INTRODUCTION

Type 1 diabetes mellitus (DM) is a condition in which there occurs an absolute insulin deficiency due to autoimmune destruction of pancreatic beta cells. Due to the damage to beta cells glucose doesn’t move into cells and it builds up in blood causing high blood sugar. It is usually diagnosed in children and young people and thus also used to be called as juvenile diabetes. The usual symptoms include extreme thirst, frequent urination, dehydration, unexplained weight loss, polyphagia, and lethargy. Major life threatening complications include retinopathy, neuropathy, nephropathy, foot problems, diabetic ketoacidosis and cardiovascular problems. The standard treatment strategy includes daily insulin injections along with proper diet regulation. Types of insulin available are rapid acting, intermediate acting, short acting and long acting insulins. Most patients with type 1 diabetes mellitus follow a regimen of multiple daily injections of basal/bolus insulin but patients with frequent or severe hyperglycemia should consider continuous subcutaneous insulin infusions. Over the past few years the understanding about many aspects of the disease, including its genetics, epidemiology, immune and β-cell phenotypes, and disease burden have been increased and many methods are assessed to improve the clinical management of the disease. However, some gaps still exist in our understanding of type 1 diabetes and to decrease the complications and burden [1].

Bacille Calmette Guerin (BCG) is an attenuated version of a bacterium called Mycobacterium bovis which is closely related to Mycobacterium tuberculosis, the agent responsible for tuberculosis infection which is a leading cause of human disease and death, particularly in developing countries. It is one of the oldest vaccines in use. It is an effective immunization against tuberculosis and also used for early stage bladder cancer therapy as the intravesical injection of BCG eradicates superficial bladder tumors by invoking a strong local immune reaction. In most tuberculosis endemic countries, BCG is usually given around birth to prevent severe TB in infants. The World Health Organization recommends the BCG vaccine for all children born in countries with a high incidence of tuberculosis and/or leprosy. BCG vaccine has a documented protective effect against meningitis. It does not prevent primary infection and, more importantly, does not prevent reactivation of latent pulmonary infection, the principal source of bacillary spread in the community. BCG vaccination confers a survival advantage in low birth weight infants against mortality from a diversity of infections unrelated to tuberculosis, and BCG vaccinations in healthy populations confer long term survival advantages [2].
The biological interaction between Mycobacterium tuberculosis and the human host is complex and only partially understood. Recent advances in areas such as mycobacterial immunology and genomics have stimulated research on numerous new experimental vaccines, but it is unlikely that any of these urgently need vaccines will be available for routine use within the next few years. Recently, in addition to the antimicrobial host defense property, BCG has shown therapeutic promise for type 1 diabetes (T1D) and several other autoimmune diseases. In multiple sclerosis, BCG decelerates disease activity through modulation of T-cell-mediated autoimmunity. Studies on non-obese diabetic (NOD) murine models have shown that the BCG vaccine produced a potent suppression of insulitis by generation of some suppressor cells. In murine models, permanent reversal of type 1 diabetes is observed in non-obese diabetic (NOD) mice if the BCG therapy is given as BCG or BCG-equivalent treatment (i.e., complete Freund’s adjuvant [CFA]) after displaying early signs of diabetes, new-onset diabetes or full-blown diabetes. However, giving a single injection of BCG at birth in diabetes-prone humans or NOD mice has no observable benefits. Thus, it appears that the disease must be apparent for BCG to be effective. A study by Willem M. Kühnreiter demonstrates that BCG vaccination improved glucose metabolism by systemically switching from oxidative phosphorylation to aerobic glycolysis (a high glucose consumption state) in diabetic mouse models. Several studies on NOD mice have shown that repeated BCG vaccination is safe and more effective than a single dose in preventing type 1 diabetes. Positive findings from such studies enabled researchers to advance to human trials. A pilot trial by Shehadeh et al. found that a single injection of the BCG vaccine induced clinical remission in 65% of recent-onset T1DM patients as compared with 7% of controls. Positive findings such as this enabled Massachusetts General Hospital researchers to advance to human trials [3].

In an eight-year trial, nine people with type 1 diabetes were given two shots of the BCG vaccine. All the participants had a statistically significant change in HbA1c levels and among control participants who received placebo, no significant HbA1c improvements were observed at either the five- or eight-year marks. Another study with 282 human participants have shown that BCG vaccine exerted major epigenetic effects on the immune system related to the regulatory T cells (Treg) tolerance and resulted in increased utilization of blood sugar by white blood cells through increased aerobic glycolysis. Also repeat BCG vaccination was associated with stable, long-term lowering of HbA1c levels. BCG produced a systemic shift in glucose metabolism from oxidative phosphorylation to aerobic glycolysis, which corrected metabolism to normal within the lymphoid compartment. In type 1 diabetes (T1D), three BCG vaccines administered in childhood lowered the incidence of T1D by age 12. The BCG vaccine is thought to activate the reprogramming of immune cells and alter cellular metabolism, including the acceleration of glycolysis. A study in children who have been recently diagnosed with insulin dependent diabetes mellitus (IDDM) does not affect the progressive decline in C-peptide levels or alter the clinical course of the disease [4].

**LITERATURE REVIEW**

i. A study “Effect of adjuvant therapy on development of diabetes in mouse and man” by Shehadeh N et al. published on March 1994 showed that Freund's complete adjuvant (CFA) and BCG vaccine modulate the development of type 1 diabetes in animal models. In non-obese diabetic mice, BCG significantly reduced the proportion of developing diabetes compared with controls. Histological examination showed that autoimmune disease still developed but had been diverted to become nondestructive. In a preliminary trial in 17 newly diagnosed, type 1 diabetic patients, intracutaneous administration of 0.1 mL of BCG 1 mg/mL led to clinical remission in 11 (65%) by week 4 in 6. Remission has been sustained in 3 for 6-10 months and no side-effects were reported [4].

ii. A study conducted by Shehadeh N, et al. evaluated the protective effect of repeated BCG vaccinations on preventing diabetes in NOD mice. 53% of the control group, 26% of the single vaccine-treated (at age 35 days) mice, and 30% of the single vaccine-treated (at age 90 days) mice developed diabetes, and none of the repeated BCG vaccination animals developed the disease, up to 250 days of age. While the severity of insulitis was lower in repeatedly BCG-treated mice at age 120 days as compared with controls and single BCG-vaccination groups, they could not detect significant differences in the Intracellular adhesion molecule-1 (ICAM-1) expression between the various groups. There were no differences in weight gain and blood hematocrit between the different groups. Their report demonstrates that repeated BCG vaccination is safe and more effective than a single dose in preventing type 1 diabetes in NOD mice [5].

iii. The effects of transfer of macrophage and T-cell fractions on the pathogenesis were examined in the study conducted by Yagi H et al. in order to obtain valid evidence for the speculation that macrophages has a suppressive effect against a variety of lymphocyte functions which can be induced by BCG. They found that transfer of macrophage-enriched spleen cell fraction harvested from the BCG-treated females to young females abolished the occurrence of spontaneous diabetes up to the age of 25 to 30 weeks and also macrophage transfer prevented the progress of insulitis. In contrast, transfer of a T-cell enriched fraction did not suppress insulitis and overt diabetes. From these results, it was concluded that the suppression of the autoimmune pathogenesis of diabetes by BCG is due to the generation of suppressor macrophages [6].

iv. A randomized double-blind placebo-controlled trial was conducted by Allen HF et al. in 94 children aged 5-18 years who were referred to the Barbara Davis Center for Childhood Diabetes or the Baystate Medical Center with a diagnosis of new-onset type 1 diabetes. The aim of the study was to test whether BCG vaccine preserves beta-cell function and increases the remission rate in children with new-onset type 1 diabetes. They received either BCG or saline intradermally within 4 months of onset of symptoms and then evaluated at 3-month intervals for 2 years. The primary end point was remission and secondary end points were C-peptide levels, insulin dose, and HbA1c.47 was
randomized to each arm. One patient from each group achieved remission. Fasting and stimulated C-peptide levels did not differ by treatment arm but declined in both groups and were lower initially and during the entire 2-year period in younger children. Insulin requirements and HbA1c levels did not differ in the two groups. The results concluded that vaccination with BCG at the time of onset of type 1 diabetes does not increase the remission rate or preserve beta-cell function [7].

v. A proof-of-principle, double-blind, placebo-controlled trial was conducted by Faustman DL et al. in adults 18-50 years age with long-term type 1 diabetes treated continuously with insulin from the time of diagnosis at one clinical center in North America. Six subjects were randomly assigned to BCG or placebo and compared to self, healthy paired controls (n=6) or reference subjects with (n=57) or without (n=16) type 1 diabetes. Weekly blood samples for 20 weeks were taken. BCG-treated patients and one placebo-treated patient who, after enrollment, unexpectedly developed acute Epstein-Barr virus infection, a known TNF inducer, exclusively showed increases in dead insulin-autoreactive T cells and induction of Tregs. C-peptide levels significantly rose transiently in two BCG-treated subjects and the EBV-infected subject in reference diabetic subjects. The study concluded that BCG treatment or EBV infection transiently modified the autoimmunity that underlies type 1 diabetes by stimulating the host innate immune response, thereby suggesting that BCG may have value in the treatment of long-term diabetes [8].

vi. A study was conducted by Elliott JF et al. with the aim to determine whether administration of BCG vaccination to newly diagnosed IDDM patients can help preserve C-peptide secretion over the subsequent 18 months. 26 IDDM patients, diagnosed within the previous year with basal C-peptide levels >0.06 nmol/l, and negative reactions to Mantoux's test, were randomized pairwise and were given either 0.1 ml BCG vaccine or 0.1 ml saline intradermally. Fasting and glucagon-induced C-peptide levels and HbA1c were measured in all patients and insulin dose was recorded at each visit. 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 HbA1c at any time between the groups. Thus the study concluded that 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 [9].

vii. This study was conducted by Stienstra R. et al. the aim the novel study reveals beneficial effects on glycaemic control in patients with long-standing type 1 diabetes mellitus (T1DM). These effects are ascribed to an accelerated glucose consumption in immune cells due to increased glycolysis and reduced oxidative phosphorylation [3].

viii. This study was conducted by kuhreiber WM. In T1D, BCG restored blood sugars to near normal, even in patients with advanced disease of >20 years duration. This clinically important effect may be driven by resetting of the immune system and the shifting of glucose metabolism from oxidative phosphorylation, a state of minimal sugar utilization, to aerobic glycolysis, a state of high glucose utilization, for energy production. The mechanistic findings support the hygiene hypothesis and reveal the immune and metabolic synergy of mycobacterial reintroduction in modern humans [10].

ix. BCG Vaccinations Up regulate Myc, a Central Switch for Improved Glucose Metabolism in Diabetes is the study conducted by kuhreiber WM. Myc has emerged as a pivotal transcription factor for four metabolic pathways: aerobic glycolysis, glutaminolysis, polyamine synthesis, and HIF-1a/mTOR. Each of these pathways accelerates the utilization of sugar. The BCG vaccine, a derivative of Mycobacteria-bovis, has been shown to trigger a long-term correction of blood sugar levels to near normal in type 1 diabetics (T1D). Here they using RNAseq in monocytes and CD4 T cells, that BCG treatment over 56 weeks in humans is associated with up regulation of Myc and activation of nearly two dozen Myc-target genes underlying the four metabolic pathways. This is the first documentation of BCG induction of Myc and its association with systemic blood sugar control in a chronic disease like diabetes [11].

x. A study Therapeutic Effects of BCG Vaccination on Type 1 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trial conducted by Yu-chenchang et al., published on 27 March 2020 performed in 198 subjects investigated the efficacy of the BCG vaccine for the treatment of T1DM. The study concluded that there is no robust evidence to support the use of the BCG vaccine for the treatment of T1DM as there’s no significant difference in HbA1c levels or fasting C-peptide levels in the BCG intervention group as compared with that in the placebo group, although the HbA1c levels tended to improve. Stating additional randomized controlled trials are needed to assess the long-term effects of the BCG vaccine on glycemic control [12].

xi. A study ‘Long-term reduction in hyperglycemia in advanced type 1 diabetes: the value of induced aerobic glycolysis with BCG vaccinations’ conducted by Willem M. Kühreibeetal., published on December 2018 with 282 participants demonstrates a randomized 8-year long prospective examination of type 1 diabetic subjects with long-term disease who received two doses of the BCG vaccine. Study showed a reduction in HbA1c levels of greater than 10% after year 3, 18% at year 4, and the HbA1c remained low for the next 5 years. These findings promotes the further testing of vaccine therapy for improved blood sugar control through changes in metabolism and durability with epigenetic changes even in advanced Type 1 diabetes [13].
Type 1 Diabetes Mellitus (T1DM) remains an incurable autoimmune disease characterized by the progressive and irreversible destruction of pancreatic beta cells. In addition to traditional insulin replacement therapy, several efforts aiming at curing T1DM have focused on altering the autoimmune reaction. The approach began with trials of immunosuppressants, such as cyclosporin, and monoclonal antibodies. Antigen-based therapies targeting the glutamate decarboxylase protein to induce immune tolerance have also been proposed. However, the high heterogeneity of the immune-mediated destruction process and large disparities between study designs affected the development of effective interventions. The considerable side effects also compromise their broad use. Cell therapies, such as islet transplantation, have been shown to promote β-cell neogenesis and proliferation in animal models, but only a minority of islet transplant recipients achieve persistent insulin independence. Dietary approaches, such as vitamin D supplementation, have been shown to have the potential to modulate autoimmunity and improve glycemic control in T1DM patients with vitamin D deficiency in few studies.

According to the systematic review and meta-analysis illustrating the therapeutic effects of the BCG vaccine for T1DM patients there was no statistical differences in HbA1c or fasting C-peptide levels after the intervention as compared with a placebo. Although HbA1c levels tended to improve following administration of the BCG vaccine. However, the combined effect size and related analysis should be interpreted with caution because of the small sample size and limited number of trials. BCG possibly generates a suppressing effect through macrophages against a variety of lymphocyte functions. If a comprehensive mechanism and appropriate regimen can be established as evidence accumulates, owing to the relatively low expense, safety, and convenience, then the BCG vaccine is a cost-effective option to be incorporated routinely into the clinical management of T1DM. The combination with a complementary therapy such as vitamin D also merits further investigation. Overall adverse reaction rate seemed higher in older people than in neonate which is also worth investigating in future research.

In an 8-year long clinical trial of monitoring subjects receiving Mycobacterium re-introduction through the BCG vaccine triggers two types of clinical effects in patients with established T1DM: stable and long-term reductions in blood sugar and epigenetic changes in Treg signature genes for restored tolerance. Both beneficial effects appear to be driven by a systemic metabolic shift from oxidative phosphorylation towards accelerated and early aerobic glycolysis. These significant clinical effects, using BCG with intradermal dosing, took three years to occur but then were steady for at least five additional years without further interventions. The induced metabolic shift in diabetic human subjects toward aerobic glycolysis, results in accelerated glucose utilization that further regulate blood sugars. There’s no reported cases of severe hypoglycemia occurred in BCG vaccination subjects during 5 years of monitoring after the HbA1Cs returned to the near normal range. The reason behind BCG’s reduction of HbA1c in humans taking place only after 3-4 years is may be due to autoimmune disease takes years to develop, the reversal of autoimmunity may also share similar time dependence.

An epidemiology study from Turkey has showed that multi-dosing BCG may not only be beneficial in T1DM treatment, but also in its diabetes prevention. Participants who received greater than 2 childhood vaccines of BCG had diminished lifelong risk for developing T1DM. In a 12-week-long Phase 1 trial showed that C-peptide production was not increased in a clinically meaningful way, although seeing any restored C-peptide in T1DM with this long standing disease was unusual. BCG therapy in human autoimmunity opened up the possibility of a safe and an effective vaccine for resetting the immune system even in existing T1DM disease states. The BCG vaccine confirmed and verified an entirely novel way to regulate blood sugars. Fully enrolled and ongoing human clinical trials continue to test the validity of BCG lowering of blood sugars in large patient populations.
of insulitis was found to be lower in repeatedly vaccinated mice but there was no significant difference seen in the expression of Intracellular adhesion molecule-1 (ICAM-1) in both groups [5] there were also no differences in weight gain and blood hematocrit values in both groups [5].

Several studies on rodent model of type 1 diabetes mellitus have been carried out which showed that BCG vaccine reverses disease by stimulating innate immunity and inducing the host to produce tumor necrosis factor (TNF), which kills disease-causing autoimmune cells and thereby causing restoration of pancreatic [8] C beta-cell function through regeneration. These findings were later translated to humans to identify the value of BCG vaccine in the treatment of long-term diabetes mellitus and have shown that in BCG treated subjects there was an increase in dead insulin-autoreactive T cells, induction of Tregs and significant transient elevation of C-peptide levels [8].

The role of BCG vaccine in children with new onset diabetes mellitus have also been studied. Such studies were carried out to analyze whether BCG vaccination preserves beta-cell function and increases the remission rate in children by monitoring remission, C-peptide levels, insulin dose, and HbA1c levels. There were no significant differences seen in C-peptide levels, insulin dose requirements or HbA1c levels [7,9]. Studies have shown that vaccination with BCG at the time of onset of type 1 diabetes or those recently diagnosed with IDDM does not increase the remission rate or preserve beta-cell function. Or alter the clinical course of the disease [7, 9].

The impact of Bacillus Calmette-Guerin (BCG) vaccination on antimicrobial host defense, a novel study reveals beneficial effects on glycaemic control in patients with long-standing type 1 diabetes mellitus (T1DM). These effects are ascribed to accelerated glucose consumption in immune cells due to increased glycolysis and reduced oxidative phosphorylation. [10]

In type 1 diabetes, BCG restores blood sugar to near normal, even in patients with advanced disease of > 20 years duration by resetting of immune system and the shifting of glucose metabolism from overactive oxidative phosphorylation, a state of minimal sugar utilization, to aerobic glycolysis, a state of high glucose utilization, for energy production [10].

CONCLUSION

There is no robust evidence to support the significant benefit of BCG vaccine for the treatment of T1DM, according to the Systematic Review and Meta-Analysis of Randomized Controlled Trials conducted by Yu chenchang et al. [12] But the HbA1c levels tended to improve following administration. [12] These are the results from quantitative analysis and it must be interpreted carefully due to the limited number of studies and small sample size. [12] Additional randomized controlled trials are needed to enhance the evidence, evaluate the long-term effects of the BCG vaccine on glycemic control, as well as elucidate the underlying mechanisms. [12] In an 8 year long prospective study with the BCG-treated T1DM patients showed a reduction in HbA1c levels of greater than 10% after year 3, 18% at year 4, and the HbA1c remained low for the next 5 years. [13] BCG vaccinations did not induce a clinically meaningful return of C-peptide levels in the pancreas by regeneration, as observed in the NOD mouse model of diabetes. [13] Thus pancreas rescue or regeneration could not fully account for the persistent and long term HbA1c lowering in humans receiving BCG. [13]. The beneficial effect of BCG in humans could be due to the induction of the beneficial Treg cells. [13]. Thus this study concluded that BCG can significantly lower blood sugars without underlying autoimmunity, and BCG has no deleterious effect by lowering blood sugars lower than normal. [13, 1] BCG treatment does not carry the risk of hypoglycemia as is the case for intense insulin therapy. [13]. The BCG vaccine confirmed and verified an entirely novel way to regulate blood sugars. [1] Fully enrolled and ongoing human clinical trials continue to test the validity of BCG lowering of blood sugars in large patient populations and to find out whether BCG vaccine was potent enough to have these beneficial clinical effects in patients with long standing diabetes. [1] Before this time, immune interventions were exclusively tried in only new onset T1DM, a clinical setting thought easier to reverse [1].

In newly diagnosed type 1 diabetes patients’ administration of vaccination induced a clinical remission [4]. Repeated BCG vaccination is more effective and safe than a single dose in preventing type 1 diabetes in NOD mice. [5] BCG causes suppression of the autoimmune pathogenesis of diabetes by the generation of suppressor macrophages. [6] The mean basal and stimulated C-peptide levels in the BCG-treated children with recently diagnosed IDDM did not differ significantly from those in the control group, and there was no difference in insulin dose or HbA1c at any time between the groups. [9] Vaccination with BCG in such children has not been found to be effective in improving the disease. [7,9] In case of adults with long standing type 1 diabetes mellitus BCG treatment transiently modified the autoimmunity that underlies type 1 diabetes by stimulating the host innate immune response [8-13].

REFERENCES

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