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Original Article

Bacillus Calmette-Guerin in controlling type 1 diabetes: A quasi-experimental randomized clinical trial

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Abstract

Background: T1DM is an autoimmune and chronic metabolic disorder characterized by the destruction of pancreatic beta cells. The Bacillus Calmette–Guérin (BCG) vaccine, originally used for tuberculosis prevention, has shown potential in modulating the immune response and improving beta-cell function. This study aimed to evaluate the therapeutic effects of two doses of BCG vaccine, administered four weeks apart, on glycemic control and selected immunological markers in patients with T1DM.

Methods: In this single-center, double-blind randomized clinical trial, 33 patients with T1DM were enrolled and randomly assigned to intervention and control groups in a 1:1 ratio, matched by age and sex. The intervention group received two intradermal doses of the BCG vaccine, with a four-week interval. Fasting blood samples were collected at baseline and during follow-up to assess biochemical and immunological parameters. Patients were followed-up for 18 months. IRCT identifier: IRCT20201012049003N1; (date of registration: 2020/10/15).

Results: The mean age of participants was 11.25±3.32 years in the control group and 10.69±3.22 years in the BCG group. Anti-ICA levels significantly decreased in the BCG group by the end of the follow-up period. Although there was no significant difference in fasting blood glucose levels between the two groups, a significant reduction in HbA1c was observed in the BCG group after 18 months.

Conclusion: The findings suggest that BCG vaccination may contribute to improved long-term glycemic control, as evidenced by reduced HbA1c levels, in patients with T1DM. Additionally, the decrease in Anti-ICA levels indicates a potential immunomodulatory effect, supporting the therapeutic promise of BCG in autoimmune diabetes.

Keywords: Diabetes, Type 1 diabetes, BCG vaccine, HbA1c, Iran

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Type 1 diabetes mellitus (T1DM) is a chronic autoimmune metabolic disorder in which T lymphocytes target and destroy pancreatic beta cells (1-3). This destruction leads to decreased insulin secretion, impairing glucose uptake by cells (4-6). Studies report that the global incidence of T1DM is increasing by 2-3% annually (4, 7). According to the International Diabetes Federation, an estimated 25 to 45 million people worldwide live with T1DM (1). The disease is associated with complications such as hypoglycemia, ketoacidosis, retinopathy, neuropathy and cardiovascular disorders (4, 8). Effective management of T1DM requires maintaining blood glucose levels within the normal range (8, 9). Current treatment strategies include daily insulin injections, immunosuppressive therapy, anti-cytokine agents, lifestyle modifications such as physical activity, and dietary control (1, 4, 10). Despite these approaches, there remains a need for more effective treatments to reduce the disease burden and complications (11).

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Recent research has suggested that BCG vaccination may offer therapeutic benefits for certain autoimmune diseases, including multiple sclerosis and T1DM (2, 12-14). BCG is a live attenuated vaccine derived from *Mycobacterium bovis*, approved by the U.S Food and Drug Administration for tuberculosis prevention (4, 15, 16). It is widely due to its low cost, ease of storage, and minimal side effects (4). Some studies indicate that BCG promotes tumor necrosis factor (TNF) production, which may help eliminate cytotoxic T cells, thereby improving beta-cell function and insulin secretion (14, 17). Additionally, BCG- induced TNF appears to shift cellular metabolism from oxidative phosphorylation to glycolysis, potentially enhancing metabolic markers in individuals with T1DM (2). However, other studies have reported no significant impact of BCG on glycemic control in T1DM patients (4, 18).Given the limited and inconsistent data from human studies, the therapeutic role of BCG in T1DM remains unclear. Therefore, the present study aimed to evaluate the effect of two doses of the BCG vaccine, administered four weeks apart, on patients with T1DM.

Methods

Participants and medications: This study was a single-center, double-blind, randomized clinical trial conducted on patients with type 1 diabetes who were referred to the Yazd Diabetes Research and Treatment Center between October 2021 and May 2023. The diagnoses of T1DM were confirmed by a pediatric endocrinologist. Participants were eligible if they were between 6 and 14 years old, had HbA1C > 7%, were receiving a full insulin dose, and had been diagnosed with T1DM for at least one year (to ensure the Honeymoon period had ended). Exclusion criteria included a history of retinopathy, nephropathy, diabetic neuropathy, macrovascular complications, chronic infectious disease, reaction to live vaccines at birth, current steroid use, primary or secondary immunodeficiency, use of immunosuppressive drugs, celiac disease, or failure to complete the two-dose vaccine protocol. The sample size was estimated based on a previous study (19), using HbA1C levels of 10% and 7% before and after intervention, respectively, with a standard deviation of 3(α=0.05, β=0.2). Considering a 15% dropout rate, 16 participants were allocated to each group. The study protocol was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd (IR.SSU.REC.1399.023), and registered in the Iranian Registry of Clinical Trials (http://www.irct.ir: IRCT20201012049003N1, registration date: 2020/10/15). The study adhered to the CONSORT guidelines.

Randomization process: Participants were stratified by age and sex, then randomly assigned in a 1:1 ratio to either the BCG or placebo group using a computer-generated randomization sequence. This sequence was generated by an independent statistician who was not involved in recruitment, data collection, or analysis. Allocation concealment was ensured through the use of sequentially numbered, opaque, sealed envelopes (SNOSE) prepared and maintained by a third party. Neither investigators nor participants were aware of group assignments (double-blind design). All syringes (BCG or saline) were pre-filled and indistinguishable in appearance to maintain blinding.

Study design and protocol: After the purpose and nature of the study were explained, written informed consent was obtained from the parents of all participants. Children were stratified by age and sex, and then randomly assigned to either the BCG or placebo group using a computer-generated randomization sequence. Both researchers and participants were blinded to group assignments. The normal function of each participant's immune system was confirmed by an immunologist based on medical history, clinical examination, complete blood count (CBC), and Nitroblue Tetrazolium (NBT) test results.

After baseline data collection, participants were referred to the laboratory.

They were then classified by age and gender and evenly distributed between the intervention and control groups. The BCG vaccine (Pasteur Institute, Tehran, Iran) was obtained from a pharmacy, and all syringes (BCG and saline) were pre-filled at the same location. Injections was administered intradermally by a physician equipped with full resuscitation tools. A dose of 0.1 ML of BCG vaccine or saline placebo was injected into participants in the intervention and control groups, respectively. Four weeks later, participants received the second injection. Throughout the study, no changes were made to participants' primary insulin therapy, and both the participants and the administering physicians remained blinded to group allocations.

Assessment of variables: Fasting blood samples were collected from participants in both groups to assess the following:

- Primary outcome: Glycosylated hemoglobin (HbA1c)
- Secondary outcomes: Fasting blood sugar (FBS), Anti-Glutamic Acid Decarboxylase (Anti-GAD), Anti-Islet Cell Antibody (Anti-ICA), and C-peptide levels (only in the intervention group for the latter three)

Participants fasted for 12 hours prior to sample collection, which was done between 7:00 a.m. and 9:00 a.m. at baseline, every three months, and up to 18 months after vaccination. Samples were processed within two hours, centrifuged at 520 × g for 10 minutes at 4°C, and stored at −70°C until analysis. FBS levels were measured using an autoanalyzer (glucose oxidase/peroxidase method, Pars Azmoun, Iran). Anti-GAD and Anti-ICA were measured via ELISA (Medizymekit, Germany), C-peptide using the CLIA method (Siemens Immulite, Germany), and HbA1c using the turbidimetric method (Pars Azmoun, Iran).

Statistical analysis: All statistical analyses were performed using SPSS software Version 20 (SPSS Inc., Chicago, USA). An independent t-test and Chi-square test were used to compare continuous and categorical variables between the two groups. Analysis of covariance (ANCOVA) was employed to assess differences in outcome changes post-intervention. Data were expressed as mean ± standard deviation (SD) for continuous variables and as percentages for categorical variables. A p-value of < 0.05 was considered statistically significance.

Results

Characteristics of the participants: From October 2021 to May 2022, a total of 33 patients with type 1 diabetes were enrolled based on the inclusion criteria. All diagnoses were confirmed by an experienced endocrinologist. Participants were allocated into two groups: 16 in the control group and 17 in the BCG vaccination group. One participant in the intervention group was excluded due to poor adherence after receiving the first vaccine dose (figure 1). Demographic and baseline laboratory parameters are presented in supplementary table 1. No significant differences were observed between the intervention and control groups in term of baseline characteristics. The mean age was 11.25±3.32 years in the control group and 10.69±3.22 years in the vaccination group (P= 0.63). Anthropometric parameters, including body weight and height, were also comparable between groups (table 1).

Laboratory indicators: Anti-ICA levels in the intervention group decreased significantly from 7.48±2.64 at baseline to 5.62±1.99 post- intervention (P= 0.03). However, FBS showed no significant changes in either group (p > 0.05). Other parameters, including anti- GAD, C-peptide, and CD25, remained unchanged (table 2). HbA1c levels in the intervention group showed a significant reduction after 18 months (8.87±0.91 vs. baseline 9.49±1.71; P = 0.01), whereas no significant changes were observed in the control group (table 3, figure 2).

Safety of two low-dose BCG vaccinations: All vaccinations were administered by trained professionals in a clinical setting. No local or systemic adverse effects were reported in any of participants.

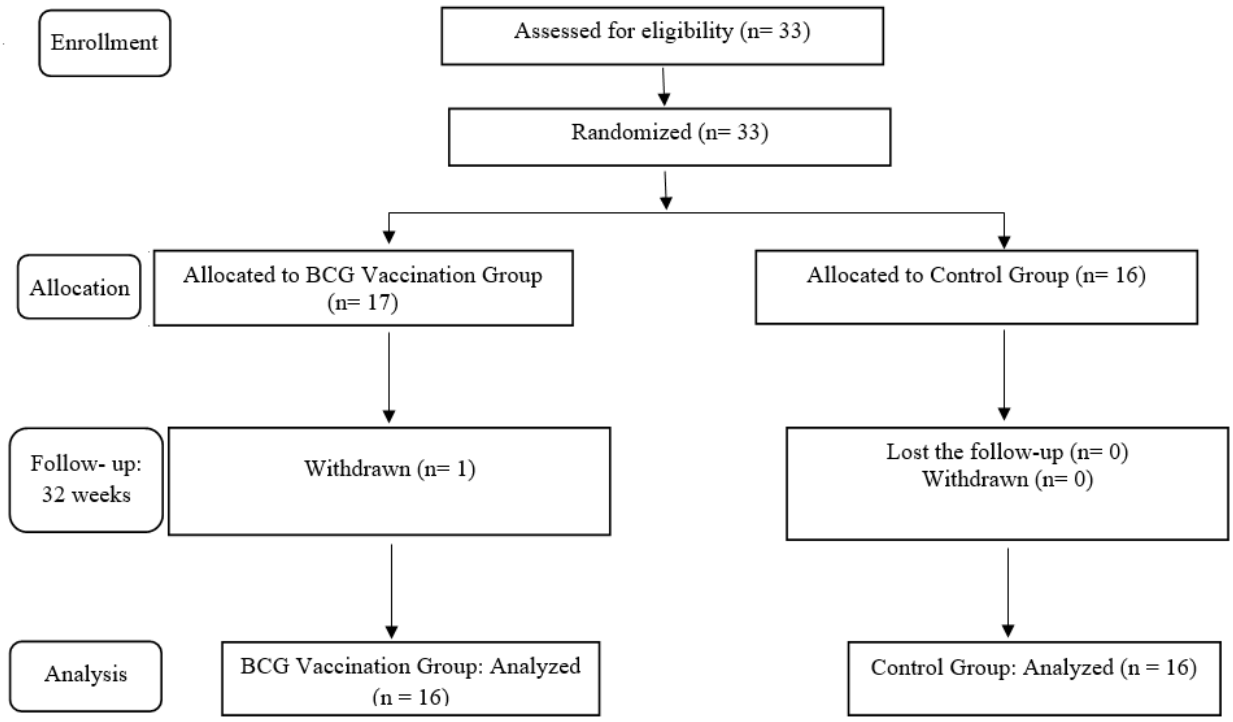

Figure 1. Flow diagram of the study

Table 1. Baseline Characteristics of Participants

Variables	Treatment group (N = 16)	Control group (N = 16)	P-value
Age (year)	10.69 (±3.22)	11.25 (±3.32)	0.63
Gender, n (%)			
Male	6 (37.5%)	8 (50%)	0.47
Female	10 (62.5%)	8 (50%)	
Body weight (kg)	36.18 (±13.73)	38.26 (±13.26)	0.67
Height (cm)	140.81 (±15.40)	147.75 (±21.09)	0.30

-Data are presented as mean±SD. The p-values were calculated using independent samples t-test (2-tailed) or chi- square test. -Abbreviations: F (Female), M (Male)

Table 2. Changes in laboratory markers following BCG vaccination

Variable	Group	Baseline	After 1 year	P-value*	Change	P-value**
FBS (mg/dl)	Treatment	232.50 (±106.07)	237.70 (±102.27)	0.85	11.80 (±48.8)	0.27
	control	161.19 (±71.57)	192 (±80.64)	0.94	30.81 (±27.22)	
Anti- GAD (nmol/L)	Treatment	10.29 (±12.40)	11.26 (±14.13)	0.54	-	-
Anti ICA (Binding Index)	Treatment	7.48 (±2.64)	5.62 (±1.99)	0.03	-	-
C- peptide (ng/ml)	Treatment	0.01 (±0.00)	0.03 (±0.00)	0.44	-	-
CD25 (%)	Treatment	1.48 (±1.81)	1.02 (±0.35)	0.87	-	-

- The data are presented as mean±SD. * P-values were obtained from pair t-tests (2-tailed). ** P-value was obtained by ANCOVA-Abbreviations: FBS (Fasting blood sugar), Anti- GAD (Anti-glutamic acid decarboxylase), Anti ICA (Anti -Islet Cell antibody) TTG IgA (Tissue transglutaminase IgA), C-peptide (Connecting peptide)

Table 3. Longitudinal Changes in HbA1c (%)

Group	Baseline	3 months	6 months	9 months	12 months	18 months	P-value*
Treatment	9.49 (±1.71)	9.76 (±1.60)	9.72 (±1.93)	9.87 (±1.91)	10.37 (±1.89)	8.87 (±0.91)	0.01
control	8.88 (±1.54)	10.02 (±1.39)	10.11 (±1.15)	9.61 (±1.25)	9.69 (±1.64)	-	0.28

- The data are presented as mean ± SD. *P-value for the linear trend was obtained from a pair t-test (2-tailed).

-Abbreviations: HbA1c (Hemoglobin A1C)

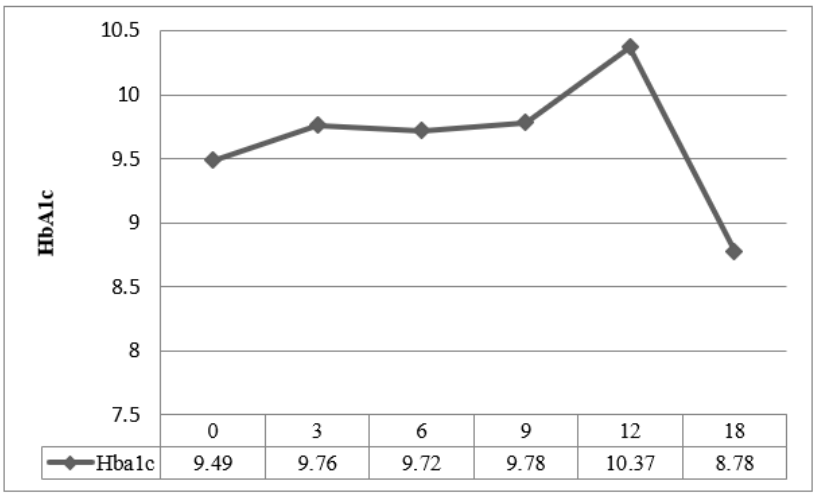

Figure 2. Effect of BCG vaccination on HbA1c

Discussion

Previous studies have shown that in certain autoimmune diseases such as lupus and type 1 diabetes (T1D) a decrease in tumor necrosis factor (TNF) levels can exacerbate autoimmunity. Accordingly, increasing TNF levels may offer therapeutic benefits for some autoimmune conditions. However, due to the toxic effects of high-dose TNF, this study utilized the BCG vaccine as a method to safely enhance TNF activity in T1D patients. As demonstrated by our clinical trial, BCG vaccination may lower HbA1c levels after 18 months and reduce anti-ICA antibodies after 12 months in children with type 1 diabetes. However, it showed no significant effect on fasting blood sugar, anti-GAD antibodies, C-peptide levels, or CD25 expression

These findings are in line with prior studies that have reported improvements in serum glucose and HbA1c levels following BCG vaccination in diabetic patients. For instance, Giovanni Ristori et al. found that BCG vaccination modulates immune activity, leading to long-term reductions in blood sugar levels even in individuals with advanced T1D (20). In a randomized, placebo-controlled study on adults, Kühtreiber et al. reported that two BCG doses administered four weeks apart led to sustained reductions in HbA1c (19). Another studies indicated that BCG vaccination did not significantly increase C-peptide levels, suggesting that its mechanism may not involve pancreatic beta cell regeneration (4, 21). These findings are consistent with the results of the current study.

Recent research has also highlighted that BCG-induced TNF production may alter cellular metabolism by shifting energy production from oxidative phosphorylation to glycolysis. This metabolic shift is thought to improve metabolic indices in T1D patients by promoting glycolysis (2, 20, 22).In our study, no significant changes were observed in anti-GAD or CD25 antibody levels; however, anti-ICA antibodies showed a significant reduction in the vaccinated group. Faustman et al. previously reported a reduction in GAD autoantibodies after BCG revaccination during adulthood. Their protocol included administering 0.1 mg of BCG at four-week intervals, with follow-up over 20 weeks (23). Similarly, in a research, VanBuecken et al. found that both BCG and placebo groups exhibited significant reductions in ICA, GAD, and ICA512 antibodies over a two-year follow-up period (24).

Other studies have shown that TNF induction via BCG vaccination promotes glycolysis, which in turn facilitates the development of regulatory T cells (Tregs) through FOXP3 activation (19). This process may help restore beta cell function by inducing apoptosis in autoreactive T cells, demethylating regulatory genes, and enhancing insulin production and pancreatic cell protection (21, 25, 27). Nevertheless, some of our findings differ from prior research. Specifically, the lack of significant changes in GAD and CD25 levels remains unclear, though it may be attributed to the small sample size.

Conflicting evidence exists regarding the efficacy of BCG vaccination in preserving beta cell function (28). For example, a study on 78,492 individuals by Rousseau et al. found no association between neonatal BCG vaccination and reduced diabetes incidence during the first year of life (28). Similarly, a systematic review and meta-analysis of randomized controlled trials involving 198 subjects showed no significant therapeutic benefit from a single BCG injection (4). Conversely, an epidemiological study in Turkey suggested that multiple BCG doses—administered at least twice could have a protective and therapeutic effect in T1D (29). Some studies propose that the benefits of BCG vaccination may emerge only after one year and require repeated administration over time (30, 31). Thus, to achieve consistent outcomes, repeated BCG vaccination over extended periods may be necessary, with informed consent from patients.

BCG vaccination has also been shown to selectively eliminate autoreactive T cells by increasing TNF production, while sparing normal T cells (32). TNF thus plays a dual role in immune regulation: it has both pro-inflammatory and immunoregulatory effects (33). In T1D, TNF appears to activate suppressive pathways that lead to the apoptosis of autoreactive T cells and the expansion of Tregs (34). This immune rebalancing can ultimately result in normoglycemia, even in advanced stages of the disease (3).The primary limitation of our study was the small sample size, which may have reduced the statistical power to detect changes in some immune markers. Moreover, given the inconclusive evidence regarding the efficacy of BCG vaccination in preventing or treating autoimmune diseases, including T1D, further large-scale, well-controlled clinical trials are necessary (35).

In summary, the findings of this study indicate that administering two doses of the BCG vaccine led to a reduction in HbA1c levels and anti-ICA antibodies, suggesting a potential immunomodulatory effect. However, no significant reduction in blood glucose levels was observed during the study period. Previous studies have suggested that repeated BCG vaccination may result in long-term reductions in blood glucose through immune suppression and metabolic modulation (2, 19). Given that the BCG vaccine is routinely administered at birth in Iran, it is likely that the observed changes in HbA1c and anti-ICA levels are attributable to the booster dose administered in

this study. To better understand the long-term implications of BCG vaccination on glycemic control, further research is recommended particularly studies that explore the effects of multiple booster doses over extended follow-up periods.

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Ethics approval: The protocol of the present study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences in Yazd (IR.SSU.REC.1399.023) and registered in the Registry Office of Clinical Trials of Iran (http://www.irct.ir: IRCT20201012049003N1). The protocol was also based on the CONSORT checklist.

Conflict of interests: There is none to declare.

Authors' contribution: M. Ordoei, N. Behniafard, and N. Namiranian equally contributed to the conception and design of the research. S. Jam, S. Asadollahi and R. Razavi collected and analyzed the data. H. Mahmoudi contributed to the interpretation of the data. N. Namiranian, R. Razavi and M. Ordoei drafted the manuscript. All the authors critically revised the manuscript, agree to be fully accountable for the integrity and accuracy of the work, and read and approved the final manuscript.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

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