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Department of Virology, Skubiszewski Medical University of Lublin

MAŁGORZATA STRYCHARZ, KATARZYNA BARTECKA,
MAŁGORZATA POLZ-DACEWICZ

The role of viruses in the etiopathogenesis of diabetes mellitus

Diabetes mellitus (DM) is a chronic disease of multiple etiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein matabolism resulting from defects in insulin secretion, insulin action, or both.

In 1999 World Health Organisation set a following classification of diabetes mellitus (16): 1. Type 1 (formerly known as insulin-dependent diabetes mellitus – IDDM) – beta-cell destruction, usually leading to absolute insulin deficiency: autoimmune, idiopathic. 2. Type 2 (formerly known as insulin-independent diabetes mellitus – NIDDM) – may range from predominantly insulin resistence with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance. 3. Other specific types (currently less common): genetic defects of beta-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (e.g. pancreatitis, trauma, cystic fibrosis), endocrinopathies (e.g. Cushing's syndrome, glucagonoma), drug- or chemical-induced diabetes (e.g. glucocorticoids, thyroid hormone), infections (e.g. congenital rubella, cytomegalovirus), uncommon but specific forms of immune-mediated diabetes mellitus (e.g. anti-insulin receptor antibodies), other genetic syndromes sometimes associated with diabetes (e.g. Down's syndrome). 4. Gestational diabetes.

Type 1 diabetes mellitus is caused by an irreversible destruction of the pancreatic insulin-secreting beta-cells. The detailed cause of the disease still remains unexplained. Many studies suggest the association between type 1 DM and immunological disorders as well as environmental and genetic factors.

An infectious etiology for insulin-dependent diabetes mellitus was suggested more than a hundred years ago (4). Many studies reported some viral infections, especially infections with Coxsackie B (particularly B4) virus as a potential etiologic factor in the pathogenesis of type 1 DM but final proof is still lacking (6). Many studies emphasize the connection between enterovirus infection and development of type 1 DM (1, 3, 5, 15).

There are probably two mechanisms of viruses influence on the islet-cells. First – enterovirus infection may cause direct beta-cell lysis by the cytotoxic life cycle of the virus (3, 15). Second – it is based on molecular mimicry, which occurs when viral antigens and self-antigens of the beta-cells share antigenic determinants, e.g. similarity between Coxsackie B4 virus protein 2C (P2-C) and the beta-cell antigen glutamic acid decarboxylase (GAD 65), between CMV (cytomegalovirus) and the beta-cell autoantigen of molecular weight 38.000, and also between rubella virus and islet protein of molecular weight 52.000 (3,15).

Several findings indicate a link between enterovirus infections and development of type 1 DM. First, Coxsackie B3 and B4 viruses were isolated from the pancreas of patients with recent-onset type 1 DM. Moreover, genetically susceptible mice developed type 1 DM after infection with strains of Coxsackie virus B4. Next, the seasonal variability of type 1 DM similar to a pattern shown by

enteroviruses was found – the peak of eneteroviruses infection occurs in late summer and early autumn, while the majority of type 1 DM appears to occur in autumn and early winter. Furthermore, several epidemiological studies found a connection between type 1 DM and antibodies to enteroviruses (3, 5). But there are also many studies which did not find any association between enteroviruses and type 1 DM (5). The disagreement of the results of different studies may be caused by differences in the methods used in the study. Many findings that failed to show the link between enteroviruses and type 1 DM used the presence of neutralizing antibodies. Because of the fact that infections with enteroviruses are common in young children and neutralising antibodies are present for a long time in the serum, the antibody rate will be high. Therefore, the presence of neutralising antibodies is a poor indicator of an association between typ 1 DM and enterovirus infection (5).

The studies that showed interdependence between type 1 diabetes mellitus and infection with enteroviruses IgM antibody assays were used. The presence of these antibodies usually shows recent infection and type 1 DM. However, it is possible that IgM positivity may sometimes indicate more distant infections e.g. in some patients with chronic cardiac disease IgM persisted for 10 years (5). Testing for many serotypes may increase the probability of identyfying an association because different serological types of enteroviruses might be associated with type 1 DM and different enteroviruses circulate each season (5).

Differences in the presence of IgM may be age related (1). Other sources stated that Coxsackie B virus may be potentially diabetogenic but some strains of Coxsackie B (especially B4) virus are common – about half the population have neutralising antibodies, but type 1 DM occurs in less than 1% of the population (7).

There are findings that mumps and rubella viruses may increase the level of glucose and on account of this they may play a role in the pathogenesis of type 1 DM (7).

Insular changes have been reported in children with fetal CMV (cytomegalovirus) infection and diabetes mellitus in infancy was reported in an infant with congenitally acquired CMV (1). According to other sources, mumps virus does not play a key role in the development of DM, but both after infection and after vaccination against mumps there are inflammatory lesions in the whole pancreas (3, 5). Diabetes or impared glucose tolerance were stated in 20% people with congenital rubella. The symptoms occur usually after many years because the virus does not damage the islet-cells but only impairs their development and shortens their lifetime (3). There was also a finding about the association between Echovirus 9 infection and development of type 1 DM, but the mechanism of this process still remains unknown (15).

The genetic susceptibility to type 1 DM is mediated in part by genes in the human leukocyte antigen (HLA) region that either predispose or protect people from developing the disease. The HLA genes operate as susceptibility factors, not as determining factors, in that the majority of patients with these disease-associated genes do not develop type 1 DM. (3, 10).

The most powerful evidence that type 1 DM is due to nongenetically determined factors comes from the study of identical twins. Differences or discordance between identical twins must be due to nongenetically determined factors. All diabetic twin studies in the United States, in the United Kingdom, Finland and Japan showed that the majority of co-twins of type 1 DM patients are not diabetic. This striking discordance between identical twins for type 1 DM indicates that nongenetically determined factors play an important role in causing that disease (10, 15).

Patients with diabetes were more often reported to have HCV (hepatitis C virus) or HBV (hepatitis B virus) infection. In patients with type 1 diabetes it is probably associated with longlasting insulin injections (3, 13). But it is uncertain whether HCV precedes the development of type 2 diabetes in adults. However, it was stated that the course of disease is more severe in diabetic patients than in non--diabetic patients and more often leads to cirrhosis which may be associated with special susceptibility of type 1 diabetic patients to autoimmune diseases (3).

There are findings about the co-infection with HBV and HCV in type 2 diabetic patients. According to some preliminary studies infection with HCV may be an additional risk factor in the development of diabetes (8, 9). In such cases diabetes is assumed as an extrahepatic lesion in the course of HCV infection. The biological mechanism remains unknown but it is suggested that the extrahepatic lesions by HCV are probably connected with the participation of the immune system but may be as well due to the replicating virus in the affected tissues, organs and systems. Several findings indicated that existing HCV infection may increase the risk for type 2 diabetes in persons with recognized diabetes risk factors such as 40 years of age or older, obesity, family history of diabetes, low socioeconomic status (12).

There are findings about more frequent prevalence of diabetes among patients with chronic HCV infection with and without cirrhosis. A study carried out in Israel showed that 33% patients with HCV infection were found to have type 2 diabetes compared with 5.6% in the control group without any liver disorders (8). However, other scientists showed that diabetes is associated with cirrhosis – according to Italian study 23.6% patients with HCV-related cirrhosis and 9.4% patients with HBV-related cirrhosis were also diabetic compared with only 1.4% patients without cirrhosis (2).

There are also findings that show an increasing prevalence of hepatitis C and B, often associated, in type 2 diabetic patients that allows the scientists to define them as a group at risk for viral hepatitis (14). Other sources, however, did not show the connection between HCV and diabetis – the authors of such studies disprove HCV infection as a trigger factor for DM and state the infection should not be listed among the various extrahepatic manifestations of this viral infection (11).

Even though there are many reports about the possible role of various viruses in etiopathogenesis of type 1 DM it is impossible to support their influence on the development of this disease. Further study is needed to explain the nature of IgM positivity, to determine how enterovirus might cause type 1 DM and to evaluate the relative importance of these infections compared with other factors leading to type 1 DM.

In the case of type 2 DM it is possible that HBV and HCV infections might contribute to diabetes, even though there were also reports that did not show it. However, it is necessary to take into account the greater susceptibility for diabetes among people infected with HBV or HCV with recognized diabetis risk factors.

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SUMMARY

Diabetes mellitus is becoming an increasingly common disease. The influence of viruses on the development of diabetes mellitus has been presented on the basis of various scientific reports.

Rola wirusów w etiopatogenezie cukrzycy

Obecnie obserwuje się coraz większe rozpowszechnienie cukrzycy. W niniejszej pracy, na podstawie piśmiennictwa, przedstawiono wpływ wirusów na rozwój cukrzycy.