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Review Article

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Viruses and Diabetes: A Long History

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ABSTRACT

Diabetes mellitus is the most common and complex problems in modern societies that causes many social and economic problems. Diabetes can cause both short- and long-term complications and can damage to the physical and physiological function of various organs of the body. So it's a threaten of human health. Diabetes is a multi-etiological disease and there is a strong correlation between T1DM and specific alleles of the MHC II genes and nongenetic factors. It can mean that environmental factors such as viruses, dietary proteins, toxin and stress play an important role in the developing of diabetes. WHO estimated that prevalence of diabetes among adults in the world would increaseto300 million by 2025.3.78 million Cases of DM (2.74 million diagnosed and 1.04 million undiagnosed) are estimated in Iran in 2009 and it is expected to rise to 9.24 million cases (6.73 million diagnosed and 2.50 million undiagnosed) by 2030. Owing to the aforementioned point and the heterogeneous etiology of diabetes there is an increasing interest in finding the factors which influence its etiology and progression. There are many evidences that show the association of several human viruses and diabetes. Here we briefly reviewed the role of viruses as a causative agent in diabetes.

Key words: Diabetes, Viruses, Bystander activation, Molecular mimicry

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INTRODUCTION

Diabetes mellitus is the most common and complex problems in modern societies that causes many social and economic problems (1). Whereas diabetes have heterogeneous etiology, it can be classified into two basic types:T1DM and T2DM (2). Type 1 diabetes is caused by a deficiency of insulin secretion, while the pathogenesis of type 2 diabetes is result of a uptrend of insulin resistance in liver and peripheral tissues, mass reduction and insulin secretion deficiency (1-4). The prevalence of diabetes is increasing worldwide and peak incidence of type I diabetes, is between 10 and 15 years old, and 75% of cases are diagnosed before age of 18 and (5, 6). The World Health Organization (WHO) estimated that prevalence of diabetes among adults in the world would increaseto300 million by 2025 (7, 8). 3.78 million cases of DM (2.74 million diagnosed and 1.04 million undiagnosed) is founded in Iran in 2009 and it is expected to rise to 9.24 million cases (6.73 millions diagnosed and 2.50 millions undiagnosed) by 2030 (9). It is estimate that, the diabetes' costs over 245 billion dollars a year (10).

The main reason of the secondary disorders of microanjiopathy and macroangiopathy, impaired antioxidant defense, osmotic pressure and lipid profile and metabolism, is the long-term (chronic) increase of glucose in diabetic patients. These disorders cause both short- and long-term complications. These complications cause damage to the physical and physiological function of various organs of the body and threaten human health. Meanwhile, late complications of diabetes mellitus (e.g., nephropathy, retinopathy, cardiovascular complications, neuropathy, skinulcer, hypertension and weight gain) are more common and more research has been done about them. The main biochemical result of chronic hyperglycemia of diabetes mellitus is glycation of proteins including structural proteins, regulatory proteins and proteins in the blood circulation. This will start a chain of chemical reactions of getting sugar including production of Schiff base, Amadorand Maillard products and in the end production of advanced glycation end-products (AGEs) which is a cause of diabetes complications (1, 3, 4, 11).

Table 1. Viruses associated with the pathogenesis of type 1 diabetes mellitus (12)

Virus	Host	Remarks
RNA viruses		
Picornaviridae Coxsackie virus B	Human	Evidence from epidemiologic studies, anecdotal reports, and isolated viruses causing diabetes in infected animals
	Nonhuman primates	Virus was passaged in monkey β-cells before infection; development of transient type 1 DM
	Mice	Virus was passaged in murine β-cells before infection; cytolytic destruction of β-cells leading to type 1 DM
Encephalomyocarditis virus	Mice	Cytolytic destruction of β-cells leading to type 1 DM; macrophages play a critical role in β-cell destruction in low-dose infections
Mengo virus	Mice	Cytolytic destruction of β-cells
Foot-and-mouth disease virus	Pigs, cattle	
Retroviridae Retrovirus	Human	Association of β-cell–specific expression of retroviral gene with development of human autoimmune type 1 DM
	Mice	Association of β-cell–specific expression of retroviral gene with development of insulitis and type 1 DM in NOD mice
Togaviridae Rubella virus	Human	Possible association with autoimmune type 1 DM, especially congenital rubella syndrome
	Hamsters Rabbits	Possible association with autoimmune type 1 DM
Bovine viral diarrhea-mucosal virus	Cattle	Suspected autoimmune response
Paramyxoviridae Mumps virus	Human	Possible induction of islet cell autoantibodies
Reoviridae Rotavirus	Human	Association with islet autoimmunity
Reovirus	Mice	Possible association with autoimmunity and diabetes in mice
DNA viruses *Parvoviridae* Kilham rat virus	Rats	No distinct infection of β-cells, but development of β-cell–specific autoimmunity leading to type 1 DM
Herpesviridae Cytomegalovirus	Human Rodents (*Octodondegu*)	Association with autoimmune type 1 DM
Epstein-Barr virus	Human	Possible induction of autoimmune type 1 DM
NOD, nonobese diabetic.		

There is a strong correlation between T1DMand specific alleles of the MHC II genes, especially HLA-DR and HLA-DQ (13, 14). Approximately 30-40% of T1DM patients are heterozygous for HLA-DR3/4 alleles (13-15). As well as a number of non-MHC genes, including the variable number of tandem repeat (VNTR) alleles upstream of the *INS/IGF2* (*IDDM2*) locus, *PTPN22*, *CCR5*, *IL2RA*, *IL10*, and *CTLA4* are found to be responsible for the genetic susceptibility to T1DM. On the other hand, more than 50% of monozygotic twins are discordant for the disease, like differences in age of onset of symptoms can show the role of nongenetic factors in T1DM (16, 17). It can mean that environmental factors such as viruses, dietary proteins, toxin and stress play an important role in the development ofT1DM (13).

For various reasons, such as seasonal incidence (It seems that there is a seasonal variation in the onset of acuteT1DM, with a peak in the autumn, one of the indicators in viral infection), viruses are one of the effective factors that involved in the etiology ofT1DM.Moreover, some viruses can prevent diabetes in animal models like mouse hepatitis virus (MHV) and Lymphocytic choriomeningitis virus (LCMV) (13). In 1899, Harris reported that

shortly after a mumps infection, diabetes developed in a patient (18). Since that time, there have been numerous reports that discussing about the role of different viruses (such as coxsackie B virus, viral hepatitis, EBV, VZV, CMV, rubella virus, mumps virus, rotavirus, retroviruses and parvovirus) in diabetes (13, 14, 16). In general viruses can be cause T1DM in two ways: first, directly infected and destruction of insulin-producing beta cell in pancreas and indirectly by operating the autoimmune destruction. This can be confirmed in studies that conducted on infected mice by EMCV(Encephalomyocarditis virus) (directly) and KRV in rats (indirectly) (13).

The mechanisms that can be used to induce or prevent diabetes by viruses will be reviewed here.

Viruses and Autoimmune Type 1 Diabetes

Virus infections have been associated with several autoimmune diseases such as multiple sclerosis, diabetes, myocarditis, autoimmune active chronic hepatitis, sjögrens syndrome, juvenile rheumatoid and arthritis and systemic lupus erythematosus. As a general rule, viruses can trigger autoimmune response in three ways: pancreatic infection, T cell molecular mimicry, and bystander activation. Viruses can infect beta cells or extra-pancreatic sites like the pancreatic lymph nodes (PLN) or the small intestine and lead to cytolysis or cell damage. Following the release of hideaway autoantigens, proinflammatory immune responses may contribute to diabetes progression. Molecular mimicry represents sequence similarity between viral and self-peptides that can initiate autoimmune response. Bystander activation is polyclonal lymphocyte activation in the absence of peptide presentation on MHCs, or B cells activation without antigen recognition (figure 1). So it is not antigen-specific and is distinct from direct pancreatic infection and the non-specific killing or damage of beta cells by virus-specific T cells. Indeed bystander activation involves dendritic cells (DCs) activation by pattern recognition receptor (PRR) like Toll-like receptors (TLR) and secretion of soluble cell-stimulating factors such as type I IFN. These factors induce the activation of bystander lymphocytes, including autoreactive T cells, which contribute to beta cell death. Bystander activation is depends on a pre-existing autoreactive cells population. Autoreactive T cells are present in human pancreas and can be expanded from the PLN of diabetic patients (19, 20).In the following section we will summarize the pathogenic mechanisms of virus-mediated autoimmune Type 1 Diabetes.

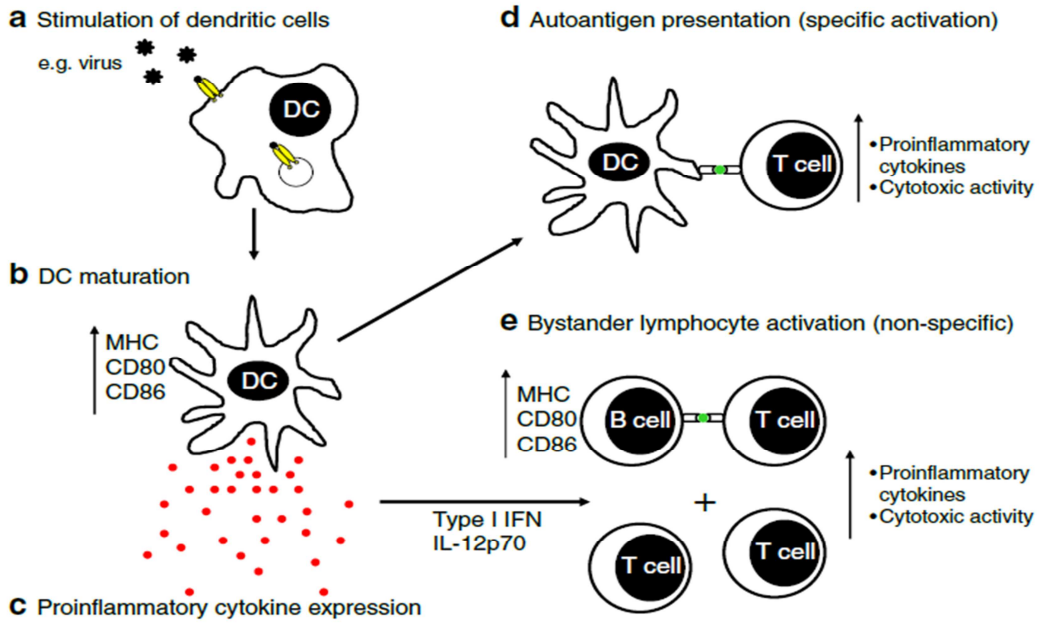

Fig. 1 Bystander activation of lymphocytes by DCs(20)

(a) DCs meeting a stimulator e. g. virus, which interact with Toll-like receptors. (b) Expression of MHC class I, MHC class II, CD80 and CD86. (c) Expression of proinflammatory cytokines. (d) Enhanced expression of MHC and co-factors also increases the ability of DCs antigen/autoantigen presenting and activation of autoreactive T cells. (e) Activation of non-specific bystander lymphocyte by secreted type I IFN and IL-12p70. Inducing of T cells expansion, including autoreactive T cells, upregulation of activation markers, secretion of proinflammatory

cytokines, such as TNF and IFNα, or increases in cytolytic activity. B cells may be activated, as shown by their elevated MHC class I, MHC class II, CD80 and CD86 expression, leading to further activation and expansion of autoreactive T cells.

Autoimmune T1D and Transgenic Mice for Viral Antigen

Some transgenic mice models (e. g. LCMV, influenza viral proteins and the Epstein-Barr viral receptor) have been designed to study virus-induced autoimmune diabetes. One of the best models is the rat insulin promoter (RIP)–lymphocytic choriomeningitis virus (LCMV) model that extensively has been used to study the role of molecular mimicry in diabetes (14).RIP-LCMV mice express some specific proteins of LCMV(GP, NP) under the control of the rat insulin promoter (RIP)in pancreatic beta cells. RIP-LCMV can show that sequential viral mimicry events can accelerate disease onset. When transgenic mice have been infected with LCMV, peripheral responsiveness to glycoprotein/nucleoprotein breaks and result in attack of β-cells by T-cells and eventual development of type 1 diabetes. This model stated that only when homology between viral and β-cell antigens is 100% viral infection can induce autoimmunity, so a single amino acid change can interfere with the development of type 1 diabetes. Indeed, molecular mimicry alone might not be capable of inducing type 1 diabetes but is an accelerator when autoimmunity has been started and viral infection can be a fortune to expressing the autoreactive T-cells and autoimmune disease (21).

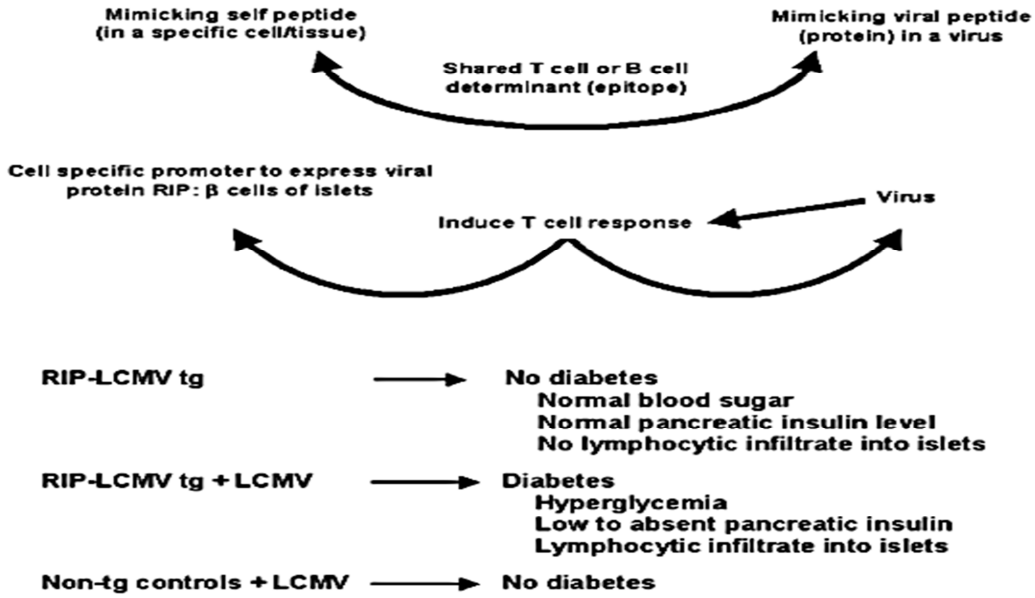

Fig. 2.Molecular mimicry and IDDM in transgenic mice

Kilham Rat Virus

Kilham rat virus (KRV) belongs to the *Parvoviridae* and originally isolated from a rat sarcoma. KRV cause a fatal neonatal disease, physical deformities and mental retardation in newborn rats (13, 14).It has been shown that KRV induces diabetes in diabetes-resistant-BioBreeding (DR-BB) rats by stimulating autoimmune responses against the beta cell. DR-BBratsare derived from diabetes-prone rats (DP-BB) but in contrast to them they don't develop diabetesnormally.2-4 weeks after infection of 21-25 days old DR-BB rats with KRV, 60% of them show diabetes or insulitis without diabetes. How KRV causes the destruction of beta cells without infection of them? May be the first idea that comes to mind is the molecular mimicry. Molecular mimicry represents a common immunologic epitope with a microbe and the host that can initiate autoimmune response. If molecular mimicry is involved in the initiation of beta cell-specific autoimmunity, so KRV antigen- specific T cells that generated by KRV peptides might cross-react with beta cells and destruct them. To test this hypothesis, recombinant vaccini a viruses (rVVs) that expressed KRV proteins (VP1, VP2 [completely overlapped by VP3]) were used. The wild type strain of vaccinia virus does not induce insulitis or diabetes in DR-BB rats. Infection of DR-BB rats with rVVs expressing the KRV peptides resulted in the generation of viral peptide-specific T cells and antibodies against the KRV peptides but none of the

DR-BB rats developed insulitis or diabetes. So molecular mimicry is unlikely to be a mechanism by which KRV induces beta cell-specific autoimmune diabetes(14).

Aimon K. Alkanani and et al. found that infection of rats with KRV results in the expression of KRV transcripts and protein in islets or beta cells from 5-day-infected rats. They have showed that KRV activates the JAK–STAT pathway in beta cells that results in signal induction of interferon type I and II. They said that KRV-induced islet destruction is associated with beta cell infection and intra-islet innate immune upregulation early in the disease process(22).

Another possibility is that infection of KRVin DR-BB rats (Ascan be seen in DP-BB rats) might disturb the finely tuned immune balance and activate auto-reactive T cells that are cytotoxic to beta cells. To test this hypothesis, after KRV infection in DR-BB rats the $CD4^+$ and $CD8^+$ T cell populations were examined in the splenocytes. During KRV infectionthe total number of both $CD4^+$ and $CD8^+$ T cells was increased but the percentage of $CD8^+$ T cells increased considerably, whereas the percentage of $CD4^+$ T cells decreased. As compared with $CD4^+$ T cells in KRV-infected DR-BB rats, $CD8^+$ T cells preferentially proliferated. Since treatment of KRV-infected DR-BB rats with OX-8 (anti-CD8) monoclonal antibody, significantly decreased the incidence of diabetes in these rats, it can be concluded thatCD8+ T cells are clearly involved in the destruction of beta cells, although the possibility involvement of NK cells cannot be excluded, because OX-8 monoclonal antibody also depletes NK cells. Ellerman and et al. reported that the treatment of DP-BB rats with anti-NK cell antibody failed to prevent diabetes, while OX-8 monoclonal antibody treatment successfully prevented diabetes.

During the recent years using biomarkers for predicting disease progression or predicting treatment response has been dramatically developed (23-27). We know that the immune balance between Th1- and Th2-type cells plays an important role in the maintenance of peripheral tolerance. In the rat, $CD4^+$ T cells can be divided into Th1-like $CD45RC^+CD4^+$ T cells(expressing IL-2 and IFNγ and play an important role in cell-mediated immune responses) and Th2-like $CD45RC^-$ $CD4^+$ T cells(expressing IL-4 and IL-10 and play an important role in humoral immune responses).The dominance of Th1 cells over Th2 cells is associated with the development of autoimmune type 1 diabetes and the dominance of Th2 cells over Th1 cells is associated with the prevention of type 1 diabetes. It is suggesting that the proportions of Th1 and Th2 cells are altered during the infection of DR-BB rats with KRV because of increased expression of Th1-type cytokines in the splenocytes and pancreatic infiltrates.

Chung et al. showed that in compared with PBS treated controls; the number of Th2-like $CD45RC^-CD4^+$T cells was significantly decreased and the number of Th1-like $CD45RC^+CD4^+$T cells significantly increased in the splenocytes of KRV-infected DR-BB rats. In addition, Chung YH and et al. showed that when both$CD45RC^+$ $CD4^+$ and $CD8^+$ T cells(isolated from KRV-infected DR-BB rats)were transferred to DP-BB rats could induce diabetes in 88% of them. This result suggests that $CD45RC^+$ $CD4^+$ and $CD8^+$T cells are major effector T cells that can induce autoimmune diabetes. On the other side, in DP-BB rats that received either $CD45RC^+CD4^+$or $CD8^+$T cells alone the incidence of diabetes significantly was lower as compared with that in rats that received a combination of$CD45RC^+CD4^+$and $CD8^+$T cells. So it can concluded that Th1-like $CD4^+$ and $CD8^+$T cells from KRV-infected rats work synergistically to destroy pancreatic beta cells. In addition, none of the recipients of both $CD45RC^-CD4^+$and $CD8^+$T cells developed diabetes, indicating that these cells have a regulatory role. Recent studies also clearly showed that the development of KRV-induced diabetes could be due to the failure to maintain the function of regulatory T cells ($CD4^+CD25^+$T cells).

Increasing of Th1-type cytokines and notTh2-type cytokines could be the result of selective increased production and secretion of IL12 by activated macrophages. Concanavalin-A (ConA)-activated splenic lymphocytes isolated from macrophage-depleted DR-BB rats injected with KRV/poly I:C did not induce insulitis and diabetes in young DP-BB rats, indicating that macrophages are essential for the initiation of diabetes by KRV and depletion of them can result in the loss of ability to transfer diabetes. In addition, deactivation of macrophages by dichloromethylene diphosphonate (lip-Cl_2MDP) that causes selective apoptosis of macrophages, nearly result incomplete protection against diabetes and insulitis in mice infected with KRV. On the basis of these observations, we can conclude that the likely mechanisms of KRV infection in DR-BB rats is the preferential activation of effector T cells, such as Th1-like $CD45RC^+CD4^+$ T cells and $CD8^+$ T cells and the down-regulation of Th2-like $CD45RC^-CD4^+$ and $CD4^+CD25^+$ T cells, that resulting in killing of beta cells (13, 14).

Retroviruses

Transposable elements (TEs) are mobile genetic elements that found in large parts of the genome (for example, about 50% of human genome) in eukaryotes. Generally, TEs are classified into two Classes: class I (called retro transposons or retro elements), which use an RNA intermediate for transposition; and Class II including DNA transposons which replicate by a cut-and-paste mechanism and without an RNA intermediate. Class I elements divide into two major subclasses based on long terminal repeats (LTRs), retro elements (REs) with LTRs and elements without LTRs (non-LTR REs) (28, 29). Endogenous retroviruses (ERVs) consist of two identical single-stranded RNA with positive polarities that are linked together by hydrogen bonds at their 5' termini. The virion contains a reverse transcriptase enzyme to produce a DNA copy from the genome (14). Because of their ability to translocation and insertion next to certain genes involved in immune regulation (displacement of such retroelement can cause pathogenic changes in very sensitive fragments of the genome) or expression of their encoded proteins (that can be regarded as a foreign and induce cross-react Abs) they can cause autoimmune diseases. Furthermore, it should be pointed out that their proteins may act as superantigens and develop auto reactive T lymphocytes. The association of human endogenous retroviruses (HERVs) with some cancers have been found, insulin-dependent diabetes mellitus, nervous system diseases (especially multiple sclerosis), schizophrenia and autoimmune rheumatic and connective tissue diseases (30, 31).

Electron microscope have shown retrovirus-like particles in the cytoplasm of beta cells of T1D patients who died shortly after the onset of diabetes, but not in the non-diabetic controls. None of the non-diabetic pancreata showed any features of insulitis but all the cases of diabetic patients show insulitis with infiltration of macrophages, $CD8^+$ T lymphocytes and NK cells, with a minority of $CD4^+$T-helper lymphocytes. The most possibility is that retroviral antigen release from beta cells and then presented to $CD4^+$ Tcells by antigen presenting cells. These activated $CD4^+$ Tcells secret IL2which amplifiesretroviral antigen-specific $CD8^+$ cytotoxic T cells that destruct beta cells. It is reported that a HERV superantigen IDDMK (1,2) 22 may cause type I diabetes by activating autoreactive T cells. The expression of the HERV-K18 provirus encoding superantigen, is inducible by IFNα that subsequently stimulates Vβ7 T cells (correlated with the onset of T1D) (14, 32).

There are several studies that show the relationship between expression of ERVs by beta cells and insulitis and T1D in NOD mice. The presence of type A and type C retrovirus in NOD mice Beta cells have been reported that can show a role of retrovirus in the development of insulitis and autoimmune T1D in these mice. Maybe the existence of these elements and presentation of their antigens by antigen presenting cells (APCs) in beta cell causes activation of $CD4^+$ T cells. This idea has been supported by elimination of macrophages that resulted in prevention of autoimmune response in NOD mice. Also they can alter the expression of beta cells genes. These altered antigens can induce auto immune response.In addition, it is possible that cellular proteins taken up in the retroviral envelope or that IFN-α-induced expression of HLA-II may trigger an autoimmune response (14).

ERVs also have been associated to human T1D. Hao W and et al. tested the cross reactivity of insulin autoantibodies and insulin antibodies associated with human IDDM with retroviral protein p73. They found that anti-insulin autoantibody-positive sera contain antibodies that recognize both insulin and p73. This indicating insulin autoantibodies and insulin antibodies recognize a common epitope between human insulin and retroviral antigen p73. Based on these finding it is suggested that retroviruses maybe involved in the pathogenesis of autoimmune T1D in humans (14, 33).

Reoviridae

The *Reoviridae* are double-stranded and segmented RNA viruses that can cause the gastrointestinal and respiratory tract infection. Reovirus has also been associated with T1D in animals. T Onodera and colleagues reported that when Reovirus type 3 that has been passaged in pancreatic beta-cell cultures inoculate into 1- to 2-week-old mice, can produced an insulitis. They could find reovirus antigens in beta cells by a double-label antibody technique (fluorescein-labeled antibody to reovirus and rhodamine-labeled antibody to insulin). Also they could show viral particles in different stages of morphogenesis were observed in insulin-containing beta cells by electron microscopy. The infection resulted in destruction of beta cells, reduction in the insulin content of the pancreas, and alteration in the host's capacity to respond normally to a glucose tolerance test (34).

Some of the autoantibodies against insulin and growth hormone have been showed by absorption studies and enzyme-linked immunosorbent. Reovirus type 3, in contrast to reovirus type 1, did not induce autoantibodies to growth hormone. By recombinant viruses, the segment of the reovirus genome responsible for the induction of

autoantibodies to growth hormone was identified. Virus containing the S1 gene segment (codes for the sigma 1 polypeptide)from reovirus type 1, infected cells in the anterior pituitary and induced autoantibodies to growth hormone, whereas virus containing the S1 gene segment from reovirus type 3 failed to infect cells and did not induce autoantibodies to growth hormone (35).

Onodera T and et al. in another study stated that reovirus type 1 induces autoantibodies reacting with surface antigens of beta cells and treatment by immunosuppressive agents prevent autoimmunity and polyendocrine disease (36).

There is some evidences that showed reovirus type-2 can induce autoimmune diabetes in new born DBA/1mice, which may be mediated by Th1 response to increased expression of IL-12 and IL-18 (37).

Reovirus type-3 also can infect human beta cells in vitro and the ability of this virus to infect human B cells is enhanced by serial passage in human pancreatic cell cultures and the infection resulted in the destruction of B cells and release of insulin (38).

Rotavirus

Rotavirus belongs to *Reoviridae* family and its infection has been proposed to enhance progression towards type 1 diabetes in at-risk children. Diabetes onset can be accelerated in NOD and T cell receptor transgenic NOD8.3 mice by rhesus monkey rotavirus (RRV). The rotavirus VP7 can be resembled with human islet autoantigen-2 (IA-2)-specific CD4+ T cells. The binding affinity of rotavirus VP7 to high-risk HLA class II molecules is comparable with IA-2. VP7 did not induce activation or proliferation of NOD8.3 mouse T cells so, molecular mimicry is not contributing the accelerated diabetes. Based on some studies, RRV induces B and T lymphocyte activation by triggering endosomal TLR7 responses in DC and the secretion of type I IFN. So, bystander activation is a possible role in type 1 diabetes acceleration by RRV (19, 39).

Picornaviridae

The members of *Picornaviridae*are non-enveloped, positive-stranded RNA viruses with an icosahedralcapsid. Several member of this family such as Coxsackie virus, Encephalomyocarditis virus, Foot-and-mouth disease virus and mengo virus have been associated with the development of type 1 diabetes mellitus (IDDM) in humans and animals (13). We will summarize the mechanisms of these viruses to induce diabetes.

Coxsackie Virus

There have been numerous epidemiological studies that showing the association of Coxsackie viruses (A and B) infections in humans and IDDM. These studies have reported significant differences in Coxsackie B (and A) viruses specific IgMand T cells responses (usually Coxsackie B4) between patients with T1D and non-diabetic controls. There are many evidences that support the correlation of Coxsackie B virus and T1D, for example Coxsackie B4 virus antigens and antibody were detected in the clinical specimens of a child that died because of diabetes and myocarditis or a boy that died of diabetes showed lymphocytic infiltration in beta cell and islets autopsy and so on. Coxsackie B3 and B4 viruses can infect human beta cells in vitro and disturb the metabolism of these cells. In animals, the capacity of Coxsackie B4 virus to induce diabetes affected by the genetic background of the host, and not all virus strains can cause diabetes. In fact the genetic and physiological properties of virus and host can determine the outcome of infection so, this can explain that why just rare variant of Coxsackie B4 virus (E2 strain of Coxsackie B4 virus) are associated with T1D (14).

Coxsackie B4 virus is strongly associated with T1D in humans. The virus is cytolytic and has sequence similarity, P2C a non-capsid protein (induces and associates with structural rearrangements of intracellular membranes) with islet autoantigen glutamic acid decarboxylase (GAD) and conflicting evidence have been found about existence of antibodies against both P2C and GAD. Moreover, the Coxsackie B4 infection can increase the beta cells expression of GAD (14).The first mechanism for Coxsackie B4 virus to induce diabetes is molecular mimicry, in fact activation of autoreactive T-cells following of Coxsackie B4 virus infection was proposed to occur by molecular mimicry. Although further studies have shown that Cross-reactivity between P2C and GAD was proposed to account for the capacity of CVB4 to induce type 1 diabetes in genetically predisposed humans. Moreover, Marc S. Horwitz and et al. reported that local infection with Coxsackie virus and subsequently inflammation, tissue damage and releasing of hidden langerhans antigen leads to stimulation of autoreactive T cells that can induce diabetes. So a by standard model and not molecular mimicry is the mechanism of Coxsackie viruses to induce diabetes and cross-reactivity

between P2C and GAD may act as an essential enhancer of disease once autoimmune attack of beta cells has been initiated (14, 21, 40).

A third strategy is the persistence of defective Coxsackie B virus in beta cells. This persistent infection can result in expression of IFN-α and chemokine which in turn could activate macrophages and T cells which can ultimately lead to beta cells death and T1D (14).

Encephalomyocarditis Virus

Diabetogenic variants of Encephalomyocarditis virus (EMC) can induce diabetes in animals. The diabetogenic variants of EMC (EMC-M) selectively infects beta cells of mice. As usual, diabetes induced by M variant of EMC (especially subtype D) is under genetic control of host and virus. Studies have showed that a single amino acid residue at position 776 of the poly protein determines viral diabetogenicity. The ability of the EMC to induce diabetes have been evaluated in several studies. In one method, the mice were injected with high dose of EMC virus (10^5PFU/mouse) that results in extensive destruction of beta cells and diabetes three days after injection. Studies show that the diabetes induced in this form has caused by destruction of beta cells as a result of viral replication rather than humoral or cellular immune responses. In fact, the active proliferation of the virus in beta cells can cause migration of macrophages and secretion of cytokines like IL-1, TNF-α, IFN-γ and nitric oxide at the center of infection and finally results in cells destruction and diabetes. In another study, mice were infected with a low dose (100 PFU/mouse) of EMC-D virus. In this model, macrophages play a key role in the development and progression of diabetes in a way that elimination of macrophages and theirs mediators prior to infection can completely prevents diabetes. Therefore, we can conclude that selective destruction of beta cells by EMC virus by accompany of macrophages is the main mechanism in EMC virus induced diabetes (13, 14).

Mengo Virus

Mengovirus is a member of genus cardio virus of Picornaviridae. Mangovirus is anti-genetically similar to EMC virus and like it causes fatal encephalitis in mice. Mengovirus2T can cause diabetes in mice resistant to the EMC-D. Evidence suggests that, like EMC Virus, Mengovirus leads to diabetes by direct infection and destruction of beta cells. Pancreas of mice infected with Mengovirus2Tshowlarge necrosis and inflammation without evidence of the autoimmune responses. This virus uses of different receptors for infection of beta-cell than EMC virus and this can cause difference in strain susceptibility between the two viruses.

Paramyxoviridae

Mumps virus

The mumps virus is an enveloped single-stranded RNA virus belonging to the paramyxoviridae. Mumps virus was one of the first viruses implicated in the development of human T1D. Several studies have shown that type 1 diabetes in childhood often coincides with viral infections such as measles, mumps, and rubella (MMR). Churku Mohan Reddy in 1976 reported that an 11 years old girl was suffering from mumps infection developed diabetes. Studies show that mumps virus can infect and replicate in beta cells and following this increase of HLA class I and II molecules and IL-6 and IL-1can be observed. The hypothesis is that the increased cytokines and HLAmolecules may induce an immune response against the beta cells or may increase pre-existing autoimmune against these cells. In addition many studies have investigated the effect of mumps vaccination on diabetes, except one study that say the mumps vaccination can decrease the risk of T1D the rest studies concluded that there is no association with childhood mumps vaccinations and increasing or decreasing the incidence of T1D (14).

Togaviridae

Rubella virus

Rubella virus is a member of togaviridae, viruses with single RNA and enveloped. It has been observedthat10-20 %of patients with congenital rubella syndrome (CRS); develop diabetes between the ages of 5-20 years. The presence of auto antibodies against beta cells shows the autoimmune basis in this disease. Rubella virus is able to directly infect beta cells. Human fetal islets exposed to rubella virus contained rubella viral antigens in both beta and non-beta cells and had lowered levels of insulin production without any demonstrable cytopathology. Rubella virus antigens on the surface of the beta cells can triggers beta cells specific autoimmunity. Instead *in vitro* studies suggest a molecular mimicry for rubella virus to induce autoimmune T1D since one monoclonal antibody that recognized a domain within the rubella virus capsid protein was found to react with extracts from rat and human islets, as well as with extracts from a rat insulinoma line. Further studies shows that T cells of diabetic patients recognize cross-reactive protein determinants from rubella virus and glutamic acid decarboxylase (GAD), which is considered to be

an important cell autoantigens in the pathogenesis of T1D. So, it can be concluded that in some cases rubella virus can induce generation of cross-reactive T cells (14).

Herpesviridae

Cytomegalovirus

Cytomegalovirus (CMV) is a member of Herpesviridae. Within Herpesviridae, CMV belongs to the Betaherpesvirinae subfamily and is a double-stranded DNA and enveloped virus. CMV infection occurs earlier in life and is widespread and can be a congenital virus. There are so many studies that show the participation of CMV in T1D. Chin Y. Pak in 1988 did a study to investigate association of CMV infection with autoimmune type 1diabetes. For this purpose, the lymphocytes of 59 newly diagnosed type 1 diabetic patients and 38 normal control subjects were examined for the presence of CMV genome by molecular hybridizations with human CMV specific probe. The CMV genome was found in 13 (22%) of 59 diabetic patients, but in 1 (2.6%) of 38 control subjects. Chin Y. Pak has reported that CMV persistent infection may be associated with diabetes. In some cases of CMV-induced diabetes molecular mimicry may be involved as immune response to CMV antigens that can trigger autoimmunity against beta cells. Chin Y. Pak in another study has reported that CMV can induce antibodies that react with a 38 kilodalt on human islet cells. In addition in one study has been stated that a clone of CD4+ T cells specific for GAD65 also can response to a CMV major DNA binding protein. Soin general it can be concluded that CMV may be involved in the induction of autoimmunity by molecular mimicry (14).

Epstein-bar virus

The Epstein–Barr virus (EBV), also called human herpesvirus 4 (HHV-4), is a member of Herpesviridae. It has been said that EBV can cause autoimmune diseases and there is some evidence that this virus has associated with T1D. According to some similar sequences between EBV epitopes and HLA sequences (like a penta peptide sequence in the Asp-57 region of the HLADQβ chain and EBVBERF4- encoded epitope), it is suggested that EBV can be induce T1D by molecular mimicry in spite of all that, further investigation is needed to find the relationship between EBV and T1D.

Orthomyxoviridae

The Orthomyxoviruses are a family of RNA viruses that consists of three types (species) of influenza virus: A, B, and C. Recent studies suggest a possible link between pandemic H1N1 influenza a virus infection and diabetes development in humans. Double transgenic mice expressing HA in β-cells and with a T-cell receptor specific to MHC class II–presented HA peptide showed only mild insulitis, but no diabetes (41). Influenza A virus induced significantly more DC-dependent IFNα secretion in diabetic patient in contrast to control group (20). By the way however, its involvement in human diabetes remains unclear.

Hepatitis C Virus

Hepatitis C virus (HCV) is a single member of the Hepacivirus genus of the *Flaviviridae* family. HCV is a major cause of acute and chronic liver disease worldwide. This virus is not only a cause of chronic liver diseases, but it is also involved in the pathogenesis of various autoimmune and rheumatic disorders (e.g., arthritis, vasculitis, sicca syndrome, porphyria cutanea tarda, lichen planus, nephropathies, and lung fibrosis) and in the development of B-cell lymphoproliferative diseases. CHC is associated with some extrahepatic manifestations, including endocrinological disorders, thyroid disorders and diabetes. Many studies have investigated the relationship between HCV and diabetes. A small number of studies indicate that interferon-α therapy can induce T1DM.Association of CHC with T2DM seems to involve by direct effects of viral infection, insulin resistance, proinflammatory cytokines and chemokines. Studies have shown a higher prevalence of DM in patients with HCV seropositive than controls without HCV infection. Khan I.A and colleague have done across sectional study to determine a relationship between the relative proportions of diabetes mellitus in patients suffering from HCV infection. They analyzed 164 hepatitis C infected and 94 hepatitis B infected cases.16.46% hepatitis C infected cases were diagnosed as diabetics while 4.25% hepatitis B infected cases were diagnosed as diabetics. This study concludes that there is a high association and relationship of diabetes mellitus with Hepatitis C virus infection as compared with Hepatitis B virus infection. In the case of T2DM, the phosphorylation of insulin receptorsubstrate-1 (IRS-1) that is the basis of insulin resistance can be increased by HCV core protein. By the way the precise molecular pathogenesis of the glucose metabolism disturbances that can be seen in HCV is much more complex. In addition to the direct effects of the virus onIRS-1/PI3K,HCV core protein can be indirectly lead to insulin resistance by induction or suppression of immune responses; cytokines (IL-6, TNF-α) and chemokines. Also, Proinflammatory cytokines can cause suppression of cytokine production as a part of anegative feedback that can leads to gluconeogenesis because of

Akt-mediated inhibition of phosphor enolpyruvate carboxy kinase gene expression. On the other side, the effect of TNF-α on the lipids metabolism can increase serum levels of free fatty acids followed by reduction of insulin sensitivity. It is declare that dysregulation of the cytokine/chemokine network, involving proinflammatory and Th1chemokines is the most important systemic HCV-related extrahepatic diseases (mixed cryoglobulinemia, lymphoproliferative disorders, thyroid autoimmune disorders, and T2DM).

Few data have been reported about association of HCV-infected patients with T1DM, but some studies reported that HCV may initiate an immune reaction against β-cells or cause an acceleration of diabetes onset when an immune reaction against β-cells is already started. In addition, a molecular mimicry mechanism also has been suggested. Antigenic regions of the HCV polyprotein shares amino acid sequence similarities not only with GAD 65, also with other microbial agents. Indeed, molecular mimicry beside proinflammatory cytokines such as IL-18, TNF-α and IL-1β can induce autoimmune diabetes. It is reported that HCV infection may up regulate CXC chemokine ligand (CXCL) 10 gene expression and subsequently recruitment of Th1and that secrete interferon IFN-γ and TNF-α. Ultimately, this leads to high serum levels of CXCL10 in HCV demonstrating higher serum levels of CXCL10 in HCV patients with T2DM than in those without. Nonetheless, many scientists haven't seen any connection between HCV and diabetes; For example, Alessandra Mangia and et al disproved HCV infection as a trigger factor for DM. Further studies are needed to understand the relationship between HCV with diabetes(2).

CONCLUSION

Diabetes mellitus is the most common and complex problems in modern societies that causes many social and economic problems (1). It has been found that chronic high blood sugar can increase glycation of inside and outside of cellular proteins in patients with diabetes mellitus. Since the function of each protein is depend on its natural structure, glycation can change the structure and function of a variety of proteins in diabetic patients and cause many secondary complications of diabetes (3, 4). Because of the heterogeneous etiology of diabetes there is an increasing interest in finding the factors which influence its etiology and progression. Environmental factors such as viruses, dietary proteins, toxin and stress can play an important role in the development of T1DM.For various reasons, such as seasonal incidence (It seems that there is a seasonal variation in the onset of acuteT1DM, with a peak in the autumn, one of the indicators in viral infection), viruses are one of the effective factors that involved in the etiology of T1DM (13). In 1899, Harris reported that shortly after a mumps infection, diabetes developed in a patient (18). Since that time, there have been numerous reports that discussing about the role of different viruses (such as coxsackie B virus, viral hepatitis, EBV, VZV, CMV, rubella virus, mumps virus, rotavirus, retroviruses and parvovirus) in diabetes (13, 14, 16). Moreover, some viruses can prevent diabetes in animal models like mouse hepatitis virus (MHV) and Lymphocytic chorio meningitis virus (LCMV).

As a general rule, viruses can trigger autoimmune response in three ways: pancreatic infection, T cell molecular mimicry and bystander activation. Viruses can infect beta cells or extra-pancreatic sites like the pancreatic lymph nodes (PLN) or the small intestine and lead to cytolysis or cell damage. Following the release of hideaway autoantigens, proinflammatory immune responses may contribute to diabetes progression. Molecular mimicry represents sequence similarity between viral and self-peptides that can initiate autoimmune response. Such mimics have been identified in several viruses including group B coxsackie virus and rotavirus. Despite classical examples of molecular mimicry in inducing autoimmunity like rheumatic fever, today there is no supporting data for a direct role of this mechanism in development of T1D by viruses except RIP-LCMV mice that express some specific proteins of LCMV under the control of the rat insulin promoter (RIP). The RIP-LCMV model extensively has been used to study the role of molecular mimicry in diabetes and it can show that sequential viral mimicry events can accelerate disease onset. Bystander activation includes Tcell activation in absence of peptide presentation on MHCs, or B cell activation without antigen recognition. It is distinct from direct pancreatic infection and the non-specific killing or damage of beta cells by virus-specific Tcells. Bystander activation is depending on a pre-existing autoreactive cells population. Pre-existing autoreactive cells suggests that bystander activation rather than initiating beta cell damage accelerates disease progression and could be an explanation to viral modulation of diabetes in the absence of virus in the pancreas. Evidence suggests that diabetes-prone mice and humans tend to respond much more to these bystander responses to viruses. This shows a role for interaction between virus infection and genetic predisposition. Recent studies have been emphasized on bystander activation as a possible mechanism that triggered by viruses (CVB, rotavirus, influenza, mumps) to accelerate diabetes onset.

By the way, it should be noted that viruses cannot be as a sole environmental triggers and all factors in development of diabetes may not be identifiable. So, further studies should be conducted to show whether the autoreactive T cells or viruses are present in other remote sites like PLN and as well as inducing bystander lymphocyte activation may contribute to diabetes progression in susceptible individuals.

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