Diabetes Mellitus and Viruses: A Review

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This review article discusses one aspect of diabetes mellitus which is a serious disease that remains a worldwide health problem. The points discussed are related to viruses which could be aetiologic agents for diabetes mellitus. The purpose of this article is to shed more light on viruses and their relationship to diabetes mellitus and to stress the need for conducting more studies in order to reach a better understanding of the pathogenesis of the disease. This in turn might strengthen the measures available to prevent and control this disease.

Under certain circumstances, some viruses, especially the Coxackievirus, are capable of infecting pancreatic beta cells. The destruction of the beta cells may actually alter the physiology of the pancreas and contribute to abnormal glucose metabolism leading to diabetes mellitus.

Insulinopenic Diabetes (IDDDM) due to Defective Pancreatic Beta Cell Function, May Have Many Causes\(^1\)-\(^2\)

Genetic defects
Genetic defects can interfere with proper insulin synthesis, storage, or release; or the beta cells may be unable to recognize glucose signals or even to replicate normally.

Extrinsic factors
Extrinsic factors that affect beta cell function include damage caused by some viruses such as mumps,\(^1\)-\(^4\) by destructive cytotoxins\(^5\)-\(^8\) or by auto-digestion in the course of an inflammatory disorder involving the adjacent exocrine pancreas.\(^2\) An underlying genetic defect in beta cell replication or function may predispose to development of beta cell failure after viral infection, and specific HLA (human lymphocyte antigens) genes may increase the susceptibility to a diabetogenic virus or be linked to certain immune response genes that predispose patients to a destructive autoimmune response against their own islet cells. Certain HLA antigens e.g. B8, BW15, DW3, and DW4 are highly associated with the development of type I diabetes.\(^4\)-\(^6\) Their genetic determinants, located on the sixth human chromosome adjacent to the immune response genes, show linkage to the genetic determinants of type I diabetes.\(^1\) It was postulated that certain human lymphocyte antigens (HLA) may code for virus receptors on the surface of beta cells; such coding would permit the absorption and penetration of specific viruses into the cells.\(^1\) So the antibody represents an immune response to components of the islet cells that have been altered by viruses or toxic chemicals. In the most severe form of type I diabetes circulating islet cell antibodies have been detected in as many as 85% of patients tested in the first weeks of their diabetes.\(^1\) In contrast, HLA linkage and islet cell antibodies are not a feature of type II diabetes.\(^7\) There is also some evidence that the incidence of type I diabetes is higher in the autumn and winter and that early in
the course of the diabetes, inflammatory cells are sometimes formed in the islets.8

**Viruses May be Aetiologic Agents for Insulin-dependent Diabetes Mellitus**

**Mumps**
The mumps virus particle has the typical paramyxovirus morphology: it is enveloped, ether-sensitive and has a ribonucleo-protein nucleocapsid. Scattered case reports suggest that human diabetes mellitus may follow mumps.3,4-11

In one example, two siblings with no family history of diabetes mellitus developed diabetes less than 1 month after having mumps following a household outbreak of mumps.1

Sultz and his associates12 noted an increase in the prevalence of new cases of diabetes in Erie County, New York, several years after community outbreaks of mumps.

If, in fact, mumps does infect beta cells and produce diabetes mellitus, it must do so only under very special circumstances, that is, a particular strain of mumps virus must be involved or the individual who develops diabetes must have an unusual, possibly genetically determined, susceptibility to the virus. Otherwise, it would be very difficult to explain why so few people develop diabetes even though millions have had clinical episodes of mumps.

**Congenital rubella**
Rubella virus is an RNA-containing, ether-sensitive virus. Some workers thought that the pathogenesis of diabetes in patients with congenital rubella is caused by the rubella virus.13 Several case reports attest to the development of diabetes in young children with a well documented, congenitally acquired infection.13 The most compelling evidence is derived from an Australian study of individuals with the stigmata of congenital rubella syndrome14 who exhibited either abnormal carbohydrate metabolism or frank diabetes.

**Encephalomyocarditis (EMC) virus**
This RNA agent belongs to the picornavirus family. Infection of mice with the M variant of EMC virus results in beta cell damage and a clinical picture characteristic of diabetes.15-17 Increasing data suggest a possible viral aetiology of IDDM onset.18 The severity of the diabetes-like syndrome was found to correlate closely with the degree of viral-induced beta cell damage19 which could be detected 48 h after infection. Craighead and coworkers15 have provided experimental evidence that mice infected with a strain of EMC virus may develop damage to the beta cells of the pancreatic islets with a resultant "diabetic-like" state. But the fact that EMC virus is not a common human pathogen appears to preclude the possibility that EMC virus itself is involved in human diabetes.

**Reovirus**
Reovirus particles are about 60-80 nm in diameter and are ether-resistant. Reoviruses possess two distinct capsid shells. The outer shell can be digested by chymotrypsin to reveal the virus core, which has 12 short spikes at the vertices of an icosahedron. About 15% of the virus particle weight is RNA, which includes the double-stranded RNA genome and many small pieces of single-stranded RNA. The unique feature of the reovirus genome is that it exists as a collection of 10 discrete segments. Viruses of this group are infectious for a wide variety of animals, including man. In 1978, Reovirus type 3 that was passaged in pancreatic beta cell cultures, produced an insulinis when inoculated into 1- to 2-week-old mice.20 Reovirus was found in beta cells and the infection resulted in the 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. This virus appears to be pantrropic in as much as virus can be recovered from a variety of organs, and lesions are found during the acute and convalescent stages of infection.

**Cytomegalovirus**
Cytomegalovirus (CMV) is a double-stranded DNA herpes virus. Cytomegalovirus infection has been suggested as a cause of the fatal acute necrotizing pancreatitis which occasionally develops in recipients of renal allografts and immunosuppressive drugs21 although concrete evidence to support this possibility is lacking. Diabetes mellitus could be a complication of congenital CMV infection.22 Whether diabetes can occur as a late complication of inapparent neonatal infection has not been adequately studied.

**Herpes zoster**
Herpes zoster (HZ) is a member of the herpes virus group. It is a DNA virus. A potential role of herpes zoster in a viral pathogenesis of diabetes mellitus23 has been suggested. More attention, however, has been given to the possibility that diabetes mellitus is a predisposing factor for herpes zoster infection. But the incidence of diabetes mellitus in patients with herpes zoster is the same as in the general population, and the subsequent incidence of diabetes mellitus in patients with herpes zoster is the same as in the general population.24 These observations are strong evidence against an association between herpes zoster and diabetes mellitus based on anything more than chance.
Human Venezuelan equine encephalitis (HVEE) This virus belongs to the family Togaviridae, whose members have a single-stranded RNA genome. The prevalence of antibodies to HVEE virus was investigated in a general diabetic population and there was no statistically significant difference from a control group. A selected study in a group of children recognized and treated as having diabetes type I revealed an absence of antibodies to HVEE virus, indicating that in these particular cases, there was no participation of the virus in the development of the disease. These results do not indicate the existence of a role of HVEE virus in the aetiology of diabetes in man; however, glucose intolerance due to HVEE may be a rare phenomenon and it deserves further prospective study in the course of epidemics.

Coxsackie viruses These small (20–30 nm) ether-resistant Picornaviruses contain single-stranded RNA and exhibit cubic symmetry. The coxsackie viruses comprise a large subgroup of the enteroviruses. They produce a variety of illness in human beings, including aseptic meningitis, herpangina, pleurodynia, hand-foot-mouth disease, myo- and pericarditis, common colds and possibly diabetes. The coxsackie viruses have been divided into two groups, A and B. It was reported that Coxsackie B virus may be associated with human diabetes and that there is a higher prevalence of antibodies to Coxsackie B virus in individuals with IDDM of recent onset than in controls or long-term diabetics.

The sudden onset of IDDM was observed in a 16-month-old infant, with no family history of diabetes mellitus, after a Coxsackie B5 infection. Other investigators reported the case of a healthy 10-year-old boy who was admitted to the hospital in diabetic ketoacidosis within 3 days of the onset of symptoms of a flu-like illness. He died 7 days later and postmortem examination showed lymphocytic infiltration of the islets of Langerhans and necrosis. Serologic studies revealed a rise in the titre of neutralizing antibody to this virus from less than 4 on the second hospital day to 32 on the day of death. Neutralizing data showed that the virus was related to a diabetogenic variant derived from Coxsackie B4. Inoculation of mice with the human isolate produced hyperglycaemia, inflammatory cells in the islets of Langerhans and beta cell necrosis. Staining of mouse pancreatic sections with fluorescein-labelled antiviral antibody revealed viral antigens in beta cells. Both the clinical picture and animal studies suggested that the patient’s diabetes was virus-induced.

Positive results were reported that in nine of twelve cases of IDDM which were investigated for evidence that a specific viral infection might be aetiologically related to their occurrence. In this study, mild diabetics had experienced a recent 'viral-like' illness, predominantly respiratory, but these illnesses bore no uniform temporal relation to the onset of diabetes. Elevated titres to only one virus, Coxsackie B3, were more prevalent in diabetics than in controls (33% vs 6%). So there is evidence that infection by Coxsackie B viruses can serve as an environmental ‘trigger’ for insulin-dependent diabetes mellitus (IDDM). Conclusion

A possible role of viruses in the pathogenesis of non-insulin-dependent diabetes has been suggested. In 20% of the cases of non-insulin-dependent diabetes in which the pancreas was examined at autopsy, no abnormalities were detected.

A diabetogenic virus may replicate in the pancreas and/or another tissue and thereby produce either transient or sustained diabetes in the host. Another factor that relates to the susceptibility of a host to subsequent development of diabetes is immuno-incompetence at the time of the viral infection. Viral replication in the islets and modification of islet cells may lead to the appearance of antibodies directed against islet-cell determinants e.g. ICA (islet cell antibody) and ICSA (islet cell surface antibody). The role of ICA and ICSA in the pathogenesis of diabetes mellitus remains to be determined. Metabolic factors may modulate the susceptibility of the host to the actions of a diabetogenic virus. Puberty in humans is a time of peak incidence of new cases of diabetes. Attention has been directed to the possible role of Coxsackie B viruses in insulin-dependent diabetes mellitus, on the basis of reports concerning diabetic children and also from studies on experimentally infected animals.

There is also a seasonal pattern consistent with Coxsackie B4 infections, but not with other viruses. In addition a multiplicity of considerations, including genetic factors in the host, metabolic factors (obesity, puberty, hormonal or drug therapy), specific variants and dose of a virus, the presence, or absence of any pre-existing damage to the host's beta cells, and immunologic competence may determine whether or not a viral infection especially with Coxsackie B leads to diabetes or not.

The prevention of diabetes may be achieved in some patients by immunization with viral vaccines. The use of anti-inflammatory or immunosuppressive agents at the time of diagnosis may alter the course of the disease by preventing complete destruction of the beta cells. Early identification of persons at increased risk by HLA typing will permit studies of provocative factors and
evaluation of preventive measures. It has been found that the repeated administration of interferon (IFN) or an IFN inducer reduced the development of diabetes in mice infected with the D variant of encephalomyocarditis virus. There is cause for optimism about the future course of insulin-deficiency diabetes mellitus using IFN as a major regulator of natural killer cell activity and more studies on its effect in diabetic patients are needed.

References