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The Relationship between Vitamin D Deficiency and Interleukins 8 and 10 in Diabetes Mellitus

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ABSTRACT
The aim of the present study is identification the relationship between vitamin D deficiency in the diabetic patient and interleukin 8 and 10 .The type of study was cross section which carried out from 12th of August 2019 to 25th of February 2020 in Salah al-Din government. The patients suffered from diabetes mellitus was (64.5%) presented with diabetic foot ulcer 70 (35.5%) were including 41 male and 29 female, blood sample was drawn and send to the lab. We found the high significant ratio in decrease blood serum concentration (p≤0.01) of vitamin D in patients with diabetic foot and in persons with diabetes mellitus compared with the control group. In addition to that we found high significant level in the elevated of blood serum concentration of interleukin 8 for patients with diabetes and diabetic foot ulcer compared with the control group (healthy individuals), while there was high significant decrease in blood serum concentration (p≤0.01) of interleukin 10 in patients with diabetic foot and in persons with diabetes mellitus compared with the control group.

Keywords: Diabetic foot ulcer, diabetes mellitus, vitamin D, IL-8 and IL-10.

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INTRODUCTION
Diabetes mellitus is common endocrine disease as a result of heterogeneous metabolic disorders, causes hyperglycemia due to deficiency in secretion and/or insulin action (Risk Factor and Outcomes.2019). It includes two main types: type 1, is resulting from destruction of insulin-producing pancreatic β-cells; while type 2, results from the peripheral resistance of insulin hormone (Nazik.2019). The prevalence of diabetes has been increasing in epidemic proportions, with long-term complications (Pu, Danlan, et al.2019). DM have many complication, one of these complication is diabetic foot ulcer (DFU) has described as infection, ulceration and/or destruction of deep tissues associated with neurological abnormalities and various degrees of peripheral vascular disease (Pu, et al.2019; Zhang X et al.2018), its commonly caused by repetitive stress in patients with peripheral neuropathy (Bus SA et al.2016), or initial injury (trauma) that is not detected by the patient (AlaviA et al.2014), together with a peripheral vascular disease, plus contributes to the development of foot ulcers (Boulton.2013). Vitamin D is steroid hormone fat-soluble (Prasad P et al.2016; Maurya, et al.2020). Its synthetizing mainly made on the skin with the effect of ultraviolet light (Gustavo Cediel et al.2018) and activated by two hydroxylation reactions in the liver and kidneys (Ozkan GO.2019). Hypovitaminosis D, will affect to the brain, heart, muscle, immune system, and bones, thus, leads to autoimmune diseases, infections, and neurological disorders (Sheetu Wadhwa1,,et al.2018; Yagüe,et al.2020), linked to the onset of diabetes by Vitamin D receptor (VDR) found on β-cell (Berridge MJ.2017 ; Sergeev, I.N..2016). Low vitamin D causes block insulin secretion (Lips P et al.2017), via autoimmune destruction β-cell lead to T1DM (Alam, et al.2016; Wimalawansa, S.J.2016), or changes in tissue response to insulin causes T2DM (Berridge MJ.2017). Cytokines is regulatory proteins for development and function of immune (Lorenzo, Joseph.2020), that exert important effects with regard to various inflammatory diseases, therefore used as biomarkers to indicate or monitor disease or its progress (Kany, Shinwan, et al. 2019). Inflammatory cytokine production is one of the mechanisms action of vitamin D in insulin resistance (Matyjaszek-Matuszek B, et al.2015). Interleukin-8 (IL-8) is a pro- inflammatory chemokine, play a significant role in the pathogenesis of type 2 diabetes (T2D) (Cimini, F. A., et al.2017). IL-10 is anti-inflammatory cytokine and suppress the activation and function of inflammatory leukocytes, specifically macrophages (van Herk, et al.2016; Lu L, et al.2017).

Material and Methods
A cross sectional study was carried out from 12th of August 2019 to 25th of February 2020 in Salah al-Din Governorate. Five ml of blood sample were collected from the vein by venipuncture in tube without having any anticoagulant. Serum were immediately separated by centrifugation and it was divided into two parts, one stored in Eppendorf tubes at -80°C for ELISA investigation, and another for measurement level of fasting blood glucose (FBG). Concentrations of serum IL-8 and IL-10 level were determined by quantitative sandwich enzyme-linked immune-sorbent assay (ELISA) kit as per manufacturer's protocol.

Result and Discussion
The total number of patients with DM were 198 of clinical samples were collected from the general surgery wards, the internal resuscitation wards, and the internal consultation at General Hospitals in Salah al-Din Governorate. Out of 198 patients with DM were 70 (64.5 %) case suffered from DFU, while 128 (35.5 %) case were presented with DM only. They were compared with 80(100%) cases healthy individuals (control group) as in (Table 1).

Table 1: Distribution of patients (DM, D.F.U) and healthy people.

Diseases	Patient		Control	
	NO.	**%**	**NO.**	**%**
Diabetic mellitus	128	64.5 %	0	0
Diabetic foot ulcer	70	35.5 %	0	0
Total	198	71 %	80	100%

***X^2 = 50.086 *P≤ 0.01 *significant**

1. **Levels of Vitamin D in patients with diabetes mellitus, diabetic foot ulcer and the control group.**

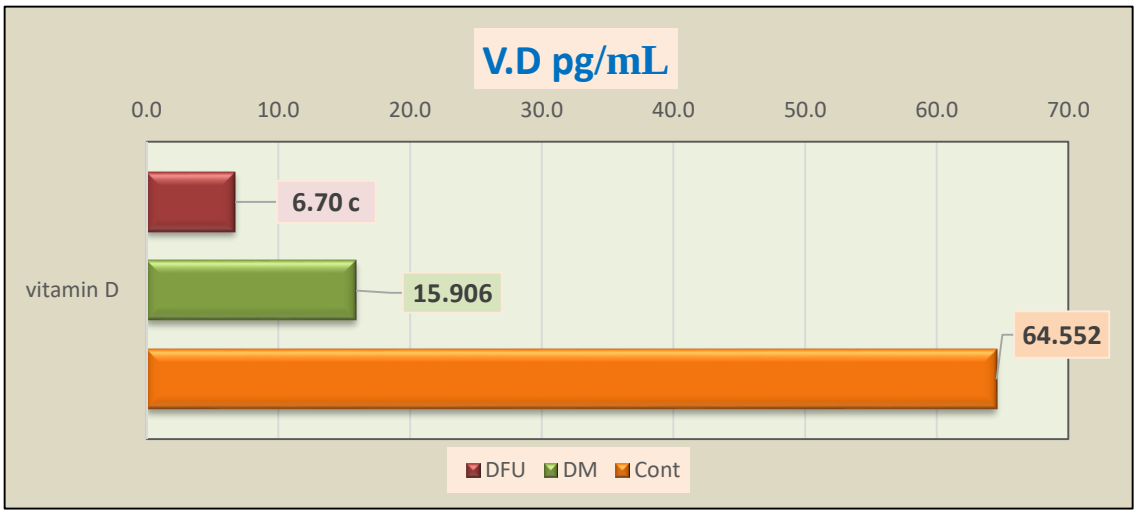


Figure 1: Levels of vitamin D in patients with DFU, DM and the control group.
***F. ratio=236.829 * P≤ 0.01 * Highly Significant (HS)**

The prevalence of this study shown in (figure 1), the mean of vitamin D level (6.70 pg. /ml) was occurred in patients with DFU who were infected with bacteria followed by patients with DM without ulcer infection (15.90 pg. /ml), while the highest mean was recorded in the control group (64.55 pg./ml). The relation was statistically highly significant. This study showed high significant decrease in Vitamin D levels in DFU and DM groups in comparison with control during the study period. These data Confirmed that diabetic foot ulcer patients were greater vitamin D deficient and harmed, because they had significant lower serum vitamin D levels than diabetic patients without these DFU complications.

These result agree with the other studies, such as Tajik, E. (2019); Onalan, E., & Gozel, N. (2018); Zubair et al. (2013); Negalur, V. (2014); Kamble, A., & Swarnkar, M. (2019); Razzaghi et al. (2017); Tiwari et al. (2013); Dash, D. P. (2016); Farhat Bashir, et al. (2016); Sarmad Saleem, et al. (2017); Macido, A. (2018); Oraby, M. I., et al.(2019); Mahmodnia, L et al. (2017); He R, et al.(2017); Nedim Ongun et al.(2017); Patel, D., & Pandya, H. (2020); Ahmadi, M. H., et al.(2018); and Dai, J., et al. (2019), that showed significantly reduced vitamin D levels in DM patients , severe with DFU , also some they reported that deficiency vitamin D an increased risk of DFU, and other complication T2DM. Also many studies such as Al-Rawaf, H. A., et al. (2019); and Tang, H., et al. (2018); He, S., et al.(2018); Hu, Z et al.(2019); and Park, S. K., et al. (2018), they were noticing, improve level Vitamin D could significantly improvement in DFU healing and less the complication T2DM by using Vitamin D because ability to modulates impaired pancreatic b-cell function, insulin resistance, and systemic inflammation (Berridge, M. J.2017; Wimalawansa, S.J. 2016).

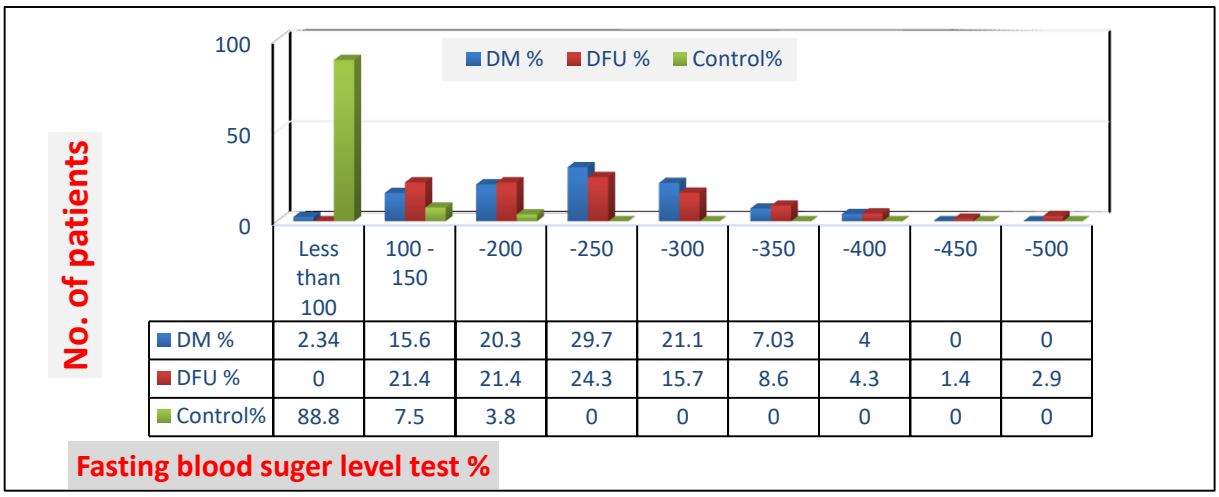
Vitamin D deficiency could be associated to the pathophysiology (Borges, J.M. 2014)), by existence 36 different tissues in the body able to interact with the physiology of vitamin D, like the kidneys, bones, intestines, the heart, liver, pancreatic beta cells, immunologic system cells pathophysiology (Negalur, V. 2014). Vitamin D deficiency contributes to both the initial insulin resistance and the subsequent onset of diabetes caused by β-cell death (Angellotti, E., & Pittas, A. G. 2017; Rak, K., & Bronkowska, M. et al.2018). Vitamin D deficiency has been linked to the onset of diabetic, by the role of Vitamin D in maintaining the normal release of insulin by the pancreatic beta cells (β-cells) and overcome this resistance by releasing more insulin, thus preventing hyperglycemia (Tajik, E. 2019; Leung PS 2016; Greenhagen, R. M., et al.2019). Poor glycemic control causes increased fatty acid and protein kinase, which reduces insulin signals due to a change in adipo-kinase secretion and phosphorylation of substance insulin receptor (Rafiq, S., et al. 2018; Onalan, E., & Gozel, N. 2018.), ditto glucose toxicity bring about Increased (calcium and AGEP) deposition thus, insulin resistance and ischemia and vascular nerve damage result of stimulation of cellular immunity, in addition (Krishna, S. M. 2019), deposition of immune complex in the blood vessels a result of the activation monocyte, release of pro-inflammatory cytokine and stimulation migration neutrophils (Jamwal S, et al.2018; Magrinelli F, et al. 2015).

Likewise Vitamin D deficiency with glucose toxicity, activation of oxidative stress and pro-inflammatory reactions, formation of non-enzymatic proteins, hypoxia and insulin resistance in type 2 diabetes, have a role in the formation and progression of diabetic peripheral neuropathy (Qu GB et al.2017; Pop-Busui R et al.2016;Alamdari A, et al. 2015). Moreover Vitamin D has play an important role in increasing the expression of insulin receptors, furthermore effect induces

antimicrobial peptides production in keratinocytes from diabetic foot ulcers hence, and healing was delayed (Angellotti, E., & Pittas, A. G. 2017). Furthermate, Vitamin D regulate the function of both innate and adoptive immune systems.

2. Blood Serum Glucose level for D.M, D.F.U and control.

From the frequency of the fasting blood glucose level testing in this study showed a significant increase in the concentration of blood glucose compared to the control group. The measurement blood level glucose for control group was ≥100 mg/dl in 71 (88.8%) persons which meant they do not have diabetes, while there was found DM 3(2.34) cases, but lack of case recorded for DFU patients in this level. Increase FBS level in DFU that exceeded the 450 mg/dl in some patients.



	Less than 100	100 - 150	-200	-250	-300	-350	-400	-450	-500
DM %	2.34	15.6	20.3	29.7	21.1	7.03	4	0	0
DFU %	0	21.4	21.4	24.3	15.7	8.6	4.3	1.4	2.9
Control%	88.8	7.5	3.8	0	0	0	0	0	0

Figure 2: Distribution of D.M, D.F.U and control according to the Sugar test.
***X^2 =236.851 * P ≤ 0.001 *Significant.**

The current study showed high significance increase in blood glucose concentration (P≤ 0.001) in DM and DFU as compared with control group. These results corresponding with the studies of Asfandiyarova, N. S. (2015) who saw that diabetes is made when the fasting blood glucose level is 126 mg/dL or higher on at least two tests. Also, Akhi, M.T., et al. (2015); Alshayban, D., & Joseph, R. (2020); Wallia, A. (2019); Swanson C, et al. (2017); Decarlo, K., & Azizi *et al*. (2016). Also Vatansever, Z., et al. (2020), who reported that the incidence of diabetic mellitus with high blood glucose level in diabetes drastically lowers insulin's effects on body by pancreas is unable to produce insulin, or by resistant tissue to the effects of insulin or doesn't produce enough insulin to maintain a normal glucose level. As a result, glucose tends to build up in your bloodstream (hyperglycemia) and may reach dangerously high levels if not treated properly. Insulin or other drugs are used to lower blood sugar levels (Schmitt, J., 2020). The presence of hyperglycemia and diabetes in elderly patients is associated with increased risk of complications, include damage to the eye, kidneys, nerves, heart, and the peripheral vascular system. and increased mortality compared with subjects with normoglycemia (Umpierrez, G. E., & Pasquel, F. J. 2017; Janež, A. et al.2020) result of accumulation cytotoxic, free radicals resulted from initial inflammation, followed by infiltration of activated macrophages and lymphocyte in the inflammatory DFU; this leads to a reduction in plasma insulin concentration, and leading chronic hyperglycemia state (Bolajoko, E. B.,et al. 2020).

3. Levels of IL-8 in patients with diabetic mellitus, diabetic foot ulcer and the control group.

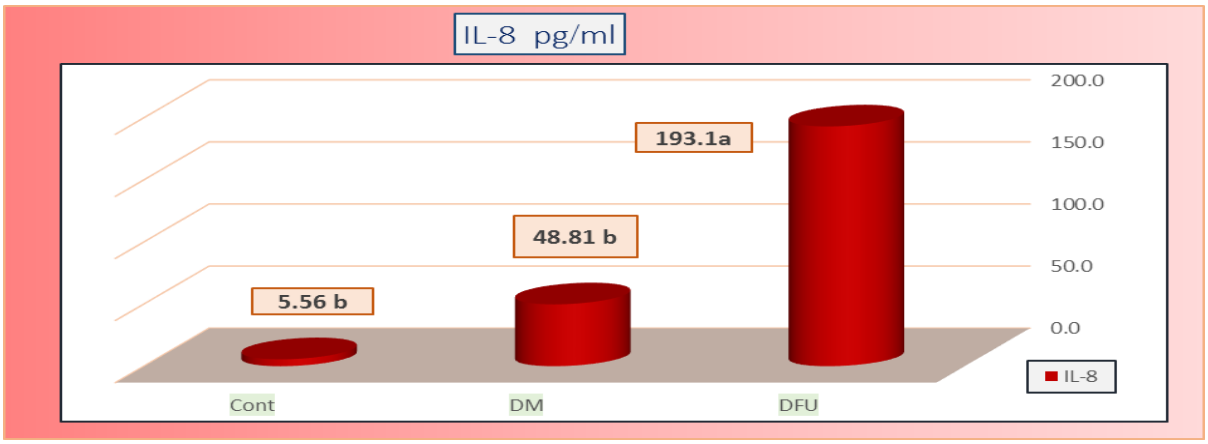


Figure 3: Levels of IL-8 in patients with DFU, DM and the control group.
F. ratio* = 32.424, P≤ 0.001 *Highly Significant (HS).

As shown in (figure 3), the highest mean of IL-8 level (193.1pg./ml) was occurred in patients with DFU who were infected with bacteria followed by patients with DM without ulcer infection (48.81pg/ml), while the lowest

mean was recorded in the control group (5.56pg/ml). The relation was statistically highly significant. This study showed significant increase in IL-8 levels in DFU and DM groups in comparison with control during the study period. These results agree with the study of Boroujeni, M., et al. (2016) who revealed significant increase of IL-8 in type 2 diabetic patients, Fadhil J. Al-Tu‟ma et al.(2011) found that IL-8 DM 38.69 (ng/ml). Peral, M et al. (2010) show greater percentage of IL-8 found in diabetics and patients with ulcers. While (Farrag, H. A et al. 2017) showed that IL-8 increase with gram negative bacteria such as *P. aeruginosa* and *K. pneumoniae.* Therefore, usefulness to measurement level IL-8, to early predictors of gram-negative bacteremia because, (IL-8) which known as crucial mediators in wound healing.

IL-8 effected by vitamin D because contain Vitamin D receptor on cell surface that effect on monocytes/macrophages and dendritic cells, so it could found on the pro-myocytes, therefore can suppress proliferation of pro-myelocytes and cause their differentiation to monocytes, too it inhibits monocyte production such as IL-8 (Ross, A., et al. 2013). This explains the high levels of IL-8 when vitamin D was low in diabetic foot patients, compared to diabetic patients and control group.

4. Levels of IL-10 in patients with diabetic mellitus, diabetic foot ulcer and the control group.

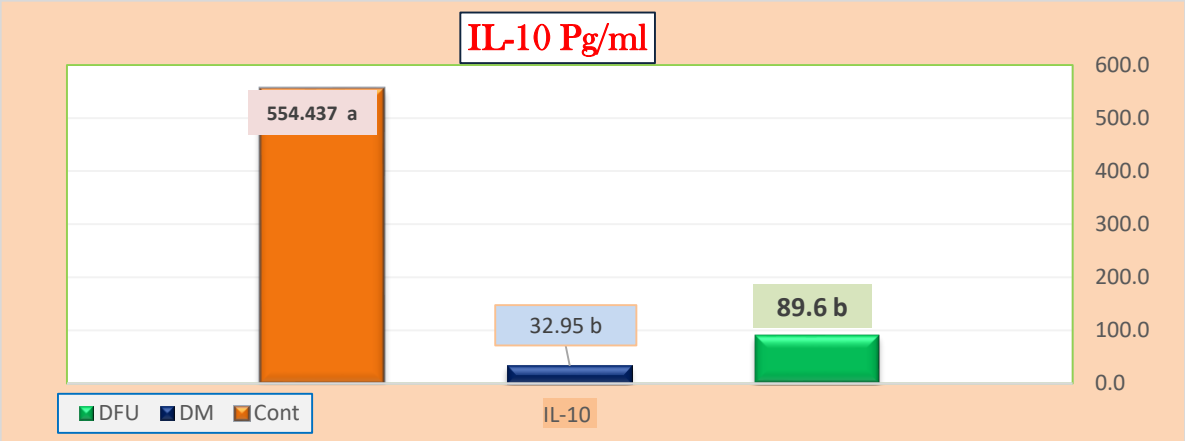


Figure 4: Levels of IL-10 in patients with DFU, DM and the control group.
F. ratio* = 71.458 * P≤ 0.001 * Highly Significant (HS).

As shown in (figure 4), the mean of IL-10 level (89.6 pg. /ml) was occurred in patients with DFU who were infected with bacteria followed by patients with DM without ulcer infection (32.958 pg. /ml), while the highest mean was recorded in the control group (554.436 pg./ml). The relation was statistically highly significant.

These results agree with the study of Shaker. N.B et al. (2019) showed that there was highly significant relation of IL-10 with bacteremia. Galkowska H et al. (2006) reported that Human diabetic foot ulcers have decreased expression of IL-10. There is relationship between hyperglycemia and immune dysfunction, including impairment in poly-morphonuclear, monocytic, white blood cell chemotaxis and phagocytosis, complement function, and cytokine dysregulation (Bode, B., et al. 2020). Chronic wounds in diabetes mainly show the persistent increase in the level of pro-inflammatory cytokine and the absence of the signals, which are responsible for signals in the damaged tissues (Gouin JP et al. 2011), lead to wound recovery delay (Tang Y et al..2013). DFU results in release of the pro-inflammatory cytokines which results in inflammation of tissues (Rachel M et al. 2018) because the prolonged expression of inflammatory cytokines leads the damage of tissues and delay repairing process of wounds.

Anti-inflammatory cytokines like IL-10 play an important role in the wound healing process by stimulate extracellular matrix and fibrinogen, collagen synthesis and activates M2 macrophages infiltration at the site of wound (Ma TY et al. 2004). High concentration of glucose at the wound site promotes microbial growth and leads to inflammatory signaling activation (Kaur P et al. 2018), also the effect insulin lead to increase release of IL-10 by decreasing pro-inflammatory cytokines release (Higashi Y et al 2010). During the study period showed that the level of IL-10 in DFU was higher than DM because some bacteria such as *P. aeruginosa* preferentially induces IL-10 and increasing IL-10 in diabetic wounds suggests an interesting in improvement of healing (Hessle C, et al. 2006 ;Lee JH, et al.2008 Declue, C. E.,et al.2015).

Conclusion

We can conclude the vitamin D-level decrease in DFU more than DM patients, plus vitamin D plays an important role in activating immune cells and enhancing their work in addition to regulating insulin secretion while reducing cell resistance to insulin. High significant level at (p≤0.01) in the number of people with DM and DFU for males compared to females. High significance in blood serum concentration (p≤0.01) in blood sugar among the patients with DFU and DM compared to the control group**.** High significant increase in blood serum concentration (p≤0.01) in interleukin-8 for persons with diabetes and diabetic foot complications with the control group (healthy individuals).

High significant decrease in blood serum concentration (p≤0.01) in interleukin 10 (IL-10) in persons with DM and DFU compared with the control group (healthy individuals).

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