Effect of Bacille Calmette-Guérin Vaccination on C-Peptide Secretion in Children Newly Diagnosed With IDDM

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OBJECTIVE — To determine whether administration of bacille Calmette-Guérin (BCG) vaccination to newly diagnosed IDDM patients can help preserve C-peptide secretion over the subsequent 18 months.

RESEARCH DESIGN AND METHODS — Twenty-six IDDM patients, all of whom had been diagnosed within the previous year, had basal C-peptide levels >0.06 nmol/l, and had negative reactions to Mantoux's test, were randomized pairwise as they presented and were given either 0.1 ml (100 μg) BCG vaccine or 0.1 ml saline intradermally. Both the patients and the investigators were blinded to the treatment. Fasting and glucagon-induced C-peptide levels and HbA_{1c} were measured in all patients at enrollment and at 1, 3, 6, 9, 12, and 18 months after vaccination, and insulin dose was recorded at each visit.

RESULTS — At enrollment, there was no significant difference in age, duration of diabetes, insulin dose, HbA_{1c}, or fasting C-peptide levels between the BCG-vaccinated and control groups. The mean basal and stimulated C-peptide levels in the BCG-treated group did not differ significantly from those in the control group at any time during the 18 months of follow-up, and there was no difference in insulin dose or HbA_{1c} at any time between the groups.

CONCLUSIONS — BCG vaccination in children who have been recently diagnosed with IDDM does not affect the progressive decline in C-peptide levels or alter the clinical course of the disease.

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IDDM is the result of autoimmune destruction of β-cells within the pancreas (1). A number of both genetic and environmental factors have been shown to contribute to the etiology of IDDM (2). A current theory suggests that a genetically susceptible individual may have a destructive, or protective, immune response to an environmental "trigger" (3). This theory has led to the suggestion that immunomodulation may prevent or ameliorate the course of IDDM.

In the NOD mouse, vaccination with complete Freund's adjuvant (CFA) or bacille Calmette-Guérin (BCG) at the prediabetic stage prevents the development of IDDM (4,5). A similar effect has been found in BB rats treated with CFA (6). In humans, a recent nonrandomized trial of BCG vaccination of newly diagnosed IDDM patients suggested preservation of C-peptide secretion (7). This latter report prompted us to perform a double-blind controlled trial in patients with newly diagnosed IDDM to see whether BCG vaccine would preserve remaining β-cell function, as determined by basal and stimulated C-peptide secretion over an 18-month period.

RESEARCH DESIGN AND METHODS

— Twenty-six Caucasian patients who had been recently diagnosed with IDDM were enrolled in the study. The study was approved by the research ethics board of the University of Alberta, and all participants or legal guardians signed informed consent forms. Patients were accepted into the study within 1 year of diagnosis of IDDM provided their basal C-peptide level was >0.06 nmol/l. The demographic characteristics of the enrolled patients are given in Table 1. All patients had negative reactions to Mantoux's test (5 tuberculin units) performed immediately before their first study visit.

Patients were studied at 0800 in the fasting state and before taking their usual morning insulin dose. C-peptide was measured by radioimmunoassay (Diagnostic Products, Los Angeles, CA) on a serum sample obtained before and 6 min after glucagon was administered (0.05 mg/kg [maximum, 1 mg/kg] i.v.). At the first study visit, patients were randomly assigned to receive either 0.1 ml (100 μg) BCG vaccine (Connaught, Toronto, Ontario, Canada) or 0.1 ml saline intradermally. Both the patients and the investigators were blinded to the treatment. The C-peptide levels and HbA_{1c} were measured again at 1, 3, 6, 9, 12, and 18 months after vaccination. Insulin dose was also recorded at each visit. Statistical analysis was performed using Student's *t* test.

RESULTS

— At enrollment, there was no significant difference in age, duration of diabetes, insulin dose, HbA_{1c}, or fasting C-peptide level between the two groups (Table 1). Mean basal and stimulated C-peptide levels in the BCG vaccine–treated patients did not differ significantly from those in the control subjects (P = 0.10–1.00) at any time during the 18 months of follow-up (Fig. 1). Also, no difference was observed between the groups in the percentage increase in C-peptide

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Abbreviations: BCG, bacille Calmette-Guérin; CFA, complete Freund's adjuvant.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Demographic characteristics of subjects at enrollment*

	BCG vaccine	Control
n	13	13
Age (years)	12.8 ± 2.6	13.4 ± 3.7
Sex (M/F)	6/7	9/4
Diabetes duration (days)	80 ± 95	148 ± 113
Insulin dose ($U \cdot kg^{-1} \cdot day^{-1}$)	0.68 ± 0.28	0.49 ± 0.22
HbA_{1c} (%)	9.7 ± 3.4	7.9 ± 2.3

Data are means ± SD or *n*. The normal range for HbA_{1c} is 4.3–6.1.

concentration induced by glucagon over basal levels. No patient in either group was able to discontinue insulin treatment, and there was no difference in insulin dose or HbA_{1c} at any time between the groups.

CONCLUSIONS — Our results indicate that BCG vaccination of children recently diagnosed with IDDM does not change the decline in endogenous insulin secretion. It also does not reduce the need for exogenous insulin administration or improve glycemic control. These results are similar to those reported by Klingensmith et al. (8). The decline in basal and stimulated C-peptide levels in the group treated with BCG vaccination was also similar to the results reported in larger cohorts followed from diagnosis (9,10).

The results of our study differ from those of Shehadeh et al. (7) and from the recent report of Vazeou et al. (11). However, both of these studies reported a benefit based on a reduction of administered insulin dose in BCG vaccine–treated patients compared with control subjects, and the follow-up periods of 6 and 9 months, respectively, was shorter than in our study. Only the latter study measured C-peptide concentrations, and although the levels were higher in the BCG vaccine–treated group, the difference was not significant (11).

Whereas the studies by Shehadeh et al. (7) and Vazeou et al. (11) enrolled only newly diagnosed patients, the present study allowed enrollment up to 1 year after diagnosis provided that the fasting C-peptide level was >0.06 nmol/l. This level is 10% of the normal fasting range in nondiabetic subjects and indicates some residual β-cell function. From a practical point of view, any patient with this level of C-peptide could have potentially benefited from BCG vaccination if it had preserved β-cell function. In NOD mouse and BB rat studies, the BCG vaccine and CFA were successful only when given well before the onset of diabetes (4–6), whereas in these rodent models, CFA and BCG have not been reported to be effective when given after the onset of hyperglycemia. On the other hand, BCG vaccination was successful in preventing recurrence of diabetes in syngeneic islet transplants in NOD mice (12), in which a fresh aliquot of healthy β-cells is given along with a relatively massive (wt/wt) dose of mycobacteria.

Clearly, the issue of timing of any potential vaccination or immunostimulation therapy in newly diagnosed diabetic patients must be carefully considered, as with any potential immunosuppressive therapy. We would argue that the "window of opportunity" for affecting the autoimmune process is quite wide when ≥10% of residual β-cell function remains. In this context, it may be difficult to make direct comparisons between rodent models, in which a small absolute β-cell mass consequently fails rather abruptly over a period of weeks, and the human, in which a much larger absolute β-cell mass is destroyed over a much longer time frame, typically several years (1,9,10).

In the NOD mouse and BB rat studies in which the BCG vaccine or CFA immunostimulation was administered before the onset of diabetes (4–6), these treatments were shown to change the histological pattern of lymphocytic infiltrate. Although there have been no human studies of BCG vaccination of individuals thought to be at high risk of developing IDDM, retrospective analysis of Swedish incidence data suggested no significant increase in IDDM when routine BCG vaccination was discontinued (13). It may be that immunostimulation with the usual doses of BCG used in vaccination is ineffective in altering the course of autoimmune diabetes in humans, whether given before or after diagnosis.

In conclusion, our study found that BCG vaccination of children recently diagnosed with IDDM does not affect the progressive decline in C-peptide levels or alter the clinical course of the disease.

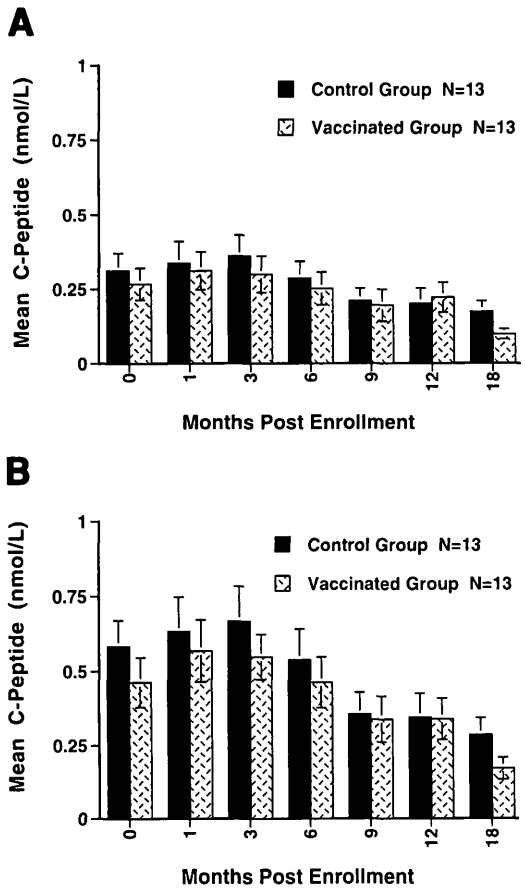

Figure 1—*Mean fasting (A) and glucagon-induced (B) C-peptide concentrations (± SEM) measured in patients at various times after enrollment.*

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