# Determination a role of some immunological markers for diabetic patients in Diyala province

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## Abstract
Background;Diabetes Mellitus (DM) is a metabolic disease, involving inappropriately elevated blood glucose levels . DM has two categories, including type 1 and type 2 diabetes. Aim of study; the present study aimed to investigation the role of interleukins IL-15, IL-33, and IL-36 in pathogenesis of diabetes mellitus. Materials and methods; 90 blood samples were obtained from the consultative clinic - Baquba Teaching Hospital - Diyala Health Department, within period from beginning of October 2021 to end of January 2022. The samples were classified into groups as follows: 60 blood samples from DM patients , where the number of males was 28 and the number of females 32 within age range 21-70 years. Addionally, 30 samples of apparently healthy people of both sexes were adopted and used as a control group, where the number of males was 15 and the number of females 15 within the age range 21-70 years and they did not suffer from any chronic or acute illness at the time of sample collection. Results; Results our study revealed significant different among age groups, where the 41-50 and 51-60 years scored highest percentage (25.60% and 28.90%) than 21-30 and 31-40 that scored least percentage (11.10% and 15.60%). Additionally results of current study mentioned the decreased median levels of IL-15, IL-33, and IL-36 parameters in patients (145.97, 222.89 , and 306.72) than healthy (149.50 , 249.33 , and 548.94) respectively with significant different for IL-36 ($p<0.05$) and non-significant ($p>0.05$) for IL-15 and IL-33. Addionally, present study revealed no significant differences between interleukins and age, gender, and disorders. Finally, IL-33 scored highest sensitivity (41%) in screening diabetes. Conclusions; decreased levels of interleukins IL-15, IL-33, and IL-36 in patients with diabetes.
Keywords: Diabetes, IL-15, IL-36, IL-36.

## Introduction
Diabetes mellitus (DM) is a metabolic condition characterized by increased blood glucose levels. There are several types of diabetes mellitus include: Type 1 diabetes mellitus (T1DM), which present in childhood or teenagers [1], and Type 2 diabetes mellitus (T2DM) is thought to affect middle-aged and older individuals who have chronic hyperglycemia as a result of poor lifestyle and nutritional choices [2].
Prediabetes and type 2 diabetes are prevalent, affecting, respectively, roughly 34% and 13% of all US people in 2018 [3]. According to the most recent data, diabetes mellitus (DM) is still a serious worldwide health concern and is expected to increase significantly over the next few decades [4].
Recent study showed the IL-15 therapy has been shown to delay the onset of diabetes in mice, possibly due to the cytokine's stimulation of NK cells, indicating a protective role for this substance in type 1 diabetes [5]. Another study showed the plasma IL-15 in humans is markedly reduced in obesity and adversely correlated with fat mass [6].
The findings of the study demonstrate that IL-33 inhibits the progression of disease in prediabetic non-obese diabetes mice and identify IL-33/ST2 as a possible therapeutic target to avert type I diabetes [7]. Another study suggests that IL-33 and/or IL-33/ST2 dynamics and biological functions may contribute to total glycemia in people and may constitute a new target for the therapeutic effects of glucose-lowering treatments [8].
There are few reports on the role of IL-36 cytokines in type 2 diabetes, despite several studies demonstrating their effects on psoriasis, arthritis, and systemic lupus erythematosus [9]. The inflammatory cytokines IL-36 and IL-36 showed elevated expression in T2DM patients, while the anti-inflammatory cytokine IL-36Ra showed lower expression. Inflammation and blood lipid levels were inversely correlated with the levels of inflammatory cytokines. According to the findings, IL-36 cytokines may one day serve as a new T2DM diagnostic marker or therapeutic target [10].
The present study aimed to investigation the role of interleukins IL-15, IL-33, and IL-36 in pathogenesis of diabetes mellitus.

## Materials and Methods
### Samples collection
90 blood samples were obtained from the consultative clinic - Baquba Teaching Hospital - Diyala Health Department, within the period from the beginning of October 2021 to the end of January 2022. The samples were classified into groups as follows: 60 blood samples from diabetes mellitus and medically diagnosed by specialized doctors in the Baquba

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Teaching Hospital Consultation, where the number of males was 28 and the number of females 32 within age range 21-70 years. Addionally, 30 samples of apparently healthy people of both sexes were adopted and used as a control group, where the number of males was 15 and the number of females 15 within the age range 21-70 years and they did not suffer from any chronic or acute illness at the time of sample collection. 5 ml of blood samples were collected by drawing venous using plastic medical syringes and left 10 minutes at room temperature for coagulation, then the serums are separated by centrifugation for 5 minutes and at a rate of 3000 cycles | min. and the serum is divided into equal quantities 250 microliters in small tubes that are stored At a temperature of ˚-20 C ˚ until use, then it was divided into a group of Eppendorf tubes.

Measuring the level of interleukins (IL-15, IL-33, IL-36) in sera of patients with diabetes.

The interleukins (IL-15, IL-33, IL-36) were quantitatively determined using the Sandwich ELISA test for (60) people with renal failure and (30) healthy people, according to the instructions contained in the examination kit made by CUSABIO company.

### Statistical analysis

The interleukins IL-15, IL-33, and IL-36 levels parameters were first tested for normality (Kolmogorov-Smirnov and Shapiro-Wilk test). Parameters that fit both tests (no significant difference) were given as mean ± standard deviation (SD), and the parameters that did not fit the normality tests (significant difference) were given as median and range, and significant difference between median was assessed by Mann-Whitney (for comparison between two groups). The sperman correlation was employed to understand the correlation between certain parameters. The statistical package SPSS version 25.0 and Graph pad prism version 6 were employed to carry out these analyses.

## Results and discussion

Results of our study show non-significant different ($p>0.05$) among patients according to gender and disorders. In contrast, our study revealed significant different among age groups, where the 41-50 and 51-60 years scored highest percentage (25.60% and 28.90%) respectively than 21-30 and 31-40 that scored lower percentage (11.10% and 15.60%) (Table 1).

Table 1. Demographic characters of patients.

| Count | | | Percent | P value |
|---|---|---|---|---|
| Gender | males | 43 | 47.80% | P >0.05 |
| | females | 47 | 52.20% | |
| Age groups (years) | 21-30 | 10 | 11.10% | p<0.001*** |
| | 31-40 | 14 | 15.60% | |
| | 41-50 | 23 | 25.60% | |
| | 51-60 | 26 | 28.90% | |
| | >60 | 17 | 18.90% | |
| Disorders | Eye | 15 | 25.00% | P >0.05 |
| | Renal | 27 | 45.00% | |
| | Foot DM | 18 | 30.00% | |

The current study indicates that gender has no appreciable influence on diabetes. The results of the study are consistent with those found, which show that DM increases as people age [11]. However, with time, both the effects of aging and the progression of the disease could become more pronounced, leading to early complications and even death in those with type 2 diabetes who were diagnosed at a younger age. To give an example, a person with type 2 diabetes who is diagnosed at age 30 has a lower absolute risk of complications than a person who is diagnosed at age 50, but by the time they both reach age 60, the person who was diagnosed earlier has a higher relative and absolute risk because of the effects of aging, which are exacerbated by the effects of having had diabetes for a longer period of time [12]. One in nine fatalities among adults between the ages of 20 and 79 is thought to be caused by diabetes. Diabetes and associated consequences must be prevented, especially in middle-income nations [13]. The present study showed the diabetes is increased with age progression due to impaired immune status, chronic diseases, and organ dysfunction. [14] demonstrate the presence of renal problems in DM patients, and these findings are consistent with our findings. End-stage renal disease is most frequently brought on by diabetic kidney disease (DKD) (ESRD). The current investigation found conditions like obesity, CKD, and retinal inflammation that are linked to diabetes, and these findings are consistent with previous findings [15].

Results of current study mentioned the decreased median levels of IL-15, IL-33, and IL-36 parameters in patients (145.97, 222.89, and 306.72) than healthy (149.50, 249.33 , and 548.94) respectively with

significant different for IL-36 ($p<0.05$) and non-significant ($p>0.05$) for IL-15 and IL-33 (table 2).\

**Table 2.** Comparative interleukins IL-15, IL-33, and IL-36 between study groups

| Groups | | IL15 | IL33 | IL36 |
|---|---|---|---|---|
| Patients | Median (range) | 145.97 (0.00-1141.67) | 222.89 (2.36-1813.72) | 306.72 (93.39-1978.15) |
| Controls | Median (range) | 149.50 (88.10-1199.00) | 249.33 (54.95-2407.34) | 548.94 (190.09-2257.89) |
| P value | | P >0.05 | P >0.05 | P<0.001*** |

The results of the our study show low level of IL-15 in DM patients than controls with non-significantly different , and these contrasted with result of [16] that revealed DM patients had higher levels of IL-15 than controls because of the IL-15 is increased with insulin resistance due to occurrence inflammation and decrease with insulin doses. These pro-inflammatory cytokines and insulin resistance may play a role in the etiology of autoimmune diabetes, as suggested by the significantly higher IL-15 concentrations found in newly diagnosed autoimmune diabetes patients and first-degree relatives [5]. The findings of the study suggested IL-15 as a viable therapeutic agent for managing diabetic wound healing because it increased dendritic epidermal T cells' (DETCs') production of Insulin-like growth factor-I (IGF-1) to promote diabetic wound repair [17]. According to GDM IL-15 expression was found to increase in the third trimester and decrease in the second trimester in both the placenta and amniotic fluid,and then increased in the third trimester [18]. This pattern of IL-15 expression in the placenta resembled that of numerous pro-inflammatory substances like IL-8, TNF, MCP-1, etc., which may help to maintain a healthy pregnancy [10].

High doses of IL-15 therapy cause metabolic changes that protect against high-fat diet-induced obesity and insulin resistance and increase insulin sensitivity and whole-body fatty acid oxidation [19].

Following eight weeks of resistance training, serum levels of IL-15 increased while those of insulin, glucose, and insulin resistance decreased, according to data analysis. According to the findings of a recent study, resistance training may reduce insulin resistance in elderly men with type 2 diabetes by raising the levels of IL-15 in the blood [16].

The result of current study show low levels of IL-33 in DM patients than controls with non-significant difference due to anti-inflammation effects of IL-33 in DM patients without overweight/obese. These result agreed with result of [20]. The ability of IL-33, a newly discovered cytokine, to control diverse immune responses and play a role in the pathogenesis of various diseases has garnered a lot of attention in recent years [21]. Although multiple earlier research using obese mouse models revealed that IL-33 could enhance glucose and lipid metabolism, reduce adiposity, and generate anti-inflammation effects in adipose tissue [20], There are no findings on the precise relationship between IL-33 levels in the blood and metabolic problems related to obesity in people. The findings of the study indicate that IL-33 is a possible therapeutic target for the prevention of type I diabetes since they demonstrate that it delays the onset of disease in prediabetic nonobese diabetic (NOD) mice [7]. In Chinese adults with metabolic diseases who were overweight or obese, circulating levels of IL-33 were noticeably higher. Increased IL-33 levels were strongly correlated with the metabolically unhealthy overweight/obese phenotype and numerous risk variables for the metabolic syndrome [22].

By controlling lipid metabolism, IL-33 may also prevent obesity and type 2 diabetes. Although the exact processes underlying these advantageous effects are still not entirely understood, it is now known that Treg, islet-resident group 2 innate lymphoid cells (ILC2s), and type 2 immune responses are involved. On the other hand, IL-33 seems to promote angiogenesis and endothelial inflammation, which are pertinent to metabolic syndrome and type 2 diabetes.

The results of the performed study show low levels of IL-36 in DM patients than controls with significant different due to presence IL-36 receptor antagonist that can be prevent binding IL-36R to IL-36 , and subsequently noticed decreases levels of IL-36 in DM patients. These result agreed with results [23]. Numerous researchers have become interested in the up-regulation of IL- IL-36 in many disorders in recent years. Inflammatory illnesses that affect the skin, joints, blood vessels, heart, and nerves are mostly regulated by these cytokines [23]. It has an anti-inflammatory impact because IL-36R antagonist, can prevent IL-36, IL-36, and IL-36 from binding to IL-36R. [9]. By interacting with cell-surface IL-36R, IL-36Ra can prevent the synthesis of IL-22 and IL-17. According to study findings, T2DM patients had lower levels of IL-36Ra. IL-36Ra may therefore have an antagonistic effect on T2DM patients' inflammatory response because it is an antagonist for IL-36, IL-37, and IL-38. Results of the study revealed a negative correlation between IL-36 and IL-36Ra, indicating that these two molecules may have opposing functions in T2DM [10]. Our results show there is non-significant difference between IL-15, IL-33 and IL-36, between patients gender ($P>0.05$) (table 3).

Table 3. Logistic regression analysis of interleukins IL-15, IL-33, and IL-36 in males versus females patients

| | | gender | | Median (range) | p value | Odd ratio Confidence intervals (95%) |
|---|---|---|---|---|---|---|
| | | Males | Females | | | |
| IL15 | > Median | 14 | 16 | 145.97 (0.00-1141.67) | p>0.05 | 1.00 (0.3625 to 2.758) |
| | <= Median | 14 | 16 | | | |
| IL33 | > Median | 14 | 16 | 222.89 (2.36-1813.72) | p>0.05 | 1.00 (0.3625 to 2.758) |
| | <= Median | 14 | 16 | | | |
| IL36 | > Median | 13 | 17 | 306.72 (93.39-1978.15) | p>0.05 | 0.76 (0.2766 to 2.114) |
| | <= Median | 15 | 15 | | | |

Innate and adaptive immune responses differ between males and females, as do their immunological reactions to self- and foreign antigens. It is possible that both genes and hormones are at play because some immunological sex differences are present throughout life while others become obvious only after puberty and before reproductive senescence. Additionally, early environmental exposures affect the immune system and the microbiota in a sex-dependent manner. Importantly, these sex-based immunological differences affect how susceptible people are to infectious infections, how they react to immunizations, and how frequently they develop autoimmune conditions and cancer [24].

Study findings the complement system exhibits significant sex and age-related variations. When researching complement-related disorders, these modifications should be taken into consideration.

The findings of the study suggested that cytokine levels may be influenced by sex. This is in line not just with sex variations in infection susceptibility, but also with the higher cardiovascular risk that men demonstrate when compared to women. Nevertheless, hormone levels can only partially account for this connection [25].

Our results show there is non-significant difference between IL-13, IL-33 and IL-36, among patients age groups (P>0.05) (table 4).

Table 4. Distribution of interleukins IL-15, IL-33, and IL-36 levels (> median and ≤ median) in patients according to age groups.

| | | Age groups (years) | | | | | Median (range) | P value |
|---|---|---|---|---|---|---|---|---|
| | | 21-30 | 31-40 | 41-50 | 51-60 | >60 | | |
| IL15 | > Median | 3 | 1 | 8 | 11 | 7 | 145.97 (0.00-1141.67) | P>0.05 |
| | <= Median | 3 | 4 | 7 | 8 | 8 | | |
| IL33 | > Median | 5 | 3 | 4 | 10 | 8 | 222.89 (2.36-1813.72) | P>0.05 |
| | <= Median | 1 | 2 | 11 | 9 | 7 | | |
| IL36 | > Median | 3 | 2 | 5 | 12 | 8 | 306.72 (93.39-1978.15) | P>0.05 |
| | <= Median | 3 | 3 | 10 | 7 | 7 | | |

The immune system is one of the major biological systems that ages, making it more susceptible to infectious diseases and less efficient in immunizing against them as a result of age-related changes in immunity. Additionally, one of the primary signs of aging—inflammaging—the rise in low-grade inflammation—is caused by the innate immune system [26]. The causes and effects of aging-related inflammation, the effects of senescence on immunity, age-related changes in immune function the effects of decreased immune function on infection and vaccination, and methods to counteract aging-related immunity are the five research challenges that need to be addressed. All of them are crucial now more than ever because aging is a significant risk factor for the emergence of serious consequences from infectious diseases as COVID-19, influenza, and bacterial pneumonia. [26]

Our results show there is non-significant difference between IL-15, IL-33 and IL-36, among patients disorders (P>0.05) (table 5).

Table 5. Distribution of interleukins IL-15, IL-33, and IL-36 levels (> median and ≤ median) in patients according to disorders.

| | | Disorders | | | Median (range) | P value |
|---|---|---|---|---|---|---|
| | | Eye | Renal | Foot DM | | |
| IL15 | > Median | 5 | 19 | 6 | 145.97 (0.00-1141.67) | p<0.05* |
| | <= Median | 10 | 8 | 12 | | |
| IL33 | > Median | 4 | 17 | 9 | 222.89 (2.36-1813.72) | p>0.05 |
| | <= Median | 11 | 10 | 9 | | |
| IL36 | > Median | 4 | 15 | 11 | 306.72 (93.39-1978.15) | p>0.05 |
| | <= Median | 11 | 12 | 7 | | |

The pathogenesis of proliferative diabetic retinopathy (PDR), which has elevated levels of IL-15, may be significantly influenced by these biomarkers, according to a prior study [27]. Several inflammatory diseases, such as rheumatoid arthritis, psoriasis, and autoimmune diabetes, express the proinflammatory cytokine IL-15, which encourages the activation of T-cells, neutrophils, and macrophages [27].

Procalcitonin, pentraxin-3, C-reactive protein (CRP), interleukins (ILs), and tumor necrosis factor- (TNF-), among others, are inflammatory biomarkers that have received widespread attention and use. However, a more thorough prediction of the risk and severity of DFU are required to take into account new biomarkers for therapeutic intervention effects [28].

These findings imply that IL-33 has a significant protective function by inhibiting Müller cell activation and guarding against inflammation-mediated damage to photoreceptors in stressful situations like retinal separation and diabetic retinopathy [29].

It is possible that IL-33 acts as a double-edged sword when tissue is injured; on the one hand, IL-33 is essential for tissue healing or the eradication of infection, but on the other hand, excessive production might harm tissues and organs. Determining the specific function of the IL-33/ST2 pathway in controlling the equilibrium between tissue inflammation and healing will require more research. The development of new therapeutic approaches for treating or preventing kidney disorders will be made easier with a better knowledge of the pathogenic role of IL-33 in renal diseases [30].

The findings of the study strongly imply that modifying the signal that is mediated by IL-33 may represent a possible therapeutic strategy for diabetic skin lesions [17].

Despite the eye being an immune-privileged organ under normal circumstances, data findings suggest IL-36, IL-37, and IL-38 might contribute to the immunologically driven pathogenesis of chronic primary angle closure glaucoma (CPACG) [31].

Results of current study revealed the IL-33 scored highest sensitivity (AUC= 0.40 and Sn=42%) in screening diabetes mellitus compared to IL-15 and IL-36 were scored least sensitivity (AUC= 0.40 and Sn=41% and AUC= 0.20 and Sn=21%) with significant different (P<0.05) . Based on specificity IL-36 scored highest specificity (73%) than IL-15 (41%) and IL-33 (42%) that scored least specificity with significant different (P<0.05) (table 6, figure 1).

Table 6. ROC curve, Sensitivity and Specificity of interleukins IL-15, IL-33, and IL-36.

| Prameters | Area | Std. Error | Sig. | Sensitivity | Specificity |
|---|---|---|---|---|---|
| IL15 | 0.406 | 0.068 | 0.148 | 41% | 43% |
| IL33 | 0.405 | 0.065 | 0.143 | 42% | 43% |
| IL36 | 0.207 | 0.05 | 0.001*** | 21% | 70% |

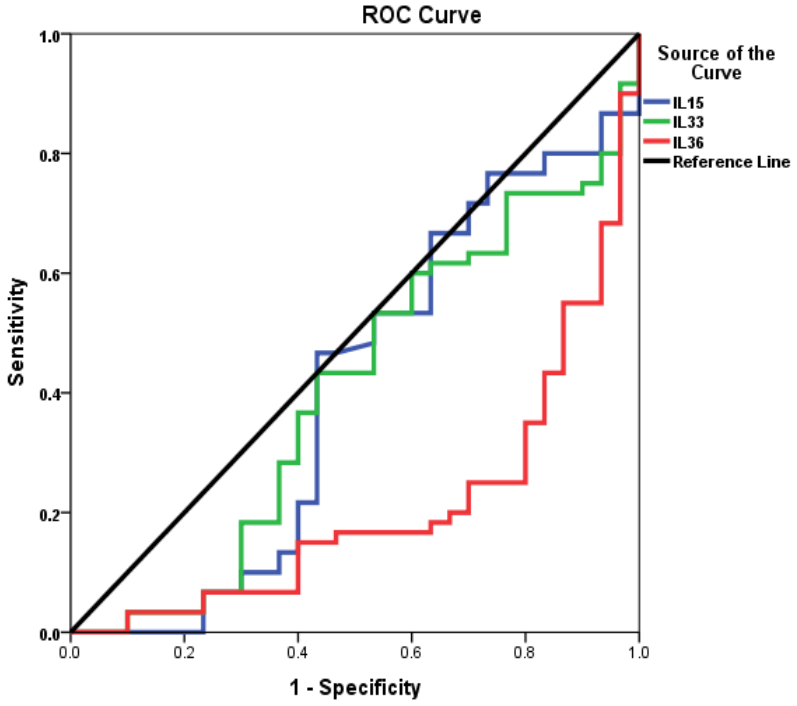


Fig 1. Receiver operating characteristic (ROC) curve of interleukins IL-15, IL-33, and IL-36

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Our results show significant correlation between IL-15 and IL-33 (r=0. 906** p<0.05), IL-15 and IL-36 (r=0. 937** p<0.05), IL-36 and IL-33 (r=0. 879** p<0.05). (Table 7).

Table 7. Correlation relationship among interleukins IL-15, IL-33, and IL-36

| Spearman rho correlation | | IL15 | IL33 | IL36 |
|---|---|---|---|---|
| IL15 | r | 1 | .906** | .937** |
| | p | | 0 | 0 |
| IL33 | r | .906** | 1 | .879** |
| | p | 0 | | 0 |
| IL36 | r | .937** | .879** | 1 |
| | p | 0 | 0 | |

Inflammatory cytokines have a crucial part in the pathophysiology of T2D, where inflammation has emerged as a key component. An inflammatory state (recently dubbed "metaflammation") is characterized by a persistent, low-grade inflammation that is triggered by metabolic and inflammatory cells in response to an excessive energetic nutrition load. Inflammatory cytokines are the key components of this state [6].

Recent research has shown some of the immune-mediated pathways that govern the onset and progression of T2D. Different anti-cytokine agents have been studied in experimental T2D models given the role of interleukin pathways in inflammation-related T2D, and clinical trials have been carried out or are in progress to determine the effects of these agents on systemic and islet inflammation, beta-cell function, insulin resistance, and overall glucose control [32].

## Conclusions

There is non-significant different among patients according to gender and disorders.

The diabetes is increase with age progression.

Decreases levels L-15, IL-33, and IL-36 in DM patients than controls .

There is non-significant different among gender, age groups, disorders DM patients according to IL-15, IL-33, IL-36.

There is a positive significant correlation among interleukins (IL-15, IL-33, IL-36).

## Recommendations

Investigation role of IL-6, IL-18, IL-38 in pathogenesis of diabetes.

Investigation role of immunoglobulins IgG and IgM in pathogenesis of diabetes.

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