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Immunisation and Type 1 Diabetes Mellitus

Is There a Link?

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Abstract

Recent evidence from animal studies has raised the possibility that immunisation by vaccines can influence the pathogenesis of type 1 (insulin-dependent) diabetes mellitus. In non-obese diabetic mice and biobreeding rats, complete Freund's adjuvant and bacillus Calmette-Guérin (BCG) vaccine have successfully been used to interrupt the development of diabetes mellitus. This effect is probably mediated by nonspecific suppression of the autoimmune process. A number of attempts have also been made to assess the impact of parenteral immunisation on type 1 diabetes mellitus in humans.

Epidemiological evidence has not indicated any clear link between BCG vaccination and the development of diabetes mellitus in humans. Some reports have suggested that natural mumps or mumps vaccinations can induce islet cell autoimmunity, but there is no evidence that mumps-measles-rubella mass vaccination programmes have changed the incidence of diabetes mellitus in any population. An independent protective role of measles virus has been suggested in one study. Recent studies have indicated that enterovirus infections may induce β cell autoimmunity and clinical diabetes. The only currently available enterovirus vaccine is the poliovirus vaccine which, in theory, could modulate the protection against other enteroviruses by inducing cross-reactive T cell immune responses; however, this hypothesis has not been tested so far.

In conclusion, there is no clear evidence that any currently used vaccine can prevent or induce diabetes in humans. However, only a few studies are available on the subject and therefore the possibility of a link between vaccination and diabetes mellitus cannot be excluded.

Type 1 (insulin-dependent) diabetes mellitus is caused by the destruction of the insulin-producing β cells in the pancreas followed by insulin deficiency and hyperglycaemia. The progressive damage of β cells seems to be mediated by autoimmune mechanisms. The incidence of type 1 diabetes mellitus varies considerably from country to country, but a gradual increase in the incidence of this disease has been a constant finding in several countries.[1] The risk of type 1 diabetes mellitus is genetically determined, but environmental factors are important in the induction of the process in genetically susceptible individuals. Current evidence supports a role for virus infections in the pathogenesis of type 1 diabetes mellitus.[2] A role for parenteral immunisation by bacterial and viral vaccines

has also been suggested. This article summarises the current data available on the possible link between vaccinations and the development of type 1 diabetes mellitus.

1. Experimental Models

Non-obese diabetic mice and biobreeding rats have been used as models of spontaneous type 1 diabetes mellitus. Many of the pathological features of the disease, including the autoimmune destruction of β cells are observed both in these animals and in humans. The effect of different immune modifiers on the development of diabetes in these rodents has widely been studied. Complete Freund's adjuvant and bacillus Calmette-Guérin (BCG) vaccine have been shown to prevent the development of diabetes in these animal models.[3]

Adjuvant therapy with a single dose of complete Freund's adjuvant or BCG, both containing potent mycobacterial antigens such as heat shock proteins prevented the development of diabetes in the non-obese diabetic mice when given at an early age probably by generating nonspecific suppressor cell activity or by altering the cytokine balance controlling the T helper cell (Th) 1 and Th2 type immune responses.[4-6] Complete Freund's adjuvant was able to protect transplanted islets from diabetic autoimmune destruction in non-obese diabetic mice.[7]

BCG, a more clinically relevant immunoadjuvant, also prevented recurrent insulitis, but not allograft rejection, in islets transplanted into non-obese diabetic mice.[8] It has been reported that when BCG prevents diabetes mellitus in non-obese diabetic mice it may, unfortunately, accelerate antibody-mediated autoimmunity to levels normally found in much older non-obese diabetic mice.[9] However, this adverse effect has not been found in all studies.[10] This may be due to different route of administration of BCG in these studies. BCG treatment may also counteract the effect of cyclophosphamide on the autoimmune process in type 1 diabetes mellitus.[11] The window of effective immunotherapy seems to be quite narrow as the progression of cyclophosphamide-induced diabetes mellitus can only be blocked when BCG is given within 3 days of cyclophosphamide administration.

Pertussigen, a major component of *Bordetella pertussis* and the pertussis vaccine, has been reported to prevent the development of streptozotocin-induced diabetes in CD-1 mice[12] and retard the progression of insulitis in non-obese diabetic mice.[13] In addition, the combined diphtheria-tetanus toxoid–pertussis vaccine prevents the development of diabetes mellitus in non-obese diabetic mice and biobreeding rats. This prevention was associated with a Th2-like insulitis profile[14] and early administration of the vaccine.[15] Additionally, it has been suggested that T-lymphocyte vaccination can prevent diabetes mellitus in non-obese diabetic mice when given prophylactically at an early age; the therapy is most effective in female mice.[16]

In summary, early immunisation by various antigens which are commonly used in human vaccines has been shown in some models to be able to prevent the development of spontaneous type 1 diabetes mellitus in non-obese diabetic mice and biobreeding rats probably by activating a nonspecific, suppressive immunological response.

2. Human studies

Encouraged by the results obtained from animal experiments, the effect of BCG was studied in a small clinical trial.[17] In a study of patients with newly-diagnosed type 1 diabetes mellitus, clinical remission occurred in 65% of 17 patients who received a single intracutaneous administration of BCG vaccine compared with 7% of 29 patients who did not receive BCG vaccine. No adverse effects were reported. In a larger multicentre trial involving 72 patients with newly-diagnosed type 1 diabetes mellitus the effect of BCG plus nicotinamide was compared to that of nicotinamide alone.[18] No significant differences were found between the 2 groups; the rate of clinical remission was 41% *vs* 46% in the BCG plus nicotinamide and nicotinamide only groups, respectively, and the length of remission was similar in the 2 groups.

In Sweden, BCG vaccination in newborns had no significant effect on the incidence of childhood-onset type 1 diabetes mellitus,[19] although this finding has been disputed by Classen and Classen.[20] Additionally, in a Canadian study[21] of 2 different case-control series of type 1 diabetes mellitus cases and their matched control participants (in series A same birth cohorts and areas of residence as the type 1 diabetes mellitus cases and in series B age- and gender-matched friends and neighbourhood control participants) the overall vaccination rates among type 1 diabetes mellitus cases and control participants were quite similar (21.5% *vs* 22.3% and 17.7% *vs* 15.1%, respectively). These results suggest that BCG vaccination does not prevent type 1 diabetes mellitus.[21] However, the proportion of birth-vaccinated type 1 diabetes mellitus cases diagnosed at a very young age was lower than the proportion of nonvaccinated type 1 diabetes mellitus cases possibly reflecting the ability of BCG vaccination to delay the onset of type 1 diabetes mellitus as hypothesised by the study authors.[21]

Besides BCG vaccination, a possible link between immunisation by mumps-measles-rubella (MMR) vaccination and the development of type 1 diabetes mellitus in humans has been suggested. Some reports have indicated type 1 diabetes mellitus and the development of islet cell antibodies after mumps vaccination and natural mumps infections.[22-26] A prospective study of 280 nondiabetic children of parents with type 1 diabetes mellitus found no evidence that MMR vaccine could trigger autoimmunity in humans.[27] The children were followed from birth and about 10% of all of the children were positive for at least 1 of the 4 islet-associated auto-antibodies tested. Four children progressed to clinical type 1 diabetes mellitus, and all of them developed islet-associated auto-antibodies, before MMR vaccination.

We have earlier reported a plateau in the rising incidence of type 1 diabetes mellitus in Finland, 6 years after the introduction of nationwide MMR vaccination and almost 10 years after the last mumps epidemic.[28] The more recent data from

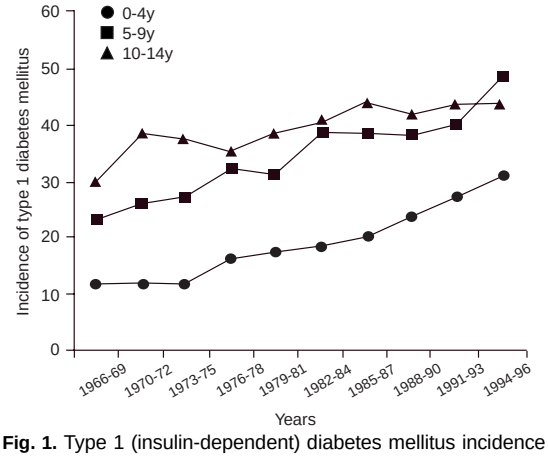

Fig. 1. Type 1 (insulin-dependent) diabetes mellitus incidence in Finland during the years 1966 to 1996 is shown as mean age-adjusted incidences of 3-year periods in children of 3 age groups. A mumps-measles-rubella mass vaccination programme was implemented in 1982. Incidence figures were calculated as described in Hyöty et al.[28]

years 1993 to 1996 (fig. 1) revealed that the incidence of type 1 diabetes mellitus continues to increase, especially in the age groups of 0 to 4 and 5- to 9-year-old children, although natural mumps has virtually disappeared and the vaccine coverage has been over 95%. We found no cohort effect consistent with the initiation of MMR mass vaccination programme, suggesting that MMR vaccine had no major effect on type 1 diabetes mellitus risk in the Finnish population. However, a possible effect of MMR may be difficult to identify on the basis of type 1 diabetes mellitus incidence data alone and additionally, serological evidence was sought to find a possible connection between MMR vaccination and type 1 diabetes mellitus.[28,29]

The mumps IgA/IgG ratio remained constantly higher in patients with type 1 diabetes mellitus compared with control participants in both epidemic and nonepidemic time periods. The low mumps IgG antibody response in patients with type 1 diabetes mellitus after standardised vaccine (MMR) exposure suggests that first, immune response against mumps virus antigens may be defective in these patients, and secondly, the high IgA mumps antibody levels in patients with type 1 diabetes mellitus during the epidemic time period

reflects an excess of past mumps or prolonged course of mumps rather than an inherited enhancement in mumps virus-specific immune responsiveness.

In another study, a protective effect of measles vaccination was indicated in Sweden where information about vaccinations was collected from 339 children with recent-onset type 1 diabetes mellitus and 528 referent children in child healthcare centres and schools.[30] According to another Swedish study the comparison of the cumulative incidence of type 1 diabetes mellitus (up to the age of 12 years) in birth cohorts with high and low exposure to pertussis vaccine did not support the hypothesis that pertussis could induce autoimmunity leading to type 1 diabetes mellitus.[31]

The role of enteroviruses, coxsackie B-viruses especially, in the aetiology of type 1 diabetes mellitus has been suggested in a number of studies and the recent prospective studies have further emphasised the role of these viruses in the initiation of the β cell damaging process.[32,33] Accordingly, enteroviruses have to be considered as the main candidates for diabetogenic viruses in humans. Coxsackie virus vaccines are effective in animal models, but the only enterovirus vaccine used in humans is the poliovirus vaccine. Polioviruses share antigenic determinants with other enteroviruses and T cell responses cross-react widely between different enteroviruses.[34] The possible association of poliovirus vaccine and type 1 diabetes mellitus is therefore of interest, as the vaccine could modulate the immune response against other enterovirus infections. However, there are no data available on the biological effects of this cross-reactivity.

3. Conclusions

Type 1 diabetes mellitus is a health problem associated with considerable morbidity, reduced life expectancy and significant health costs. The incidence of type 1 diabetes mellitus has rapidly increased in many countries and a possible role of vaccinations in this increased incidence has been suggested. Vaccines could modulate the immune system in a way that promotes the development of autoimmunity[35] or, alternatively, they could be beneficial by suppressing the autoimmune process or by protecting from diabetogenic infections.

BCG vaccination prevents the development of spontaneous diabetes mellitus in a mouse model. Based on the findings in non-obese diabetic mice, it has been suggested that the timing of vaccination may be essential in preventing the induction of type 1 diabetes mellitus by BCG vaccination.[15,36] However, human studies have not found any strong evidence for protection against type 1 diabetes mellitus, suggesting that BCG vaccination can hardly be a potent prevention strategy in the future. The value of animal studies is diminished by the fact that the spontaneous development of diabetes mellitus in non-obese diabetic mouse and bio-breeding rat may reflect different pathogenetic mechanisms than those operating in type 1 diabetes mellitus in humans. Clinical trials among prediabetic individuals are needed to get more precise information and to assess the possible impact of timing and administration of the immunisation.

The eradication of mumps, measles and rubella by MMR vaccination has not caused major changes in the epidemiology of type 1 diabetes mellitus in Finland. At the present time, 15 years after the introduction of MMR vaccination, no cohort effect on incidence can be seen in Finland, suggesting that the role of these infections, if any, has to be restricted to some particularly susceptible individuals comprising perhaps only a small proportion of all cases of diabetes mellitus. The incidence of type 1 diabetes mellitus shows a constant linear increase which is difficult to explain by the effect of any single vaccine implemented during the last 20 years in Finland. BCG vaccination has also been given at birth for decades and still, the incidence of type 1 diabetes mellitus is the highest in the world. There has not been any general shift in the timing of vaccinations either.

Enteroviruses, especially the group of coxsackie B viruses, have been linked with type 1 diabetes mellitus in a number of studies and they are currently the most interesting viruses in diabetes

research. Coxsackie B virus vaccines are effective in animal models but they have not been tested in humans. The only enterovirus vaccine used in humans, so far, is the poliovirus vaccine, but there is no evidence that it could influence the risk of type 1 diabetes mellitus.

No further conclusions can be drawn concerning the link between immunisation and type 1 diabetes mellitus based on the studies that have been currently performed on the topic. There is no clear evidence that any vaccine could induce type 1 diabetes mellitus in humans, and more information is needed on the possible benefits of current vaccines or totally new vaccines to prevent type 1 diabetes mellitus. Accordingly, children at an increased risk of developing type 1 diabetes mellitus, for example those children with first degree relatives with type 1 diabetes mellitus, should not be withdrawn from the recommended vaccination programmes. In future, more efforts should be taken to monitor the possible long term effects of new vaccines and other changes in vaccination programmes on incidence of type 1 diabetes mellitus.

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