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IL-24 AND IL-29 IN T2DM WITH AND WITHOUT DIABETIC FOOT ULCERS

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Abstract: Type 2 Diabetes Mellitus (T2DM) is a common chronic metabolic disease that spread worldwide. Uncontrolled T2DM cause many complications such as neurological diseases and lower limb amputations, in addition to other health problems. Insulin resistance and low-grade chronic inflammation in adipose tissue is a characteristic of people with obesity and diabetes. In fact, T2DM is inflammatory cytokines are involved in the pathophysiology of this disease. About 1.4 million Iraqis suffer from diabetes. In this study, some clinical characteristics and parameters level sixty patients with T2DM (32 male and 28 female) and thirty as controls were quantified. There are no significant differences between patients and controls in both age and BMI. There are expected significant increase in FBG, HbA1c and HOMA-IR in T2DM patients than healthy groups. There is a significant decline ($p = 0.003$) in serum IL-24 level in T2DM patients as compared with the controls. The low level of interleukin-24 in patients with T2DM has serious consequences. Despite the neuropathies in patients and the disease-causing nerve damage and non-healing of wounds, the decrease of this interleukin leads to may decrease in the patients' immunity. The skin acts as a barrier against harmful microbes on several levels: colonization, pH, mechanical/physical and immunological IL-24 significant decrease ($p < 0.001$) in patients with type 2 diabetes and those who suffer from diabetic foot (DF) ulcers in particular affects the healing of ulcers and poorly in wound healing. There is a significant decline ($p = 0.03$) in serum IL-29 level in T2DM patients as compared with controls. The decreased IL-29 levels in patients may be defect in immune system particularly patients with T2DM, where IL-29 is secreted from T-helper that affects keratinocytes and activated against viruses. In contrast, an IL-29 level decrease in patients with DF ulcers induce an inflammatory response.

Keywords: T2DM, Interleukins, Foot ulcers, overweight.

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Introduction

Type 2 Diabetes Mellitus (T2DM) is a common chronic metabolic disease that spread worldwide.[1] Diabetes Mellitus is a condition characterized by high blood glucose levels caused by the pancreas which does not produce enough insulin or because of insulin resistance when cells do not respond to insulin.[2,3] Islet cells generate and secrete insulin into the bloodstream in response to elevated blood glucose levels after eating. The binding of insulin and insulin receptors in cell membranes induces glucose transporter translocation to the cell membrane, allowing cells to absorb more glucose and lowering blood glucose levels. The pancreas' inability to produce enough insulin, or improper insulin action, causes hyperglycemia. This has been connected to long-term organ and tissue damage and failure.[2] In fact, the inflammatory cytokines are involved in the pathophysiology of this disease.[4] Neurological diseases and lower limb amputations are among the most common consequences of T2DM, in addition to kidney disease, blindness, heart attacks and strokes around the world.[5,6] About 1.4 million Iraqis suffer from diabetes. The prevalence of type 2 diabetes in Iraq ranged from 8.5% (IDF age-adjusted) to 13.9%.[7] The prevalence of diabetes in the world in 2019 is about 9.3 % and by 2030, the population will have risen to 10.2 (578) million, with 10.9 (700) million in 2045. In 2019, the prevalence of diabetes was predicted to be around 9% among women and 9.6% among men.[8] Uncontrolled T2DM cause many complication, therefore as the treatment of diabetes includes taking antibiotics and changing lifestyle for diabetics in terms of healthy nutrition and sports on a daily basis.[9] Given that T2DM is a metabolic syndrome linked to an increased risk of heart disease and stroke, and that more severe disease courses are linked to more late complications, it's possible that the presence of any diabetic foot ulcers

disease could be linked to a patient's history of cardiovascular disease and peripheral vascular disease.[10,11] Moreover, it is estimated that one out of every six diabetes patients would develop a plantar ulcer over their lifetime.[12] Long term of poorly controlled hyperglycemia lead to multiple dysfunctions, mainly vascular complications that affect small vessels (microvascular), large vessels (macrovascular), or both. Many interleukins are affected by various diseases, and one of these diseases is diabetes mellitus because of the complications that this disease causes from infections and inflammation. Interleukin-24 (IL-24) plays an important role in the inflammatory autoimmune disorder for example psoriasis, arthritis and other allergic skin conditions.[13] IL-24 a multi-directional cytokine that affects a number of cells such as immune cells and epithelial cells and acts on anti-bacterial response, anti-tumor actions, wound healing, tissue remodeling. Therefore, the effect of this cytokine might lead to further complication because its role varies depending on the cell, the target and the stage of the immune response.[14] Interleukin 29 (IL-29), a new member of the type II cytokine family, was discovered in 2003. The presence of interleukin-29 in the skin reduces the incidence of infections. A difference has been observed in the protective capabilities of skin affected in some skin diseases. The skin that contains interleukin-29 is less prone to infection in comparison to that from patients where IL-29 is absent.[15]

Materials and Methods

Subjects

Patients. Sixty patients with T2DM (32 male and 28 female) were selected. A mean of their age was 53.18 ± 9 years. In the present study, only 10 patients suffering from diabetes food (DF) syndrome were investigated. The specimens were collected from Al-Sader medical city (Diabetes and

Endocrinology center) in Najaf governorate-Iraq for the period November 2021 till February 2022. All patients were diagnosed according to the WHO criteria,[16] where they had fasting plasma glucose levels≥ 7.0 mmol/L, and HbA1c > 6.5%. Patients were evaluated based on their medical histories to see if they had any systemic disorders, which might have an effect on the studied parameters, kidney diseases, liver diseases, heart diseases, thyroid disease, hypertension and positively CRP were excluded from the study.

Control group. Thirty apparently healthy subjects (12 males and 18 females) were classified as a control group. The ages were like investigated patients. The healthy groups remarked by negative CRP values.

Anthropometric values

Body mass index (BMI) was used to define obesity and calculated from the formula: BMI (kg/m^2) =Weight (kg) / $(Height)^2$ (m^2). In the present study we will use the WHO classification of underweight (BMI<18.5kg/m^2), normal weight (BMI=18.5-24.9kg/m^2), overweight (BMI25.0-30.0 kg/m^2) and obese (BMI>30.0kg/m^2) for adults.

Biochemical Investigations

Blood samples. A specimen of 5 mL of venous blood was drowning by using single-use needle plastic syringes from every patient or control. The samples were divided in to two tubes. Anticoagulant tubes have 2 mL from blood, and the remaining blood samples were transferred into clean tubes. Blood was left at room temperature for quarter of hour until clotting and centrifuged at 3000 rpm for ten minutes, thereafter the serum was separated and transported into new disposable plain tube (hemolysis samples were discarded) and stored in freeze (-20 °C) till analysis.

Experimental Apparatus.

Table1. Laboratory equipment's and apparatus.

Instruments	Company	Origin
Centrifuge	Hettich	Germany
Deep freezer	Hitachi	Japan
ELIA Microplate reader	BioTek	USA
Glass gel tube	Q.L.lab	China
Micropipette	Dragon	China
Refrigerator	Hitachi	Japan
Spectrophotometer	Spctra721	Taiwan
Water bath	Hettich	Germany

Chemicals.

Table 2. Chemicals and kits used in the study.

Type of Kits	Company/Country
Blood Glucose Kit	Spinreact/Spain
CRP	LTD/Britain
HbA1c Kit	KAMIYA BIOMEDICAL
IL-24 kit	BT LAB/ China
IL-29 kit	BT LAB/ China
Insulin Kit	BT LAB/ China
Triglyceride Kit	Spinreact/Spain

Statistical Analysis

The Kolmogorov-Smirnov test was used to examine the distribution types of the results group. A statistical distribution divided variable results into two types; nonparametric variables and normally distributed variables. The results were expressed for the variable normally distributed, like (mean ± standard deviation). The control and patient groups and subdivided groups were compared by use Pooled t-test in the measured parameters. The

distinction among groups is considered like different of statistically when $p < 0.05$. SPSS Statistics base 26 and IBM-USA performed was used for all statistical analysis. The data were analyzed using Excel Microsoft Office 2016.

Results and Discussion

Initial comparison of the Patients and Controls

Firstly, the demographic and clinical characteristics of T2DM patients and healthy controls were compared. All these variables, for both T2DM patient and controls, were illustrated in Table 3.

Table 3. the comparison between T2DM patients and controls.

Variables	Patients	controls	P- value
Age (year)	53.18±9.57	50.27±7.5	0.13
BMI (Kg/m^2)	28.83±4	28.9±5.2	0.929
FBG (mmol/L)	11.17±3.42	5.46±0.31	<0.001
HbA1c %	9.97±1.98	5.54±0.6	<0.001
Insulin pM	30.96±4.28	44.43±3.99	<0.001
HOMA-IR	2.5±0.83	1.78±0.19	<0.001

BMI: Body mass index, **FBG**: Fasting blood glucose, **HbA1c**: Glycated hemoglobin, **HOMA-IR**: Homeostasis Model Assessment-Insulin Resistance

There are no significant differences between patients and controls in both age and BMI. The age at which T2DM individuals develop the disease has an impact on their overall health. Increasing evidence suggests that T2DM causes a faster decrease of β-cell function than later-onset T2DM. Young-onset T2DM has also been linked to an increased risk of death and morbidity.[17] Patients with early-onset T2DM (defined as a diagnosis before the age of 40) are more likely to have vascular problems.[18] There is expected a significant increase in FBG, HbA1c and HOMA-insulin resistance in T2DM patients than healthy groups. While, there is a significant reduction in serum fasting insulin. High FBG adversely affects

lipid profile, adipocytokines and liver function that may have desirable effects on metabolic markers in the patients.[19] There is now increasing evidence that the adipose tissue produces free fatty acids that contribute to insulin resistance, as well as mediators (adipokines) that can influence insulin signaling pathways.[20] Identifying the molecular pathophysiological mechanisms of insulin resistance and T2DM is critical for the development of new and more effective drugs to properly treat our insulin resistance and T2DM patients.[21] The concept that released insulin first functions as a friend that contributes to -cell compensation before becoming a foe and contributing to -cell decompensation during the development of T2DM is a source of controversy.[22] Obesity is a low-grade chronic inflammatory syndrome characterized by systemic and peregrine increases in cytokines, chemokines, and adipokines.[23] The increase of macrophages in adipose tissues is linked to obesity. This adipose tissue inflammation plays a key role in the pathophysiology of various obesity-related diseases, including insulin resistance.[24]

Comparison of the Interlukine-24 levels

A graphical profile of the IL-24 levels in T2DM patients and the control groups is displayed in Figure 1.

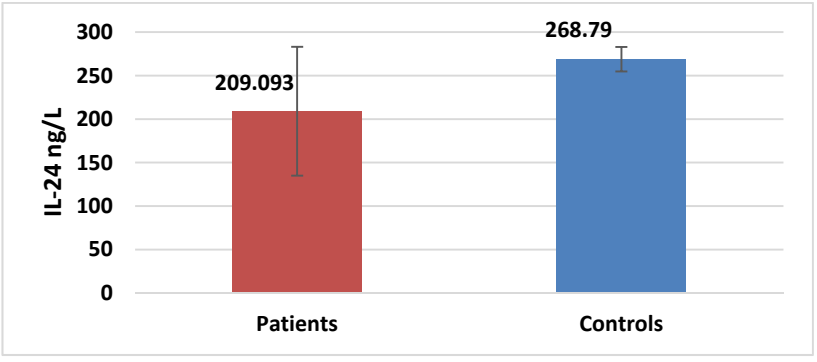

Figure 1. Serum IL-24 levels in T2DM patients and control groups.

There is a significant decline ($p = 0.003$) in serum IL-24 level in T2DM patients as compared with the controls. Insulin resistance and low-grade chronic inflammation in adipose tissue characterize obesity and diabetes.[25] The low level of interleukin-24 in patients with T2DM has serious consequences. Despite the neuropathies in patients and the disease-causing nerve damage and non-healing of wounds, the decrease of this interleukin leads to may decrease in the patients' immunity. IL-24 maintains tissue homeostasis by inducing innate defense systems during infection and inflammation in epithelial tissues. This role is accomplished by encouraging the production of antimicrobial peptides such as the S100 family proteins and the calprotectin subunits S100A8 and S100A9.[26] IL-24 enhances the recruitment and activation of leukocytes at the site of inflammation by increasing cytokine and chemokine production in epithelial cells.[27] IL-24 is a multifunctional cytokine that has effects on immune cells, epithelial cells, and cancer cells, among others. Antibacterial responses, tissue remodeling, wound healing, and anti-tumor actions are only a few of the functions of IL-24. Because its role varies depending on the cellular source, target, and phase of the immune response, the effects of IL-24 appear to be highly complex. Overall, might think of IL-24 as an immunoregulatory cytokine and antitumor molecule.[14] Other studies were found plasma IL-24 levels were increased in the pathogenesis of spondylarthritis.[28]

There is a significant decrease ($p < 0.001$) in serum IL-24 level in diabetes foot ulcers as compared with T2DM patients.

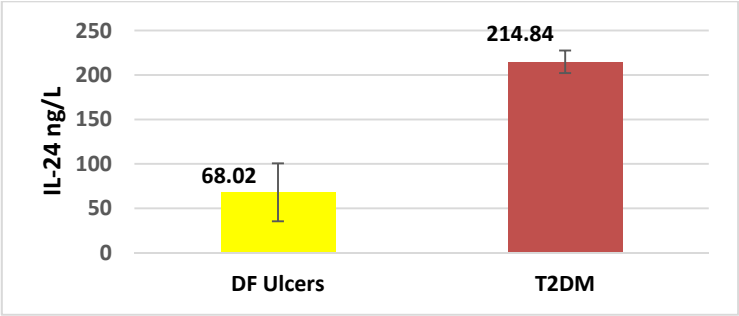

Figure 2. Serum IL-24 levels in DF patients and T2DM.

The skin serves as the primary wall (protective) between the organism and its surroundings. In truth, the skin protects the body organism against UV radiation, physical trauma, viruses, allergens, toxins, and electrolyte loss with excessive water, among other things.[29] The skin acts as a barrier against harmful microbes on several levels: mechanical/physical, colonization, pH, and immunological.[30] The significant decrease of IL-24 in patients with type 2 diabetes and those who suffer from diabetic foot (DF) ulcers in particular affects the healing of ulcers and poorly in wound healing. Recently, both in vitro and in vivo, IL-24 has been shown to modulate wound healing responses.[31] DF ulcers are a prevalent consequence of diabetes mellitus, and there are currently no completely effective therapeutic alternatives.[32] DF ulcers, pressure ulcers, and venous ulcers are all chronic lesions result from significant delays in wound healing processes.[33] DF ulcers are becoming more common as the global incidence of diabetes mellitus rises, resulting in significant morbidity and mortality and a large unmet medical need.[34] A neuropathic DF ulcer has a five-year death rate of roughly 50%, which is comparable to colon cancer.[35]

IL-24 influence on wound healing has been found to be contradictory in several studies. IL-24 has varied functions in wound healing based on the type of cell and process stage. Further research will be required to determine why these inconsistencies exist.[36] Another study was

conducted on mice, as a diabetic wound healing model. It was emphasized that IL-20, IL-22, and IL-24 can speed up epithelial closure, therefore, the findings show that cytokines from the IL-20 family, notably IL-24, IL-22, and, IL-20 may be beneficial to patients with DF ulcers.[34]

Comparison of the Interleukine-29 levels

Analogously, a graphical plot of the IL-29 concentration in T2DM patients and the control groups is displayed in Figure 3. There is a slightly decrease ($p < 0.03$) in serum IL-29 level in than T2DM patients than healthy group.

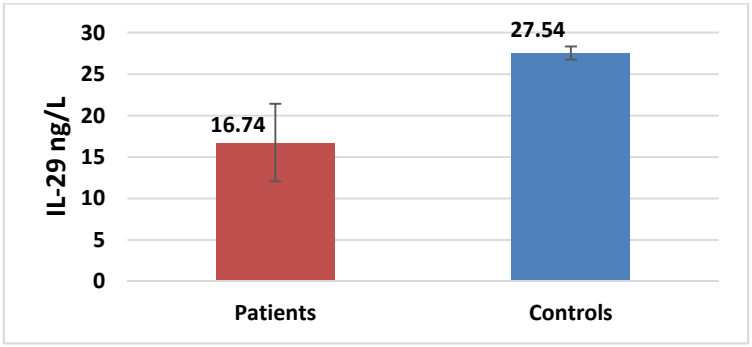

Figure 3. Serum IL-29 levels in T2DM patients and controls.

IL-29 has many immune regulatory functions and has a functional role in immune cells. In various immune cells, IL-29 regulates the production of inflammatory cytokines and chemokines.[37] The decreased IL-29 in patients may be defect in immune system particularly patients with T2DM, which suffering from weak immunity. In patients with metabolic diseases such as DM, IL-29 could be a promising new target for treating obesity and insulin resistance.[38] In 2020, Lin et al. discovered that patients with overweight and obesity had significantly higher serum levels of IL-29 than healthy people, in this investigation the patients and controls have no

significant in BMI. Functional role of IL-29 in immune cells. IL-29 regulates the generation of inflammatory cytokines, and chemokines in different immune cells.[37] IL-29 may modulate the immune and response and protect people from viral infection by producing an antiviral state. Furthermore, these cytokines are attractive proteins for studying the cell-mediated immune response because they can change the cytokine profile of T cells.[39, 40] Both obese and overweight people possess an increased IL-29 level due to a superior mass of adipose tissue.[25] Other researchers have discovered low-grade chronic inflammation in the adipose tissue of obese people.[41] IL-29 is increased in virally infected cells and plays an important role in host defense against microorganisms. In tumors such as lung cancer, esophageal carcinomas, and colorectal cancer, IL-29 has an anticancer effect [15]. In rheumatoid arthritis and allergic asthma, IL-29 works as an immunological modulator in addition to its antiviral and anticancer properties.[42, 43]

There is a slightly decrease (p= 0.04) in serum IL-29 level in diabetes foot ulcers than T2DM patients (Figure 4).

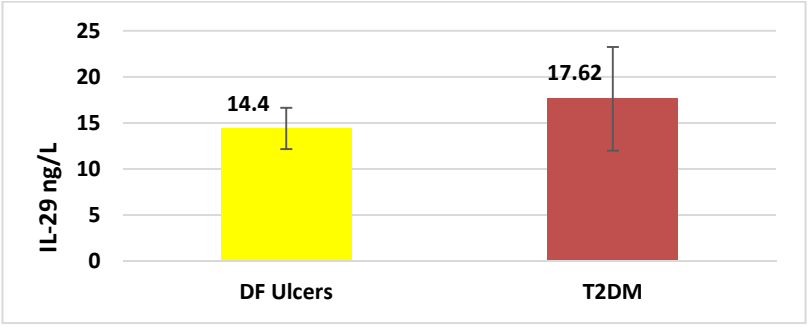

Figure 4. Serum IL-29 levels in DF ulcers and T2DM patients.

Dendritic cells and to a lesser extent keratinocytes appear to release IL-29 in the skin in response to viral and bacterial infection. IL-29 secreted

from T-helper that effected on keratinocytes and activated agist viruses.[44] Decrease IL-29 in patients with DF ulcers inflammation increases and the matter becomes more complicated. In diabetes individuals, long-term exposure to excessive sugar reduced keratinocyte migration and proliferation, resulting in insufficient wound re-epithelialization, which further hampered wound healing.[12] The protective abilities of the skin in psoriasis and atopic dermatitis patients were shown to be different. Both skin conditions weaken the skin, but psoriatic lesions with IL-29 are less susceptible to viral infection than atopic dermatitis lesions without IL-29.[45] Crosstalk between macrophages and adipocytes is regulated by IL-29,[38] where Platelets, keratinocytes, endothelial cells, and macrophages were among the cell types that contributed to wound healing. IL-29, a novel member of the IL-10- interferon cytokine family, is an important regulator of some of wound healing and pathogens.[30] IL-29 inhibits the development of keratinocytes. Simultaneously, this cytokine enhances the preparedness to transmit viral antigens to immune cells by increasing cellular manufacture of proteins that directly inhibit virus replication. In non-infected skin, IL-29 increases keratinocytes' ability to react to viral and microbial products, hence upregulating their inflammatory potential and innate immunity [46]. Other mediators secreted during dendritic cells maturation can work in concert with IL-29 (eg, IL-20).[47] Kerstin et al 2010 concluded, IL-29 may play a significant role in the elimination of tumors and the clearance of viral and microbial infections in the skin.[48]

Conclusions

In conclusion, this study reveals that both interleukins (24 and 29) levels are decreased in patients with type 2 diabetes. Most of the

interleukins are affected by the weight mass factor. Therefore, there is no significant change between the T2DM and healthy group. The decrease in these interleukins causes many immune complications because of their important role in regulating cytokines and chemokines. IL-24 activates the leukocytes in the inflammatory area to secrete chemokines and cytokines. Moreover, IL-29 may modulate the immune and response and protect people from viral infection by producing an antiviral effect. The decrease in interleukins (24 and 29) in patients with foot ulcers may expose the patient to serious complications, whereas a decline of IL-24 and 29 level might cause poor wound healing progress. Because IL-29 activates keratinocytes its lower level in T2DM patients could impair the defense mechanism against bacteria and viruses.

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