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The Non-Significant Benefit of BCG Vaccination for the Treatment of Iranian Patients with Type 1 Diabetes up to 48 Weeks: A Controversial Result

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Abstract

Background: There has been considerable interest in target immunotherapy in patients with diabetes. This study was designed to identify the effect of BCG vaccination in the treatment of Iranian patients with longstanding diabetes mellitus type 1.

Methods: After approval of the cross-sectional study protocol by the ethics committee under number IRCT2017042919940N2, a total of 19 Iranian volunteers with diabetes mellitus type 1 completed this 48-month study. These patients received three 0.1 ml intradermal injections of BCG vaccination in weeks 0, 4 and 24. The serum level of glucose, HgbA1C and c-peptide was measured before and serially after the interventions. Insulin requirements were recorded for each patient in different weeks as the mean and standard deviation..

Results: This study showed a decrease in the blood sugar level of 171.15±75.54 mg/dL in baseline to 133.77±76.97 mg/dL in 12 weeks after the first dose of BCG vaccination in these patients. There was no significant change in the mean± SD of serum blood sugar, HgbA1C and c-peptide after BCG vaccination in the baseline and week 48.

Conclusion: Our results showed that small doses of BCG vaccination were not effective in long-term treatment of Iranian patients with diabetes mellitus type 1 up to 48 weeks.

Keywords: BCG Vaccine, Iran, DIABETES Mellitus, Glycated Hemoglobin A, C-peptide

Conflicts of Interest: *None declared*
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Introduction

Diabetes mellitus is a long-standing genetic disease from which many people suffer in the world. In 2011, approximately 4.5 million adult people were living with diabetes in Iran and 11.4% of them are classified as type 1 diabetes mellitus (T1DM) (1, 2). T1DM results in the autoimmune destruction of a large number of functioning β cells of the pancreas over a period of many months to years, followed by insulin deficiency. The process of this autoimmune destruction occurs most probably via apoptosis, also named programmed cell death (3, 4).

In the two recent decades, animal studies showed the importance of the cytokine TNF-α (tumor necrosis factor-α) as new potential immunotherapy in the diabetic mouse model (5, 6). TNF is a cytokine involved in cell signaling and it can make intracellular signaling defects in insulin-autoreactive T cells without any effect on the healthy

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↑What is "already known" in this topic:
Some tried-and-tested studies have shown effective results of the BCG vaccine in treating type 1 diabetes. However, clinical trials related to the effect of BCG vaccination in the treatment of T1DM are still scanty in Iran.

→What this article adds:
In our patients with type 1 diabetes, there was no significant change in serum blood sugar, HgbA1C, and c-peptide after BCG vaccination in the baseline and week 48.

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cells. The other mechanism of TNF is an increased level of regulatory T cells, a group of T cells with a suppression role for insulin-autoreactive T cells (7, 8). Using a high dose of TNF can cause new or aggravated forms of autoimmunity in humans (9).

The Bacillus Calmette-Guérin (BCG) vaccine has been used since the 1920s to immunize individuals against tuberculosis (10). The strain of mycobacterium in BCG is a virulent Mycobacterium bovis which is different from the virulent Mycobacterium tuberculosis. Some mechanisms have been proposed to explain the effect of BCG on the immune system; the vaccine stimulates antibody production by Th2 lymphocytes, induces cell-mediated immunity via Th1and Th17 lymphocytes, and stimulates the host's innate immune for secretion of TNF-α (11-13).

Some tried-and-tested studies have shown effective results of the BCG vaccine in treating T1DM by researchers at Massachusetts General Hospital (14, 15). A preliminary trial found a single dose of the BCG vaccine in 17 newly diagnosed T1DM patients lead to clinical remission of 65% of subjects by week 4 and a sustained effect in three cases for 6–10 months (16).

In Iran, clinical trials related to the effect of BCG vaccination in the treatment of T1DM are still scanty. The present study aimed to determine whether the administration of the BCG vaccine induces the control of blood sugar, HgA1C and also c-peptide as an indicator of endogenous insulin secretion in patients with T1DM. Frequent blood sampling was conducted to measure these biomarkers for up to 48 weeks.

Methods

Participants

After approval of this cross-sectional study by the ethics committee of Shiraz University of Medical Sciences in compliance with Iran Clinical Trials Registry under number IRCT2017042919940N2, to recruit volunteers, we distributed an announcement in the diabetes Clinic Center at Ali-Asghar Hospital, affiliated with Shiraz University of Medical Sciences in Shiraz, Iran from October to December 2017. In 2018, 22 adult patients with long-term T1DM who had been continuously treated with insulin and were aged from 18 to 55 years participated in the study. Exclusion criteria included subjects with a history of tuberculosis or current tuberculosis; those with human immunodeficiency virus (HIV); and those under treatment with glucocorticoids, immunosuppressive medications and a high dose of aspirin (>160 mg/day).

After obtaining informed consent from the patients, demographic characteristics about gender, age, duration of diabetes, and organ involvement were recorded. Analysis of laboratory parameters including cell blood count, blood urea nitrogen, serum creatinine, biochemical blood tests, liver function tests, fasting blood sugar were done for all included patients in the first visit.

Intervention protocol

All BCG injections were administrated in a diabetes clinic in the hospital. Each interventional diabetic patient received three doses of 0.1 cc intradermal injections of BCG vaccine (1173 P2 Pasteur strain, Iran) into deltoid muscle at week 0, week 4 and week 24. Any abnormal reactions after administrating injection were asked to be reported from all the patients by phone to the physician.

Detection of blood sugar, HgbA1C, and C-peptide

Fasting blood sugar was measured in the serum samples of all patients in 0, 8, 12, 20, 32, 36 weeks, and finally monitored at week 48. All blood samples were sent and processed within 1-2 hours of being drawn in the same hospital laboratory. All human HgbA1Cs were processed directly from fresh blood at the baseline, 8, 12, 20, 32 weeks and finally 48 weeks.

The levels of C-peptide were measured in the serum samples of patients with a commercial kit (Architect C-Peptide immunoassay, Abbott Diagnostics, Barcelona, Spain) based on a Chemiluminescent microparticle immunoassay according to the manufacturer's instructions. The lower detection limit of the ELISA assays was < 0.01 ng/L. The time of measuring c-peptide was at the baseline before BCG injection, after 20 weeks, and following 48 weeks of injection. Required daily insulin was calculated by the sum of various types of insulin in each patient.

Statistical Analysis

Continuous variables were presented as the mean and standard deviation (Mean ± SD). The repeated measurement test was used for serial blood sugar, HgbA1C and c-peptide. Data analyses were performed using SPSS version 25 (SPSS Inc., Chicago, IL, USA) and $p<0.05$ was considered statistically significant.

Results

Twenty-two adult patients with T1DM were included in this study, three of whom dropped out because they were unable to attend the follow-up visits. Nineteen patients (7 females, 12 males) completed the study. Demographic data and baseline laboratory results in the studied patients are shown in Table 1. One patient with T1DM had hypothyroidism and another one had asthma.

There was no significant change in the mean ± SD of serum blood sugar, HgbA1C, and c- peptide of 19 BCG-vaccinated T1Ds at the baseline and the following weeks; it is shown in Table 2. BCG-treated T1Ds showed a first reduction in blood sugar 12 weeks after the first BCG at baseline; the second reduction of blood sugar occurred 12 till 24 weeks after the third dose at 36 weeks to 48 weeks.

There was a reduction in fasting blood sugar, Hgb A1C, and the required insulin at the baseline and 48 weeks in BCG-treated patients, but it was not significant as shown in Figure 1.

Two patients showed red indurated skin reactions and subsequently ulceration in the injection site of the vaccine; they were well approximately 3 months later.

Discussion

There are several studies on the beneficial effects of mycobacterium re-introduction through the BCG vaccine in the control of blood sugar on T1DM subjects. The results of the current study showed no significant changes in

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Table 1. Baseline demographic data and laboratory results in 19 patients with diabetes type 1

Characteristic	Mean ± SD	Min	Max
Age (year)	29.78 ± 8.77	15.0	52.0
Duration of diabetes (year)	13.78 ± 7.48	5.0	30.0
Hemoglobin (g/dL)	14.68 ± 2.27	11.2	20.9
White blood count (cell/mm^3)	6483.33 ± 1513.56	4500.0	8900.0
Platelet count(cell/mm^3)	237.88 ± 58.68	137.0	343.0
Blood urea nitrogen (mg/dL)	13.30 ± 3.57	10.0	23.0
Creatinine (mg/ dL)	1.03 ± 0.19	0.6	1.3
SGOT(U/L)	23.30 ± 9.69	13.0	47.0
SGPT(U/L)	24.36 ± 10.36	11.0	46.0
TSH (mIU/L)	2.04 ± 0.94	1.79 ± 1.14	0.32
Fasting blood sugar (mg/dL)	171.15 ± 75.54	55.0	271.0
HgbA1C (%)	8.20 ± 2.34	4.3	13.1
C-peptide(ng/mL)	0.02 ± 0.07	< 0.01	0.32

Table 2. Serial level of fasting blood sugar, HgbA1C, and c- peptide in 19 BCG-vaccinated patients with diabetes type 1

Variable	Mean ± SD	p-value
Fasting blood sugar baseline	171.15 ± 75.54	
Fasting blood sugar week 8	174.63 ± 93.81	
Fasting blood sugar week 12	133.77 ± 76.97	
Fasting blood sugar week 20	178.20 ± 104.88	0.112
Fasting blood sugar week 32	140.92 ± 90.10	
Fasting blood sugar week 36	123.78 ± 67.24	
Fasting blood sugar week 48	115.70 ± 57.87	
HgA1C baseline	8.200 ± 2.34	
HgA1C week 8	6.889 ± 1.99	
HgA1C week 12	7.518 ± 1.27	0.123
HgA1Cweek 20	7.931 ± 1.90	
HgA1C week 32	7.419 ± 2.11	
HgA1C week 48	7.79 4 ± 2.29	
Insulin baseline	56.4 2 ± 19.18	
Insulin week 8	49.42 ± 17.96	
Insulin week 12	48.26 ± 17.34	0.272
Insulin week 20	47.06 ± 19.70	
Insulin week 32	48.14 ± 16.82	
Insulin week 48	52.29 ± 21.02	
C-peptide baseline	0.02 ± 0.07	
C-peptide week 20	0.03 ± 0.11	0.443
C-peptide week 48	0.02 ± 0.08	

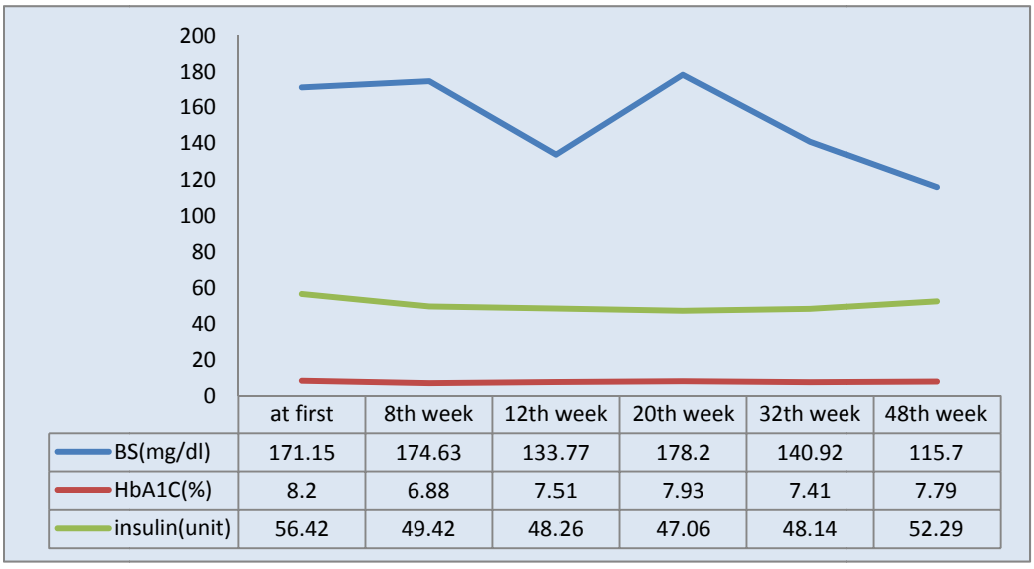

Fig. 1. The amount of fasting blood sugar, Hgb A1C and insulin at the baseline and the following weeks in BCG-vaccinated patients with diabetes type 1

the blood sugar, HgbA1C and c- peptide after injection of three doses of BCG vaccine up to 48 weeks.

Faustman et al. showed two low doses of BCG reverse the TIDM by restoring insulin secretion and increasing the level of C-peptide above the 95th percentile of the reference subjects. This positive achievement leads to the approval of BCG for T1DM by the FDA; another same clinical trial is currently in progress in the US (7, 14).

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Some studies reported that there was no effect of the BCG vaccine in the treatment of patients with TIDM. Huppmann et al. compared BCG vaccinated and non-vaccinated newborns in Germany, indicating that the use of BCG vaccination in the neonatal period does not prevent the development of diabetes (17). Allen et al. showed vaccination with BCG at the time of the onset of T1DM did not affect the preservation of beta-cell function (18). Consistent with our study, Kashef et al. reported 10 Iranian patients with T1DM who received one dose of BCG vaccine; there was no effect of BCG vaccine on the decreased level of blood sugar in patients compared with the control group during the 9 months of follow-up (19).

A new systematic review showed no statistical differences in Hgb A1C and C-peptide after using BCG as compared with the placebo group (20). However, it has been shown that decreased level of Hgb A1C in BCG-treated T1DM takes 3-4 years. It is explained that diabetes as an autoimmune disease lasts many years for development; therefore, the effect of BCG to become systemic for reducing HbA1 takes years. More research is required to study the new recombinant BCG for shortening the lag time and systemic delay of absorption (15).

According to the Iranian general vaccination program, vaccination with BCG was practiced in all newborns as a single injection at birth. Timing of early BCG administration may be a cause of failed efficacy in Iranian patients with type 1 diabetes.

The genetic defect of T1DM is mainly located in the HLA locus of the chromosome 6p21, including HLA-DR3-DQ2 or HLA-DR4-DQ8 haplotypes or both in the world; it appears that HLA-DR3-DQ2 haplotype has a very modest effect on patients with T1DM in the East Azerbaijan State of Iran with Turkish ethnicity, too (21, 22). Further investigation is required to clarify the genetic background of the population; resistance to BCG vaccination in this study could explain the heterogeneity of ethnic origin of Iranian patients with T1DM

An increase in the incidence of diabetes is estimated to be about 9.2 million in the Iranian population by the year 2030. This continuous increase in the prevalence of diabetes reflects the high burden of environmental factors such as viral and bacterial infections, dietary factors as well as toxins and chemical compounds. Different environmental factors induce various patterns of infiltration of the lymphocytes including CD4, CD8, and CD20 lymphocytes in the islets of the pancreas (23); however, islet autoantibodies might create an entirely different immune reservoir for blood sugar regulation with BCG administration.

The current BCG vaccine shows variable efficacy against T1DM in different parts of the world. An advanced new recombinant BCG vaccine for more and long-term protective immunity of the islet cells against autoantibodies is recommended (24).

Injection of BCG is considered a safe vaccination; however, induration, abscesses at the site of inoculation, adenitis, and disseminated disease in patients with immunodeficiency have been reported.

Conclusion

We have no evidence of the beneficial effects of BCG in the treatment of patients with T1DM. Further studies are suggested to investigate the importance of probable changing of early BCG vaccination, more frequent dosing of BCG and new recombinant BCG strain for the efficacy of BCG in blood sugar regulation in Iranian patients.

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Conflict of Interests

The authors declare that they have no competing interests.

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