JOBS
مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد السادس والثلاثون
٢٠٢٦م /١٤٤٧هـ
العدد السادس والثلاثون
(636) (617)

تأثير فيروس كوكساكي ب(CVB) وفيروس الهربس البسيط ١(HSV١) وفيروس بارفو (B19) على مرضى السكري المعتمدين على الأنسولين.

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المستخلص:

يُعدّ داء السكري المعتمد على الأنسولين (T1DM) مرضًا مناعيًا ذاتيًا يُعتقد أنه ينجم عن عوامل بيئية لدى الأفراد ذوي الاستعداد الوراثي. وقد ذُكرت الفيروسات المعوية باعتبارها المُسبب الأكثر احتمالًا للمرض. ومع ذلك، فإن الدراسات المنشورة متضاربة فيما يتعلق بارتباط داء السكري المعتمد على الأنسولين بالعدوى الفيروسية ومكون الدفاع المضاد للفيروسات في الخط الأول. هدفت هذه الدراسة إلى تحليل مدى انتشار ثلاثة فيروسات يمكن أن تُسبب عدوى مزمنة – فيروس كوكساكي (B4)، وفيروس الهربس البسيط من النوع الأول (HSV-1)، وفيروس بارفو (B19) – لدى مرضى داء السكري المعتمد على الأنسولين. شملت دراستنا ٦٨ مريضًا بداء السكري المعتمد على الأنسولين و ٢٤ فردًا سليمًا كمجموعة ضابطة. جُمعت عينات دم من جميع المشاركين في الدراسة. استُخدمت تقنية ELISA لقياس الأجسام المضادة للفيروسات. بشكل عام، أظهرت نتائجنا أن فيروس كوكساكي (B4) فقط هو الذي يلعب دورًا في تطور داء السكري المعتمد على الأنسولين. ومع ذلك، فإن فيروس B19 مفيد في التمييز بين أنواع DM1 و LADA، وكذلك بين الأطفال والبالغين المصابين بمرض السكري من النوع الأول، في حين لا يوجد دور لفيروس HSV-1 في مرضى السكري من النوع الأول.

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الكلمات المفتاحية: داء السكري المعتمد على الأنسولين (T1DM)، فيروس كوكساكي ب (CVB)، فيروس الهربس البسيط ١ (HSV1)، وفيروس بارفو (B19).

Investigation of the effect of Coxsackieviruse B (CVB), Herpes simplex virus 1 (HSV1), and Parvovirus(B19), in patients with insulin-dependent diabetes mellitus

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ABSTRACT:

Insulin-dependent diabetes mellitus (T1DM) is an autoimmune condition thought to arise from environmental exposures in genetically predisposed individuals. Enteroviruses have frequently been proposed as key candidates in triggering the disease. However, the current body of literature presents conflicting findings concerning the relationship between viral infections and T1DM, in addition to uncertainties surrounding first-line antiviral strategies for protective immunity The direct of this study was to examine the currency of three viruses which can cause dogged infections Coxsackievirus (B4), herpes simplex virus type1 (HSV-1), and parvovirus (B19) in patients with T1DM. Our study involved 68 T1DM patients and 24 healthy individuals as a control group. Blood was taken from all the study participants. Methodological considerations of the ELISA technique were used to measure virus antibodies. In general, our results showed that only CVB4 has a role in the development of T1DM patients. However B19 virus is useful in distinguishing between DM1 and LADA types, as well as between children and adults with T1DM disease, while no role for HSV-1 in T1DM patients.

Key words: Insulin-dependent diabetes mellitus (T1DM), Coxsackievirus B (CVB), Herpes simplex virus 1 (HSV1), and Parvovirus(B19).

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Introduction

Insulin-dependent diabetes mellitus (T1DM) is one of the most well-known autoimmune chronic incessant infections in adolescence, pediatric, and adult populations brought about by insulin inadequacy following autoimmune devastation of the pancreatic beta cells. It is now well established that insulin-dependent diabetes mellitus (T1DM), including Type 1 diabetes, is a well-recognized autoimmune disorder, and Latent autoimmune diabetes in adults (LADA) has been extensively investigated to clarify the pathogenic mechanisms of type 1 diabetes. Nevertheless, the exact causes and molecular pathways responsible for disease development are not yet fully elucidated, and mechanisms are still far from being completely understood. The consequence is a lack of effective preventive measures or causal therapies; however, one of the risk factors for diabetes development might be viral infection. (1)

Virally induced inflammatory responses, beta cell destruction, and release of beta cell autoantigens may lead to autoimmune reactions culminating in type1 diabetes. Latent Autoimmune Diabetes in Adults (LADA), sometimes called type1.5 diabetes, commonly referred to as LADA, which is considered a subcategory of type1 diabetes but is commonly misdiagnosed as (LADA) is frequently mistaken for type2 diabetes due to its later clinical presentation. Most affected individuals are over 30 years of age at diagnosis, and unlike classical type 1 diabetes, residual pancreatic β-cell activity permits limited endogenous insulin secretion during the initial phase of the disorder.(2)

Accumulating experimental evidence indicates that Coxsackievirus B4 (CVB4) may contribute to the development of insulin-dependent diabetes mellitus by promoting acute cytolytic damage to pancreatic β-cells in animal models. Notably, the CVB4 E2 strain—originally isolated from individuals with T1DM—has been reported to induce β-cell–directed autoimmunity and subsequent hyperglycemia in susceptible mouse strains. Additionally,

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persistent viral RNA detected in the pancreatic tissue of CD1 mice has been strongly correlated with diabetes onset six months after infection. Further support for the viral etiology is provided by studies linking type 1 diabetes susceptibility to polymorphisms in the interferon-induced helicase C domain 1 (IFIH1) gene, a critical cytoplasmic sensor of viral RNA commonly referred to as MDA5. (3)

Herpes simplex virus1 (HSV-1), also known as human herpesvirus 1 (HHV-1), is a member of the herpesvirus family, Herpesviridae, that infects humans. HSV employs sophisticated mechanisms to escape immune detection, primarily by impairing major histocompatibility complex (MHC) class I–mediated antigen presentation. This process involves the viral protein infected cell protein 47 (ICP47), which inhibits the transporter associated with antigen processing (TAP). Physiologically, TAP facilitates the transfer of proteolytically generated viral peptides from the cytosol into the endoplasmic reticulum, enabling their loading onto MHC class I molecules for presentation to cytotoxic T cells. By blocking this pathway, HSV effectively reduces antigen presentation and limits immune recognition. (4)

The results of Zaman I. and Kareem H. (2020) showed that the genes responsible for antiviral CXCL9 & IFIH1 cytokines are involved in the development of type 1 diabetes. (33)

Primate erythroparvovirus1, for the most part, alluded to Parvovirus B19-sometimes termed erythrovirus B19—represents the first human virus discovered within the Parvoviridae family, genus Erythroparvovirus. (5) Measuring approximately 23–26 nm in diameter, it is regarded as one of the smallest DNA viruses infecting humans. (6) The term “parvovirus” is derived from the Latin word parvum, meaning “small,” reflecting its minimal structural size. This virus is associated with a wide spectrum of clinically significant manifestations, primarily affecting the pediatric population, although adults may also be infected. It is the classic etiological agent of the childhood exanthem known as fifth disease, or erythema infectiosum, commonly referred to as “slapped cheek syndrome.” (7,8).

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An expanding body of experimental data supports the hypothesis that Coxsackievirus B4 (CVB4) is implicated in the pathogenesis of insulin-dependent diabetes mellitus through acute cytolytic damage to pancreatic β-cells. In particular, the CVB4 E2 strain, originally isolated from individuals with T1DM, has been reported to induce β-cell–specific autoimmunity and subsequent hyperglycemia in susceptible mouse models. Persistent viral RNA in the pancreatic tissue of CD1 mice infected with the CVB4 E2 strain has been strongly correlated with diabetes onset six months after infection. The viral theory was further helped after the disclosure of the relationship of DM1 with polymorphisms in a gene encoding a cytoplasmic viral sensor, interferon-induced helicase C domain 1 (IFIH), also known as MDA5 (melanoma differentiation-associated protein 5). (8)

HSV-1 has been identified as a potential contributor to cardiovascular diseases, with seropositivity linked to an increased risk of myocardial infarction and coronary heart disease.(9) Type 2 diabetes mellitus is a well-established risk factor for cardiovascular morbidity and mortality and is considered a coronary artery disease risk equivalent. Therefore, the present study was designed to evaluate the possible link between herpes simplex virus type 1 (HSV-1) infection and type 2 diabetes mellitus (T2DM). (10)

Parvovirus B19 derives its name from the Latin term parvum, meaning “small,” reflecting its classification among the smallest known DNA viruses. Although infection predominantly occurs in the pediatric population, adults are also susceptible. The virus is most widely recognized as the etiological agent of erythema infectiosum, commonly referred to as fifth disease. (11)

Serum levels of B19-IgM and antibodies to the diabetic autoantigen tyrosine phosphatase antibodies (Islet antigen 2), IA-2, were significantly elevated. The creators noted homology in amino acid groupings among B19 and the extracellular area of tyrosine phosphatase antibodies (Islet antigen 2) IA-2 (12).

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Materials and Methods

The patients were attended to the Al-Karamah and Al-Zahra Teaching Hospitals from September 2018 to September 2019. The control group consisted of persons who visited the hospital as blood donors .Peripheral blood samples were collected from 68 patients recently diagnosed with T1DM (28 females and 40 males), and 24 control groups (13 females and 11 males). Among the T1DM patients, 31 were children younger than 19 years of age, and 37 were adult patients. The patients were divided into subgroups according to age groups. Patients were also divided according to subtype of disease; 53(78%) of them were recorded as type 1(DM1), while the rest (22%) were recorded as LADA type.
The ELISA technique was used to measure the levels of virus antibodies in the serum of patients.

Statistical Analysis

Statistical analyses were conducted using SPSS (version 20, 2012). The chi-square test was employed to examine significant differences in categorical variables, and the independent t-test was applied to assess differences in group means. Correlation analyses were performed to estimate the strength and direction of relationships among study variables.

Results and Discussion

TABLE 1: Distribution of T1DM patients according to gender.

Gender	Frequency	Percent (100%)
Males	40	58.82
Females	28	41.18
Total	68	100%

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Tables (1) and Figure (1) showed the distribution of patients according to gender and age group. The results showed that 58.82% of patients were males, while the rest were females, with no significant difference between them.

The patients were divided into (4) age groups (1-4) with a (12) years interval. The first age group was (8-19) years, while the last was (44+) years. Estimation of patients' age group showed that age group 1(8-19) were 31 cases (45.6%), age group 2 (20-31) were 22 cases (32.4 %), age group 3 (32-43) were 12 cases (17.6 %) and age group 4 (44+) were 3 cases (4.4 %).

TABLE 2: Distribution of T1DM patients according to age group

Type of disease		**Age _Categories**				**Total**	**P-value**
		8 - 19	20 – 31	32 - 43	44+		
DM1 patients	Count	31	22	0	0	53	P<0.001
	% within Type of disease	58.5%	41.5%	0.0%	0.0%	100.0%	
LADA patients	Count	0	0	12	3	15	
	% within Type of disease	0.0%	0.0%	80.0%	20.0%	100.0%	
Total	Count	31	22	12	3	68	
	% within Type of disease	45.6%	32.4%	17.6%	4.4%	100.0%	

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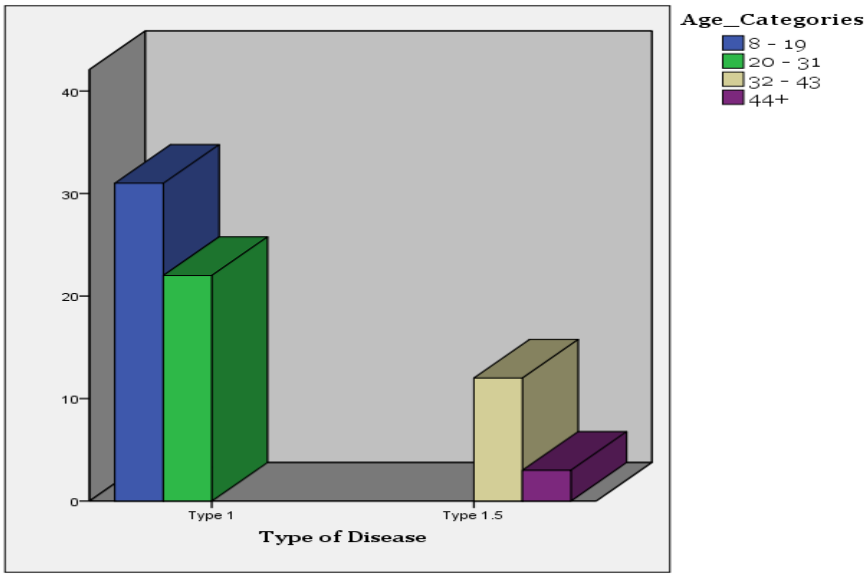

FIGURE 1: Distribution of T1DM patients according to age group

In Estonian children aged 0-14.9 years, 310 new cases of DM1 were diagnosed between 1999 and 2006. The age-standardized incidence rate for that period was 17.2 [95% confidence interval (CI) 13.1-21.2]. The highest incidence was 21.2 (95% CI 17.7-25.3) in years. Childhood-onset DM1 increased annually by an average of 3.3% in Estonian children under 15 years of age over the period 1983-2006, with the most rapid increase observed among the youngest age groups. Childhood-onset type 1 diabetes mellitus (T1DM) is increasing in Estonia, and the age of onset is getting younger. (10)

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Statistical Analysis.

1- Coxsackievirus group B (CVB4) in T1DM patients.

As presented in Table 3 and Figure 2, the statistical analysis demonstrated that the mean level of CVB4-IgG in T1DM patients (1.233 U/ml) was significantly higher ($P<0.05$) in patients with insulin-dependent diabetes mellitus (T1DM) compared to the control group (0.584U/ml).

In relation to CVB4-IgG level, the result showed that the level of CVB4-IgG was lower in DM1 patients (1.095U/ml) than that in LADA patients (2.18033), with a significant difference ($P<0.05$).

The statistical analyses revealed a non-significant difference ($P>0.05$) between the mean level of CVB4-IgG in T1DM male patients (1.577 U/ml) when compared with T1DM female patients (0.988 U/ml).

As well as, the same results showed a non-significant ($P>0.05$) difference between the mean level of CVB4-IgG in T1DM adult patients (1.443 U/ml) and kids patients (1.205 U/ml).

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Case	No.	Concentration of CVB4 mean U / ml	± Std. deviation	±Std. error	P-value
T1DM patients	68	1.233	±2.351	±0.479	P<0.05
Control group	24	0.584	±1.114	±0.227	
DM 1 patients	53	1.095	±1.619	±0.222	P<0.05
LADA patients	15	2.18033	±1.644	±0.424	
T1DM Male patients	40	1.577	±1.720	±0.272	P>0.05
T1DM Female patients	28	0.988	±1.574	±0.297	

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TABLE (3): Level of CVB4 in studied groups.

T1DM Adult patients	37	1.443	±1.688	±0.277	P>0.05
T1DM Kids patients	31	1.205	±1.678	±0.301	

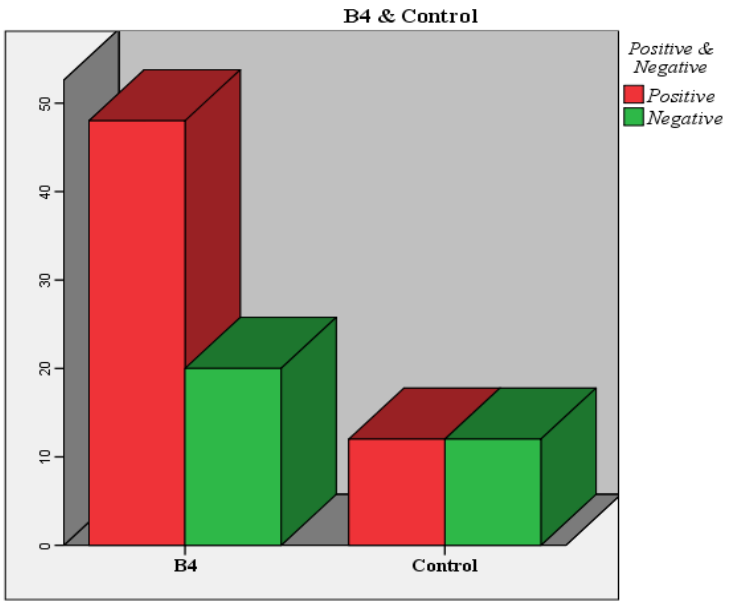

FIGURE 2: Distribution of patients and control group according to CVB4 infection.

The findings indicate that evidence of viral infection may contribute to the pathogenesis of insulin-dependent diabetes mellitus (T1DM). However, the epidemiological studies showed an increased incidence of DM1 after enterovirus epidemics. (11,12)

An investigation in human pancreatic cells exhibited that CVB4 prompts the creation of proinflammatory cytokines, especially IL-6 and TNFα. TLR4 is important for setting off this invulnerable reaction; be that as it may, this reaction is free of CVB4 disguise and

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replication. Consequently, the association between TLR4 and CVB4 in pancreatic cells may instigate an intrinsic invulnerable reaction (12).

Hober et al. (13) showed that CVB4 –IgG with high levels of IFN-alpha have been found in patients with type 1 diabetes who have detectable levels of CVB4 RNA in their blood.

Some authors clarified that infections with CVBs are associated with human diseases, including aseptic meningitis, myocarditis, and autoimmune DM1 (14).

The diabetes and autoimmunity study in young (DAISY) reported that 8% of children progressing to DM1 had enteroviral RNA to CVB (15).

Svensson et al. (16) showed that the odds ratio in boys was different from that in girls; most of the published studies reported no significant difference between the type 1 diabetes incidence in boys and girls (17-18).

2- Herpes simplex virus 1(HSV1) in T1DM patients

As shown in Table 4, statistical analysis demonstrated that the mean level of HSV1-IgG in T1DM (2.463U/ml) was non-significantly (P>0.05) higher in diabetic patients than in the control group (1.751U/ml). There was no significant (P>0.05) difference between patients with type 1 diabetes and LADA patients. The statistical analyses indicated that the mean level of HSV1-IgG was non-significantly different (P>0.05) when comparing male diabetic patients (2.309 U/ml) and female patients (2.682 U/ml).

The same results revealed that there was no significant (P>0.05) difference between the mean level of HSV1-IgG in T1DM adult patients (2.644 U/ml) and kids patients (2.246 U/ml).

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Cases	NO.	Concentration of HSV1 mean U / ml	±Std. Deviation	Error Mean	P-value
T1DM Patients	68	2.463	±1.214	±0.147	p>0.05
Control group	24	1.751	±0.758	±0.154	
DM1 patients	53	2.392	±1.348	±0.185	P>0.05
LADA patients	15	2.712	±0.473	±0.122	
Male patients	40	2.309	±1.344	±0.212	P>0.05
Female patients	28	2.682	±0.981	±0.185	
Adult patients	37	2.644	±0.963	±0.158	p>0.05
Kid patients	31	2.246	±1.445	±0.259	

TABLE (4): Level of HSV1in studied groups

The animal virus-initiated DM1 gives a great deal of data concerning the potential role of infectious diseases in the acceptance of T1DM (22). While other studies suggested that diabetic patients may be at a higher danger of developing different malignancies because of high rates of oncogenic viral diseases (23,24). Another surprising results that LADA shares genetic features with type 2 diabetes (25). Herpes simplex virus type 1 (HSV-1) is capable of vertical transmission from mother to infant, and studies have demonstrated that the virus can establish persistent colonization in the brains of offspring from infected mothers. Moreover, multiple studies have provided evidence of herpes simplex virus type1 (HSV-1) infection, immunoreactivity, and reactivation in the neurons of the hippocampus. (26)

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The current study may refer to the fact that there is no effect of HSV1 on T1DM patients.

3. Parvovirus B19 in T1DM patients.

The statistical analyses in Table 5 and Figure ٣ recorded that the mean level of B19-IgM in the T1DM group (0.119U/ml) was no significant (P>0.05) compared with the control group (0.855 U/ml).
In relation to B19-IgM expression, there was a highly significant (P<0.05) difference between DM1 patients with diabetes and LADA patients; the level of B19-IgM in DM1 patients was reported to be (0.170U/ml), while in LADA patients it was (0.058 U/ml).

Also the statistical analyses revealed that the mean level of B19-IgM in T1DM male patients (0.091U/ml), while T1DM female patients (0.159 U/ml). Those results showed no significant differences between male and female T1DM patients. The same results showed that the mean level of B19-IgM in T1DM adult patients (0.043 U/ml) was significantly (P<0.05) lower than in kids T1DM kids (0.210 U/ml).

TABLE (5): Level of Parvovirus B19 in studied groups

Case	No.	Concentration of B19 mean U / ml	±Std. Deviation	Std. Error±	P-value
T1DM Patient	68	0.119	±0.413	±0.050	P>0.05
Control group	24	0.855	±0.371	±0.075	
DM1 patient	53	0.170	±0.455	±0.062	P<0.05
LADA patients	15	0.058	±0.073	±0.018	

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Male patients	40	0.091	±0.371	±0.058	p>0.05
Female patients	28	0.159	±0.472	±0.089	
Adults patent	37	0.043	±0.329	±0.054	P<0.05
Kid patients	31	0.210	±0.486	±0.087	

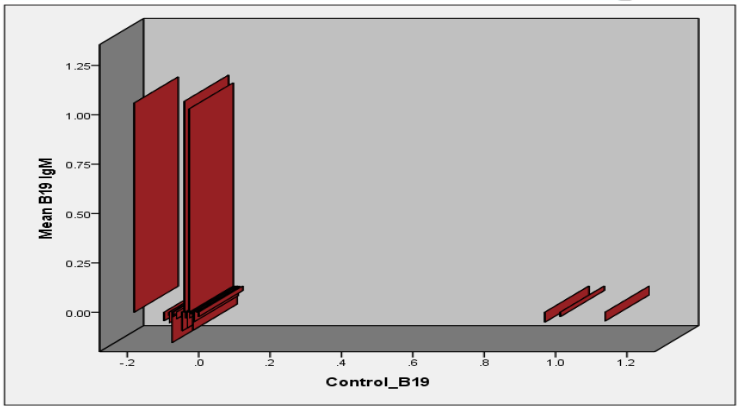

FIGURE ٣: Distribution of patients and control group according to B19 infection.

Although the pathophysiological mechanisms underlying fulminant type1 diabetes mellitus remain incompletely elucidated, accumulating evidence suggests that virus-induced autoimmune responses may play a critical role in its onset. (27)

Most diabetic patients are diagnosed with type 2 diabetes (T2D), which, unlike type1 diabetes (T1D), is not autoimmune in origin and develops due to the interplay between peripheral insulin resistance and insufficient pancreatic β-cell compensation. In T1D, clinical symptoms—including polyuria, polydipsia, weight loss, and ketosis—usually emerge only after 60–80% of β-cells have been destroyed. (28)

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Infection with human parvovirus B19 is widespread, with approximately 30–50% of pregnant women remaining seronegative. Vertical transmission is common when maternal infection occurs during gestation, posing potential risks to the fetus. (29)

Human parvovirus B19 infection has been studied for its potential involvement in pediatric patients newly diagnosed with type 1 diabetes mellitus (T1DM). Viral infections, broadly, have been hypothesized to contribute to the initiation of autoimmune processes leading to T1D. While various viral agents have been suggested as potential triggers, compelling epidemiological, serological, and molecular data indicate a significant association between enterovirus infections and the development of type 1 diabetes mellitus in humans. (30) Nevertheless, the exact pathogenic mechanisms linking enterovirus infections to type 1 diabetes, and the fraction of cases directly attributable to these viruses, have yet to be fully elucidated. (30) A multistage pathogenic framework has been suggested, whereby successive environmental or infectious insults, initiated by a primary trigger, culminate in pancreatic β-cell destruction. (31)
From the results of the table (5), it is clear that the parvovirus B19 has no role in T1DM patients generally. However, it appears that the identification of antibodies to this virus is important to distinguish between DM1 and LADA patients. It also seems that this virus is related to infecting children with the disease more than infected adults. (33)

Conclusion

Our results refer to a highly important role of CVB4 in T1DM patients, while the HSV virus did not show any role in the development of any type of diabetes in this study. While determining levels of antibody of B19 virus is useful in distinguishing between DM1 and LADA types, as well as between children and adults with T1DM disease.

ACKNOWLEDGMENT

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I would like to thank all those who, in one way or another, have contributed to this research, especially to Dr. Jalal Abdel Razaq. T., Doaa Alaa', Noha Alaa Asyad Abdel Abbas, Nour Aziz, and Nawras Nagah.

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