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Research Article

Elevated levels of IL-1 and IL-12 in type 1 diabetic patients infected with Coxsackievirus

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Abstract

It is generally accepted that Coxsackievirus B (CVB) infections are a major factor in initiating or hastening the development of type 1 diabetes (T1D) and islet autoimmunity, especially in people with genetic predispositions. These viruses have the ability to directly destroy cells and release beta-cell antigens by infecting beta cells in the pancreas. Both the innate and adaptive immune systems are activated in response to this viral invasion, as seen by the activation of T lymphocytes, B cells, dendritic cells, and macrophages. Initially designed to eradicate the virus, the immune system may inadvertently attack the body's own insulin-producing cells, triggering or exacerbating autoimmune reactions that aid in the pathophysiology of type 1 diabetes and beta-cell loss. During the period from November 1, 2024, to February 1, 2025, blood samples were collected from 60 patients (40 males and 20 females) diagnosed with type 1 diabetes, as well as 30 healthy individuals who were visiting private laboratories in Al-Najaf Governorate. The diagnosis was confirmed through molecular detection using Real Time -qPCR to detect CVB infection. Positive results were seen in 20 (33.3%) of suspected patients in compared with 40 (66.7%) were negative. While all healthy control subjects 30 (100.0%) were have negative results of Real-time PCR, and the difference was significant, (P= 0.001). The effect of Coxsackievirus infection on the immune response was evaluated by analyzing the immunological parameters (IL-1, 12) in 60 individuals with type 1 diabetes. The purpose of this assessment was to ascertain whether the virus may be involved in initiating or intensifying inflammatory processes that lead to the death of beta cells. Gaining knowledge of the immunological processes connected to CVB infection could help explain how viral infections and autoimmune disorders, especially type 1 diabetes, are related. The comparison of Interleukin-1β (IL-1β) level between DM with CVB, DM without CVB and control groups has been carried out. Mean levels of IL-1β were 18.69 ± 4.3, 16.33 ± 2.31 and 11.01 ± 1.06, in DM with CVB, DM without CVB and control groups respectively; the mean levels were higher in both groups of patients in compared to healthy control and the difference was significant ($P < 0.05$). But the mean levels was non-significant difference between patients groups themselves (DM with CVB and DM without CVB) themselves ($P < 0.05$). The comparison of Interleukin-12 (IL-12) level between DM patients and control groups has been carried out. Mean levels of IL-12 were 26.89 ± 5.4, 21.77 ± 3.86 and 10.68 ± 2.26, in DM with CVB, DM without CVB and control groups respectively; the mean levels were higher in both groups of patients in compared to healthy control and the difference was significant ($P < 0.05$). But the mean levels was non-significant difference between patients groups themselves (DM with CVB and DM without CVB) themselves ($P < 0.05$). The current study recorded the week correlation between each of interleukin 1 levels and Type 1 diabetes patients with CVB (r= 0.61); and were acceptable correlation between each of IL-12 and Type 1 diabetes patients with CVB (r = 0.77).

1. Introduction

Coxsackievirus group B belongs to the family Picornaviridae and the genus enterovirus. Enteroviruses (EVs) are positive-sense, single-stranded RNA viruses, named for their gastrointestinal route of transmission. These viruses are categorized based on their pathogenesis in humans and laboratory animals into four groups: polioviruses, coxsackie A viruses (CA), coxsackie B viruses (CB), and echoviruses [1].

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Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by reduced insulin production and caused by a specific immune-mediated loss of insulin producing beta cells [2], certain viruses generate viral regulatory molecules to contribute to their pathogenesis and life cycle, including long non-coding RNAs (lncRNAs) and miRNAs. However, viruses exploit cellular components to force viral replication, escape immune responses, and steal host bioenergy [3]. Viral infections in humans are a growing public health concern and an important cause of disease, so this study aims to investigate Coxsackie B virus ligands with diabetes, which enable reliable and in immunosuppression, associated with progresses disease such as diabetes foot. And reveal the role of some cytokines in immune competence to fight viral infection and when it increased the disease progressed.

The pathophysiology includes humoral and cellular autoimmune destruction of beta cells at the molecular level. Beta cells expressing autoantigen epitopes such as insulin, GAD65, IA-2, and ZnT8 are directly attacked by CD4+ and CD8+ T lymphocytes. Autoantibodies against these antigens are significant diagnostic markers that exist for years before a clinical diagnosis. When immune cells infiltrate the islets, they release pro-inflammatory cytokines such IL-1β, IFNγ, and TNFα, which damage beta cells by creating a toxic microenvironment [4].

More than 60 genetic loci have been linked to an increased risk of T1D by thorough genome-wide association studies. The human leukocyte antigen (HLA) genotype is responsible for about half of the genetic risk, with significant contributions also coming from the INS, PTPN22, CTLA4, and IL2RA genes. Haplotypes of the HLA-class II DR and DQ alleles the highest risk is shown by DRB1*03:01-DQA1*05:01-DQB1*02:01 and DRB1*04-DQA1*03:01-DQB1* 03:02; DR3/DR4 (DQ2/DQ8) heterozygotes have a 30-fold higher risk of IA and T1D in the general population. While a combination of islet autoantibodies has been used in the past to predict a higher likelihood of first-degree relatives developing type 1 diabetes [5]. Studies concentrating on the isolation of viruses from individuals who developed the condition following an episode of flu-like symptoms during the colder seasons of the year first demonstrated the direct correlation between viral infection and type 1 diabetes. Recent T1DM patients and diabetic children of infected moms both had virus-specific antibodies, suggesting a possible link. Connection this metabolic condition and viral infections [6]. The coincidence of newly diagnosed type 1 diabetes mellitus with IgM antibody positivity to enteroviruses and respiratory tract viruses.

But the link between viruses and type 1 diabetes became more apparent after explanation of the occurrence of fulminant type 1 diabetes mellitus (FT1D) and diabetic ketoacidosis in reaction to viral infections [7].

Children born by caesarean section or whose moms are obese or older than 35 have a slightly increased risk of type 1 diabetes. Similarly, there is a modest increase in the risk of type 1 diabetes due to a child's weight gain during the first year of life, total weight, increased maternal age, increased postnatal growth rate, vitamin D deficiency, chemical exposure, gut microbiome changes, and body mass index (BMI). The risk of type 1 diabetes has also been linked to certain dietary practices, including the intake of dietary fiber, sugar, gluten, and cow's milk [8].

The inflammatory response and the course of disease are significantly shaped by interleukins (IL)-1, IL-12, and IL-15. IL-1 is a strong pro-inflammatory cytokine that increases oxidative stress and local immunological responses, which in turn leads to β-cell death [9].

T-cell differentiation is the main function of IL-12, which also increases autoreactive T cell activation and exacerbates β-cell destruction by promoting memory T cell survival and proliferation [9].

2. Materials and Methods

Study design and sampling period

The patients were referred to Private laboratories in AL Najaf Province from the period of November, 2024 until the end of February 2025. It consisted of 60 patients with type 1 diabetes, both males and females, of various ages, and 30 control individuals. All information about patients was noted in a questionnaire forma during direct meeting with Patients' families and staff, the questionnaire forma, which contain name, age, sex, family history, residency.

Blood sample collection

Two milliliters of blood were taken from each patient. and collected into tube containing EDTA for molecular study, then stored at $-20^{\circ}C$.

RT-qPCR technique

The Real Time PCR Primers and RT-PCR primers for detection Coxsackievirus B virus based on viral capsid VP1 gene were designed in this study using NCBI GenBank sequence (GQ329737.1)) [10] and primer3 plus and these primers were provided by (Scientific Researcher. Co. Ltd, Iraq) as following Table 1.

Table 1: Real Time PCR Primers and RT-PCR primers.

Primer	Sequence 5'-3'	PCR product size
qPCR-Vp1-F Primer	TAACGAGTGCACAACAACCC	147bp
qPCR-Vp1-R Primer	AGAAAACGCTGGGGTTTGTG	
qPCR-Vp1-probe	FAM-ATGTGCCTCCAGGTGGCCCT-TAMRA	
RT-PCR-Vp1-F Primer	TGGAGGAGTCTGTGGATCGT	515bp
RT-PCR-Vp1-R Primer	GGCGTTTCCTTCTGTCCAGA	

3. Results And Discussion

Confirmed diagnosis of coxsackievirus B (CVB) in DM patients by Real-time PCR

To confirm the seroprevalence of coxsackievirus B (CVB) infection, the suspected DM patients and healthy control subjects submitted to genetic detection by Real-time PCR and the results demonstrated in Figure 1 and 2. Positive results were seen in 20 (33.3%) of suspected patients in compared with 40 (66.7%) was negative. While all healthy control subjects 30 (100.0%) were have negative results of Real-time PCR, and the difference was significant, (P= 0.001).

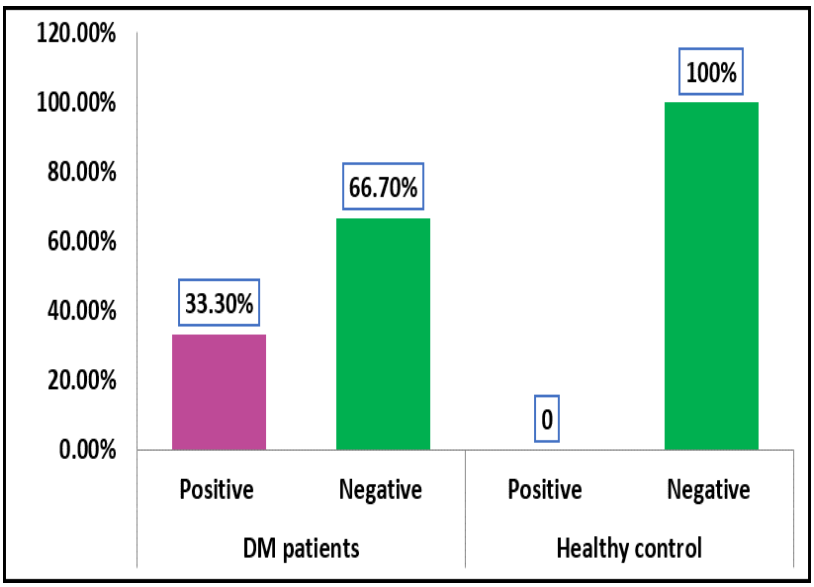

Figure 1: Prevalence CVB infection according to Real-time PCR in studied groups

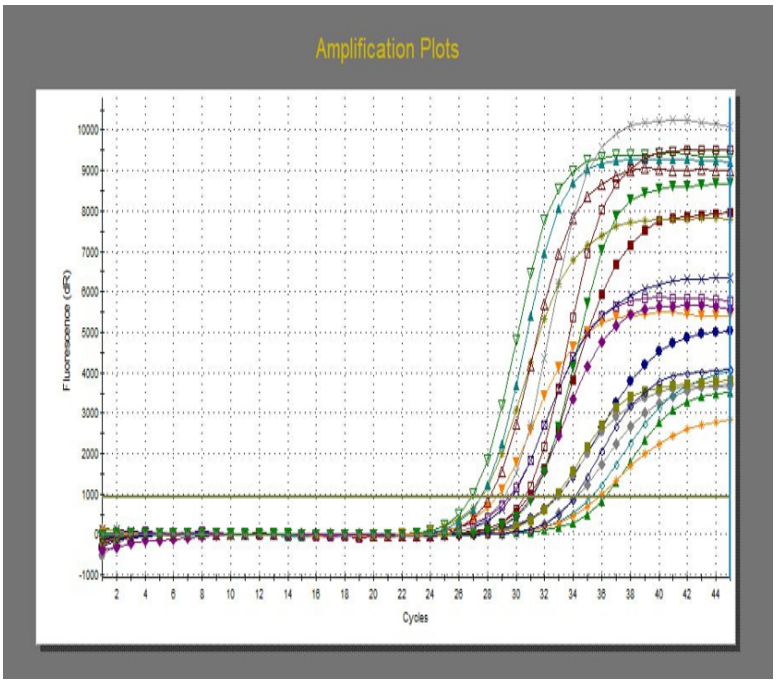

Figure 2: The Amplification plots of Real-time PCR

Similarly, a study conducted by [11] revealed that the ratio of CVB-RNA was 35% (21 out of 60) in seropositive CVB-T1D patients, compared to a completely negative result in the control group, which recorded 0% (0 out of 30). These findings are almost in agreement with the results of my study. Also, a study conducted by [10] showed that the results of QRT-PCR amplification revealed a positive detection rate of Coxsackievirus B infection, identifying 20 cases out of 56 children with type 1 diabetes mellitus (T1DM), equivalent to 35.7%. These findings are almost in agreement with the results of my study.

For the detection and monitoring of viral infections, particularly in individuals with compromised immune systems, quantitative PCR is incredibly helpful. When it comes to diagnosing coxsackievirus B (CVB) infections, this approach is effective. Real-time PCR allows for

the immediate and accurate measurement of PCR results because of its speed and accuracy. Because of this, it is now an essential tool for identifying and monitoring viral infections, [12].

The comparison of mean age, sex distribution according to results of Real-time PCR

After detection of coxsackievirus B infection, the DM patients categories into two groups included 20 DM patients with coxsackievirus B infection, and 40 DM patients without coxsackievirus B infection. The comparison of mean age and gender distribution according to results of Real-time PCR examination for detection of Coxsackievirus B infection is shown in Table 2.

The mean age of DM patients with Coxsackievirus B infection was 55.25 ±9.73 years and the range was 36-74 years, whereas the mean age of DM patients without Coxsackievirus B infection was 56.82 ±9.52 years and the range was 35-81 years. Indeed, there was non-significant difference in mean age between both groups (P = 0.579). On the other hand, most of DM patients with Coxsackievirus B infection enrolled in the present study were more than 60 years of age, 9 (45.0%), as shown in Table 4-5.

Regarding gender, DM patients with coxsackievirus B infection constituted 50.0% (10 out of 20) male whereas, those with female gender accounted for 50.0 % (10 out of 20). On the other hand, DM patients without coxsackievirus B infection included 30 (75.0%) and 10 (25.0%) with male and female respectively. Moreover, there was no statistical significance difference in the distribution of both groups with respect to gender (P = 0.053). Also, there was no statistical significance difference in the distribution of both groups with respect to residency (P = 0.326).

Table 2: The comparison of mean age, sex and residency distribution according to results of Real-time PCR

Characteristic	Total n = 60	CVB-Positive n =20	CVB-Negative n =40	P
Age (years)				
Mean ± SD	56.30± 8.24	55.25 ±9.73	56.82 ±9.52	0.579 † NS
Range	35 -81	36-74	35 -81	
< 50 years, n (%)	13 (21.7%)	7 (35.0%)	6 (15.0%)	0.090 ¥ NS
50-59 year, n (%)	22 (36.6%)	4 (20.0%)	18 (45.0%)	
≥ 60 years, n (%)	25 (41.7%)	9 (45.0%)	16 (40.0%)	
Sex				
Male, n (%)	40 (66.7%)	10 (50.0 %)	30 (75.0 %)	0.053 ¥ NS
Female, n (%)	20 (33.3%)	10 (50.0%)	10 (25.0%)	
Residency				
Urban, n (%)	41 (68.3%)	12 (60.0 %)	29 (72.5 %)	0.326 ¥ NS
Rural, n (%)	19 (31.7%)	8 (40.0%)	11 (27.5%)	

In a study conducted by [13], found T1DM patients with Coxsackievirus B infection exhibit a sex susceptibility pattern, with females, being more vulnerable to T1DM-CVB infection. This agrees with the results of my study. In a study conducted by [13], it was reported that across gender and age, the positivity rates between males and females were the same. However, the odds of a positive result increased significantly with age; individuals aged over 80 years had 2.5 times higher odds of testing positive compared to those aged 0–10 years (a OR 2.5, 95% CI 2.3–2.7). And this agrees with the findings of my study in terms of age but contradicts them in terms of sex. other result corresponds to the researcher's results, [14] which confirms that the female infection rate is higher than the male infection rate. Moreover, CVB infection has been shown to prompt changes in the intestinal microbiome, potentially contributing to autoimmune responses and T1DM onset in females [15]. rural areas face challenges like frequent marriage of relatives, which is a genetic factor. Moreover, residents in remote and socially deprived areas have a higher risk of diabetes-related avoidable hospitalization, indicating a potential link to increased CVB infections in rural settings [16]. Environmental and lifestyle factors contributing to a higher incidence of Coxsackievirus B infection in rural areas compared to urban areas among Type 1 Diabetes Mellitus (T1DM) patients include temperature exposure and lifestyle behaviors.

Subject immunological parameter Analysis Result

Interleukin-1β (IL-1β) level in patients and healthy controls

The comparison of Interleukin-1β (IL-1β) level between DM with CVB, DM without CVB and control groups has been carried out and the results were demonstrated in Table 3, Figure 3-4. Mean levels of IL-1β were 18.69 ± 4.3, 16.33 ± 2.31 and 11.01 ± 1.06, in DM with CVB, DM without CVB and control groups respectively; the mean levels were higher in both groups of patients in compared to healthy control and the difference was significant ($P < 0.05$). But the mean levels was non-significant difference between patients groups themselves (DM with CVB and DM without CVB) themselves ($P < 0.05$).

A recent study published by [17] discusses the role of IL-1β in Type 1 Diabetes (T1D) patients following viral infections, particularly Coxsackievirus B. The research highlights that IL-1β is significantly upregulated in newly diagnosed T1D patients, contributing to beta-cell dysfunction and destruction. A study indicated that Coxsackievirus infection can lead to an excessive immune response, contributing to pancreatic beta-cell damage through the activation of interleukin-1β (IL-1β), which is one of the key inflammatory cytokines involved in cell death [9].

Table 3: Interleukin-1β (IL-1β) level in patients and healthy control

Groups		Interleukin-1β (IL-1β) level
DM with CVB	Mean ± SE	18.69 ± 4.3^{A}
	Range	1.91-67.58
DM without CVB	Mean ± SE	16.33 ± 2.31^{A}
	Range	3.24-77.75
Healthy control	Mean ± SE	11.01 ± 1.06^{B}
	Range	2.18-23.61
p-value		0.041** †
Different latters denote to the significant differences at p< 0.05		

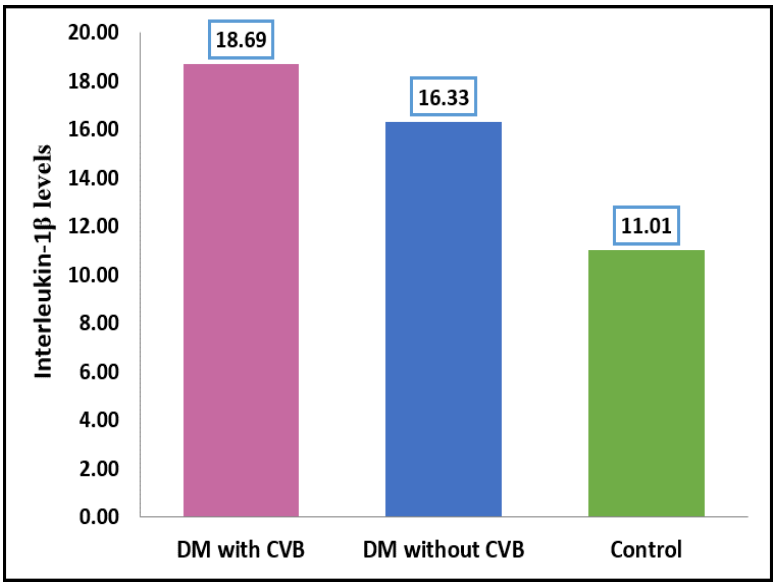

Figure 3: The means level of IL-1β in patients and control groups

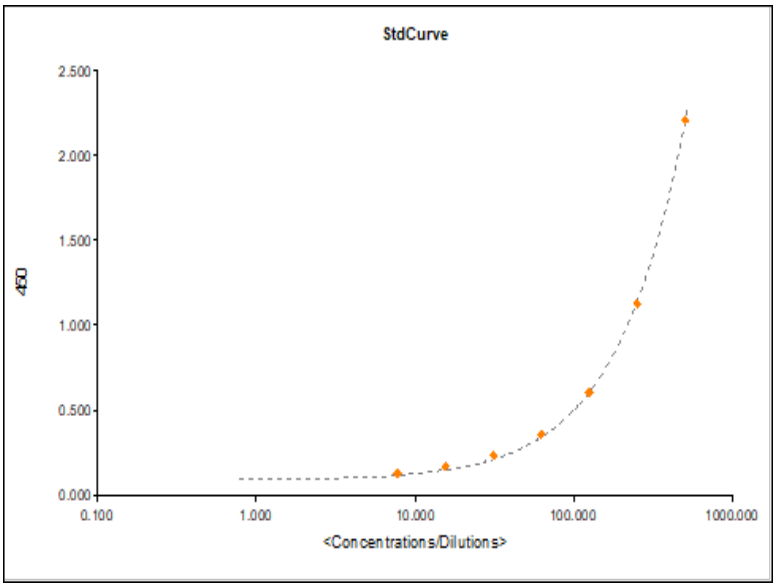

Figure 4: Slandered curve of Interleukin-1β (IL-1β)

Diagnostic accuracy of Interleukin-1β (IL-1β) level

Receiver operating characteristic (ROC) analysis was performed to reveal the diagnostic accuracy of using IL-1β concentrations to distinguish DM with CVB from healthy control subjects and the results are shown in Table 4, and Figure 5. The IL-1β cutoff value was $<$ 10.9-fold with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under curve of 65.0%, 63.3%, 54.2%, 73.1% and 0.616 (0.494- 0.739). The present results indicate IL-1β is considered as a moderate diagnostic marker.

Table 4: Sensitivity and specificity of IL-1β level ($<$ 10.9-fold) in DM with CVB

IL-1β level	DM with CVB n = 20	Healthy control n = 30
10.9 >	13 (%)	11 (%)
10.9 <	7 (%)	19 (%)
Sensitivity %	65.0 %	
Specificity %	63.3 %	
PPV %	54.2 %	
NPV %	73.1%	
AUC (95% CI)	0.616 (0.494- 0.739)	

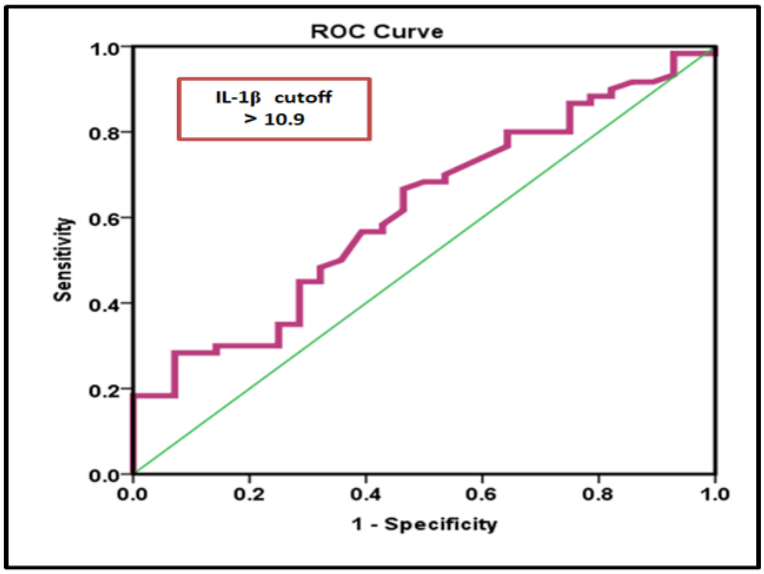

Figure 5: Receiver operator characteristic curve analysis of IL-1β for the calculation of possible diagnostic cutoff value.

Interleukin-12 (IL-12) level in patients and healthy controls

The comparison of Interleukin-12 (IL-12) level between DM patients and control groups has been carried out and the results were demonstrated in Table 5 and Figure 6-7. Mean levels of IL-12 were 26.89 ± 5.4, 21.77 ± 3.86 and 10.68 ± 2.26, in DM with CVB, DM without CVB and control groups respectively; the mean levels were higher in both groups of patients in compared to healthy control and the difference was significant ($P < 0.05$). But the mean levels was non-significant difference between patients groups themselves (DM with CVB and DM without CVB) themselves ($P < 0.05$).

Table 5: Interleukin-12 (IL-12) level in patients and healthy control

Groups		Interleukin-12 (IL-12) level
DM with CVB	Mean ± SE	26.89 ± 5.4^{A}
	Range	2.96-95.40
DM without CVB	Mean ± SE	21.77 ± 3.86^{A}
	Range	2.36-110.0
Healthy control	Mean ± SE	10.68 ± 2.26^{B}
	Range	0.10-81.79
p-value		0.032** †
Different letters denote to the significant differences at p< 0.05		

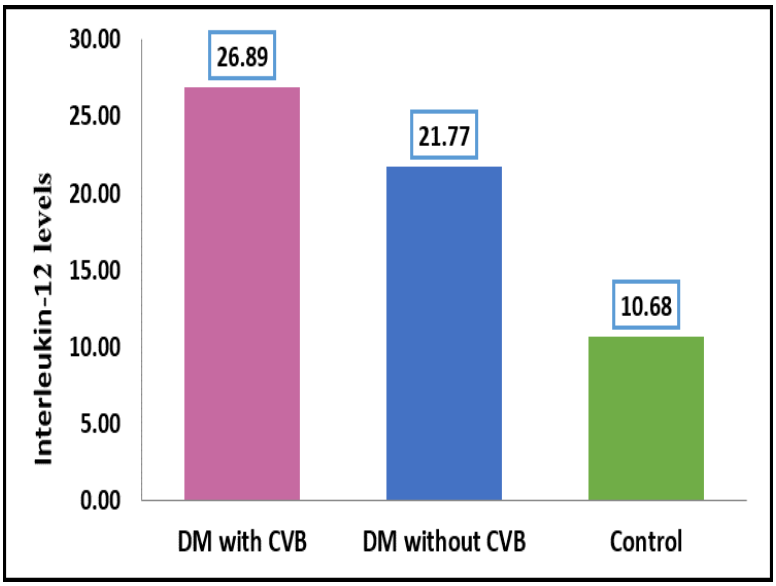

Figure 6: The means level of IL-12 in patients and control groups

A recent study in [18] discusses the role of IL-12 in Type 1 Diabetes (T1D) patients following viral infections. The research highlights that viral infections, particularly enteroviruses, can trigger immune dysregulation, leading to increased IL-12 levels and promoting Th1 immune responses. This elevation in IL-12 contributes to beta-cell destruction and autoimmune progression, reinforcing the link between viral exposure and T1D onset. Furthermore, research [19] that IL-12 plays a part in T-cell activation and inflammatory signaling, and that chronic enteroviral infections may serve as a precursor to autoimmune diabetes. The study highlights that two important ways that viruses contribute to the development of T1D are molecular mimicry and immunological activation. A study conducted by [20] observed that IL-12 levels were significantly elevated in Type 1 Diabetic Nephropathy (T1DN) patients infected with Epstein-Barr Nuclear Antigen 1 (EBNA1) IgG. The mean IL-12 level in infected patients was 33.84 ± 4.47 pg/ml, whereas in non-infected patients, it was 13.21 ± 4.36 pg/ml, with a statistically significant difference (P = 0.01).

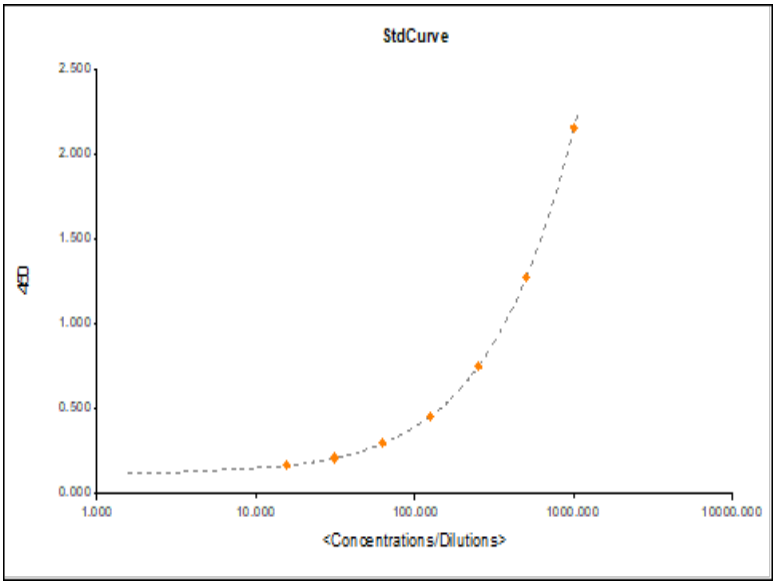

Figure 7: Slandered curve of Interleukin-12 (IL-12)

Diagnostic accuracy of Interleukin-12 (IL-12) level

Receiver operating characteristic (ROC) analysis was performed to reveal the diagnostic accuracy of using IL-12 concentrations to distinguish DM with CVB from healthy control subjects and the results are shown in Table 6, and Figure 8. The IL-12 cutoff value was < 8.79-fold with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under curve of 75.0%, 76.7%, 68.2%, 82.1% and 0.772 (0.661- 0.882). The present results indicate IL-12 is considered as acceptable diagnostic marker.

Table 6: Sensitivity and specificity of IL-12 level (¡ 10.9-fold) in DM with CVB

IL-12 level	DM with CVB n =20	Healthy control n = 30
8.79 >	47 (%)	7 (%)
8.79 <	13 (%)	23 (%)
Sensitivity %	75.0 %	
Specificity %	76.7 %	
PPV %	68.2 %	
NPV %	82.1%	
AUC (95% CI)	0.772 (0.661- 0.882)	

The association between interleukins parameters level and sex groups

The association between interleukins parameters level and sex groups in all study groups has been carried out and the results were demonstrated in Table 7. The present results show non-significant difference between male and female in all study groups according to all interleukins parameters ($p<0.05$).

It was discovered that female patients had greater exposure rates to Enterovirus C and D than male patients in a study with 25 type 1 diabetic patients (13 females and 12 males). When 48 cytokines were analyzed, clear sex-based differences were found: male patients had higher levels of IL-22 than healthy males, whereas female patients had considerably lower levels of IL-4, IL-13, and IL-22—all of which are anti-inflammatory cytokines [21].

The association between interleukins parameters level and age groups

The association between interleukins parameters level and age groups in all study groups has been carried out and the results were demonstrated in Table 8. The present results show there was non-significant difference among different age groups in all study groups according to all other interleukins parameters ($p<0.05$).

According to a study, low-grade chronic inflammation (inflammation) causes the elderly to secrete higher quantities of IL-1. This ongoing increase in IL-1 plays a part in chronic immune Related disorders and deteriorates the function of hematopoietic stem cells Children's IL1 responses, on the other hand, are typically more severe but transient, indicating an age-related variation in inflammatory processes [22].

Another study showed that the balance and production of cytokines, such as IL-12, are impacted by aging. Age-related disruptions in the Th1 response linked to IL-12 result in decreased susceptibility to viral infections. The IL-12 response in children, on the other hand, is more robust and balanced in the early phases of infection [23].

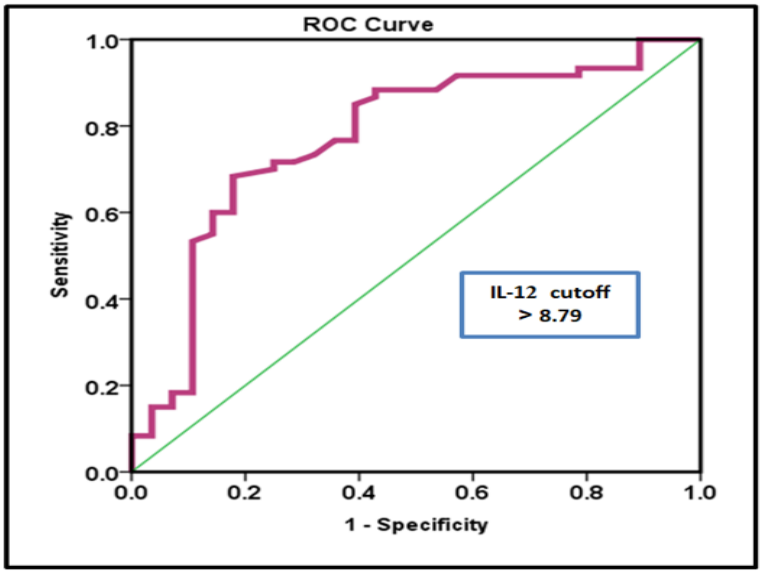

Figure 8: Receiver operator characteristic curve analysis of IL-12 for the calculation of possible diagnostic cutoff value

Table 7: The association between interleukins parameters level and sex groups in all study groups

Sex groups	IL-1α	IL-12
DM with CVB		
Male	20.07 ± 3.49	29.53 ± 5.2
Female	16.52 ± 5.01	22.20 ± 6.3
p-value	0.607 †	0.567 †
DM without CVB		
Male	16.32 ± 2.73	20.56 ± 5.11
Female	16.36 ± 4.5	25.42 ± 3.93
p-value	0.801 †	0.407 †
Healthy control		
Male	10.60 ± 1.35	9.79 ± 2.2
Female	13.29 ± 2.14	9.15 ± 1.72
p-value	0.934 †	0.927 †

Logistic regression correlations between immunological parameters in DM with CVB

The Logistic regression model shows that the correlation immunological parameter such as IL-1β in which have directly correlate with IL-12 among DM patients as in Figure 9 this result might be refer to that DM condition enhances production of IL-1β in relation the expression of IL-12, the study indicated that IL-1 contributes to chronic inflammation and the destruction of insulin-producing cells. As for IL-12, it plays a key role in promoting the Th1-type immune response, leading to the activation of autoreactive cytotoxic T cells [9].

Table 8: The association between interleukins parameters level and age groups in all study groups

Age groups	IL-1α	IL-12
DM with CVB		
< 50 years	15.60 ± 2.72	11.81 ± 3.1
50-59 years	14.15 ± 3.6	23.23 ± 4.5
≥ 60 years	22.89 ± 5.98	38.67 ± 7.8
p-value	0.520 +	0.167 +
DM without CVB		
< 50 years	18.44 ± 5.8	15.72 ± 2.83
50-59 years	16.92 ± 2.7	17.87 ± 4.2
≥ 60 years	14.44 ± 4.1	27.31 ± 5.9
p-value	0.861 +	0.163 +
Healthy control		
< 50 years	11.83 ± 1.72	9.43 ± 2.5
50-59 years	11.55 ± 2.11	8.82 ± 2.6
≥ 60 years	10.28 ± 2.48	10.74 ±2.51
p-value	0.864 +	0.980 +

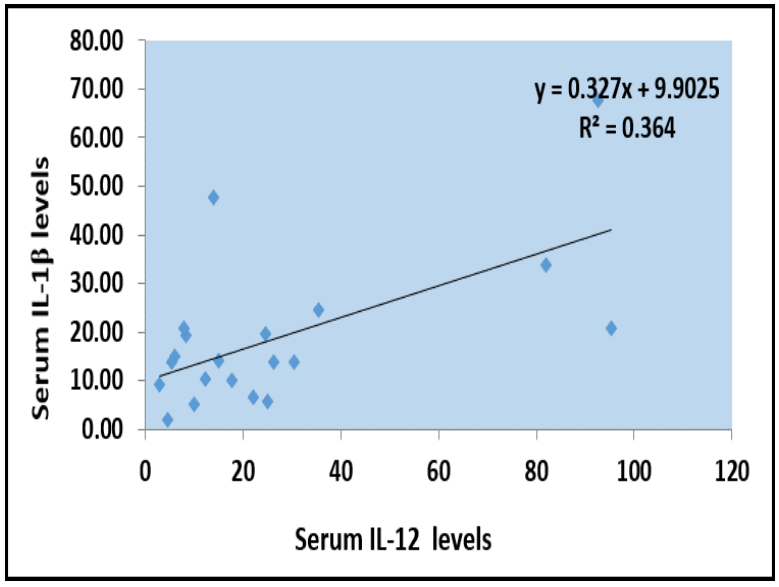

Figure 9: The Logistic scatter IL-1β and IL-12 levels among patients.

4. Conclusions

In individuals with Type 1 Diabetes Mellitus (T1DM), coxsackievirus seems to have a possible immunological role in initiating or intensifying autoimmune activity. According to this study, T1DM patients with Coxsackievirus infection show a slight rise in IL-1β and IL-12 levels, suggesting a minor immune activation that is pro-inflammatory. Both IL-1β and IL-12 may worsen the underlying autoimmune process in type 1 diabetes by promoting Th1-mediated autoimmunity and pancreatic β-cell destruction, respectively.

Moreover, epidemiological investigation revealed that the virus was more commonly found in older people, women, and people living in rural areas, indicating a pattern of environmental and demographic susceptibility. These results provide credence to the theory that among genetically predisposed people with type 1 diabetes, Coxsackievirus may function as an immunological trigger. RT-PCR was used to confirm the virus's presence, guaranteeing high diagnostic.

Article Information

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Conflict of Interest Disclosure: No potential conflict of interest was declared by the authors.

Ethical Approval and Participant Consent: All the participants provided informed consent for inclusion in the study and were assured that all the information provided would be used solely for the purposes of this study and treated confidentially.

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