



## Review Article

### A REVIEW ON FUTURE PROSPECT OF BCG VACCINE ON BENEFICIAL EFFECTS TO IMPROVE THE IMMUNE AND METABOLISM IN TREATING T1DM

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#### ABSTRACT

The purpose of this study is BCG vaccine can improve beneficial immune and metabolic effect on T<sub>1</sub>DM. The BCG vaccine originally developed for tuberculosis and found to be an extremely safe and lowers HbA1C levels after administering in specified doses in T<sub>1</sub>DM participates. T<sub>1</sub>DM is an autoimmune disease in which the body's immune system mistakenly attacks insulin producing Beta cells in the pancreas. This condition necessitates take insulin through injections or via a small tube inserted in the skin and attached to an insulin pump. BCG in T<sub>1</sub>DM acts by increasing the production of TNF which kills an auto reactive T cell that attacks pancreatic islets in case of T<sub>1</sub>DM. Besides this, in this article it is also shown that BCG decreases blood glucose levels by shifting process of glucose metabolism from oxidative Phosphorylation, the most common pathway by which cells convert glucose into energy, to aerobic glycolysis through which cells consume greater amount of glucose significantly.

**KEY WORDS:** Type-1 diabetes mellitus (T<sub>1</sub>DM), BCG vaccine, Phosphorylation, immune & metabolic effect.

#### INTRODUCTION

The main aim of this study is to strongly support the use of BCG vaccine for type -1 diabetes and it's relevant mechanisms which helps to lower the blood glucose levels nearer to normal HbA1c levels. It also discusses the further development needed to be done for FDA approval of BCG for type-1 diabetes. It also includes the doubts need to be clarified in further trials<sup>1&2</sup>.

#### BCG VACCINE:

Bacillus Calmette Guerin vaccine is a safe derivative of a strain of mycobacterium bacteria. The vaccine was originally developed 100 years back and is still used on the universal basis to prevent tuberculosis. Over the past century more than 3 billion people have received BCG vaccine, typically at birth. The WHO has heralded BCG vaccine as the safest vaccine in the history of world<sup>3</sup>.

Interestingly Mycobacterium has co-evolved with humans from many years but with today's cleaner modernized human environments, this Mycobacterial species is typically not found within humans. This has led many to believe the Hygiene hypothesis of why autoimmune disease and allergies and are on the rise in civilized countries that humans have lost evolutionary advantages conferred by living with safe variants of Mycobacterium has been using from almost a century. BCG vaccine is most commonly has been using from almost a century for tuberculosis prevention which is also used widely to treat bladder cancer and leprosy<sup>4</sup>.

#### TYPE-1 DIABETES:

Type-1 Diabetes is an autoimmune disease in which immune system destroy the insulin secreting pancreatic beta cells. Human with this problem needs to administer insulin through injections for via a small tube inserted in the skin and attached to an insulin pump<sup>5&6</sup>.

#### MECHANISM OF BCG VACCINE:

Researchers have proven that BCG increases have actions of increasing the production of TNF or TNFR2 agonism which helps in killing auto reactive T-cells that attack tissues in the body pancreatic islets in autoimmune diabetes mellitus (T<sub>1</sub>DM). It also increases production of regulatory T cells which inhibits autoimmune response<sup>7</sup>.

Apart from killing or eliminating the auto reactive cells TNF induction or TNFR2 agonism may act by triggering the initiating or expanding Tregs. Tregs are the subtype of CD4 cells which helps to treat or prevent autoimmunity by improving self tolerance, immune homeostasis and suppression of cytotoxic T cells<sup>8</sup>.

#### OTHER MECHANISM

The specific BCG impact on blood sugars in humans is driven by a novel mechanism as part by increasing taste of WBC for sugar, they switch their normal energy consumption habits to process called aerobic glycolysis. Aerobic glycolysis is metabolic state in

which high cellular glucose utilization and rapid ATP production takes place<sup>9</sup>.

A systemic shift in glucose metabolism from oxidative Phosphorylation to aerobic glycolysis on a highly regulated level result in increased glucose uptake and its regulation at the cellular level prevent the potential risk of hypoglycemia which can be result from insulin treatment. The BCG specific effect on metabolism induce increase in key early glycolytic enzymes up regulation, glucose uptake which leads to the systemic lowering of blood sugars, shunting the accelerated glucose utilization through the pentose phosphate pathway, increased utilization of late glycolysis steps including the Krebs cycle, increased lactate production and decreased oxidative Phosphorylation<sup>10</sup>.

#### RESEARCH:

Faustman's team first reported in 2001 that inducing TNF production could cure T1DM in mice but since TNF dosing is toxic in humans clinical trials have utilized BCG for its ability to elevate TNF levels safely. In 20 week phase-I trial there is a transient increase in Insulin production but at the end of trial there was no reduction in HbA<sub>1c</sub>, the established measure of blood sugar levels over time<sup>11</sup>.

An extension and expansion of that trial with long term follow up with 282 human study participants of which 52 with type -1 diabetes mellitus participated in the BCG trails and 230 also contributed blood samples for mechanistic studies. Regular monitoring of blood glucose levels in clinical trial participants found that HbA<sub>1c</sub> levels of those receiving BCG has dropped more than 10% in 3 years after introduction of BCG and by more than 18% in 4 years and that reduction was maintained over next four years with treated participants having an average HbA<sub>1c</sub> of 6.65 close to 6.5 considered the threshold for type -1 diabetes mellitus diagnosis. This trail was approved for phase II trials by FDA<sup>12</sup>.

#### Advantages of BCG over Insulin

- Increasing the Insulin production
- Improvement in the HbA<sub>1c</sub>
- Change in Immune response
- No History of Hypoglycemic

There is only one licensed manufacturer of the vaccine in USA, Organon Teknika Corporation a division of Merck even though the vaccine is generic only pharmaceutical companies with vaccine manufacturing facilities, a large capital investment, would properly get involved<sup>13</sup>.

If the BCG shows more promise in the phase-II trail, good money you will get thus one or more of the major manufacturer of vaccine can fund for the phase-III trail to get an indication of treating or preventing T<sub>1</sub>DM. They may also improve vaccine to increase the immune response which might improve the effectiveness short and long term.

There is one more reason that the manufacturer of the BCG vaccine needs to eventually be involved in the trail. The whole purpose of phase I, II, III clinical trials is to eventually gain FDA approval for a new drug, or in this case for a new indication. Even if Dr. Faustman's research shows that the vaccine can prevent DM, without FDA approval for a change in the labeling of the vaccine, it technical cannot be used for T<sub>1</sub>DM and legally, organonTeknika cannot promote it for T<sub>1</sub>DM without FDA approval<sup>14</sup>.

#### SEVERAL THINGS DON'T KNOW WHICH NEED TO BE FULLY EVALUATED BEFORE THIS VACCINE BECOMES A MEDICAL TOOL

1. How does BCG vaccine will be most effective to reverse type-1 diabetes mellitus.
2. Is there significant ADE after the appropriate dose is determined.
3. How long does it show the effect.
4. Does the autoimmune disease remission occurs after a few years or decades.
5. Does the patient still need to use insulin to maintain proper blood glucose levels.
6. Faustman's team was unable to determine actual levels of insulin since currently available analytical techniques cannot tell the difference between injected and endogenous insulin.

Trails so far involve adult patients with established T<sub>1</sub>DM at least as 2 years of disease and in many cases more than 15 years duration. Thus how BCG works in pediatric patients how BCG works in new onset patients and how BCG works in T<sub>1</sub>DM patients with more than 2 decades of disease are all questions, we hope to study in trails soon. There is growing evidence that BCG may play a role in metabolic disease including T<sub>2</sub>DM that data is extremely early but a mechanism are definitely interested in exploring.

#### SUBSEQUENT PROSPECTS OF BCG VACCINE

The future of the BCG vaccine, the Faustman's is moving the BCG vaccine into a phase- II clinical trial soon that will include 150 patients followed over 5 years. The study will examine whether repeated BCG vaccinations will clinically improve T<sub>1</sub>DM outcomes in adults with the disease. The trail is enrolling patients funded involvement of any pharmaceutical companies. However the phase-III trail, which will provides definite data on the effectiveness of the BCG vaccine, is significantly more.

The mechanism of BCG which never previously seen in response to treatment with any drug, a shifting of the process of glucose metabolism from oxidative Phosphorylation which is the most common pathway by which cells convert glucose into energy, to aerobic glycolysis which improves glucose consumption by cells. Apart from this BCG can reduce blood sugar elevations by acting on autoimmune system without causing hypoglycemia and without requiring too many continuous doses, also increasing the insulin production by conserving pancreatic beta cells from autoimmune attack.

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