerous studies have shown that a drop in 25(OH)D (25-hydroxy vitamin D) levels is linked to a forty percent higher risk of developing diabetes, while an increase in 25(OH)D concentration is linked to a twenty-four percent lower risk of developing diabetes (Bleizgys, 2021).

In this study, all DM patients with DFU (30; 4.6%) have vitamin D deficiency, with an average serum level of vitamin D 11.727 ng/mL. Samples from DM without DFU group have an average serum vitamin D level of 24.736 ng/mL. The average value of serum vitamin D levels in patients who do not suffer from diabetes mellitus is 22.849 ng/mL

We used the Pearson chi-square test to examine the relationship between blood vitamin D levels and the prevalence of DM. A p-value of 0.026 indicated a significant relationship between vitamin D levels and the occurrence of diabetes mellitus. According to research by Arafat et al. (2020), vitamin D deficiency has been associated to poor control and outcomes in T2DM patients, and it is commonly observed in DFU patients. Furthermore, vitamin D has been shown by Mousa et al. (2018) to lessen persistent low-grade inflammation in people with type 2 diabetes (Arafat et al., 2020).

The relationship between blood vitamin D levels and DFU's Diabetes Mellitus status was examined using the chi-square test. With a p-value of 0.036 (<0.05), the findings indicated a

significant relationship between blood vitamin D levels and DM with DFU. Serum vitamin D levels and DFU with infection have been linked in several studies. For instance, vitamin D administration has been shown in the research by Karonova et al. (2020) to improve clinical symptoms and decrease indicators of inflammation in individuals with type 2 diabetes.

Vitamin D plays a role in immune system regulation as well as in the generation of genes that code for two antimicrobial peptides (AMP) that fight infections and keep the right balance of skin flora: cathelicidin and β-defensin (Benson et al., 2023).

Vitamin D is associated with the control of infections and immune responses because it is a critical regulator of the innate immune response to the threat of bacterial infection. This has been stated in a number of papers. Decreased immune ability against microbial infections and excessive inflammatory response are the causes of delayed wound healing in DFU patients (Furtado et al., 2020). In DFU patients, there is a decrease in levels of Antimicrobial Peptides (AMP) such as cathelicidin (LL-37), an increase in inflammatory cytokines, and excessive biofilm formation (Wang et al., 2022).

According to Irma Gonzalez-Curiel et al., patients with DFU showed reduced antimicrobial peptides (AMP) levels in the lesion region, which may have impeded the healing process of their wounds. It showed the potential for vitamin D as supplementation therapy in treating DFU (Afonso et al., 2021; Gonzalez-Curiel et al., 2014; Mendoza-Marí et al., 2022; Miranda et al., 2023).

Several other studies found that patients with DM and DFU tended to have low serum vitamin D levels (Mozaffari-Khosravi et al., 2016; Wang et al., 2022). Thus, it is postulated that in individuals with diabetes mellitus and DFU, persistent inflammation and infections that are hard to cure are linked to vitamin D insufficiency (Lin et al., 2023; Y. Tang et al., 2023). The use of vitamin D can be considered as an additional therapy for DFU to reduce infection (Macido, 2018; W. Tang et al., 2022).

According to Dai et al. (2019), there is a strong correlation between severe vitamin D deficiency and a high incidence of diabetic foot ulcers, as well as a large drop in vitamin D levels in diabetic foot ulcers. According to Zubair et al. (2013), low levels of 25(OH)D are correlated with the ulcer's grade and have a major influence in the etiology of foot ulcers. According to Tiwari et al. (2014), patients with diabetes who also had ulcer infection had substantially lower 25(OH)D levels.

Conclusion

The average vitamin D level in 658 samples was 11.727 ng/mL. Of them, 492 (74.8%) were female, 302 (45.9%) were over 60, 555 (84.3%) had vitamin D insufficiency, 120 (85.1%) had DM, and sample DM had DFU 30 (100%). Every patient in the study had significant associations between their serum vitamin D levels and diabetes mellitus (p-value of $0.026 < 0.05$) and between their serum vitamin D levels and DFU (p-value of $0.036 < 0.05$). This suggests that individuals with Diabetes Mellitus, both those with and those without DFU, have low blood levels of Vitamin D.

Our research led us to conclude that, in order to effectively treat individuals with diabetic foot ulcers, vitamin D must be given and blood vitamin D levels must be monitored.

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