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BCG vaccine found to improve blood sugar levels in type-1 diabetics

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A study from a Massachusetts General Hospital (MGH) research team reports that after three years of receiving two administrations of the bacillus Calmette-Guérin (BCG) vaccine four weeks apart, participants in clinical trials with longstanding type 1 diabetes showed an improvement in HbA1c to near normal levels which persisted for the following five years.

"This is clinical validation of the potential to stably lower blood sugars to near normal levels with a safe vaccine, even in patients with longstanding disease," says Denise Faustman, MD, PhD, director of the MGH Immunobiology Laboratory, principal investigator of BCG clinical trials at MGH and senior author of the *npj Vaccines* report. "In addition to the clinical outcomes, we now have a clear understanding of the mechanisms through which limited BCG vaccine doses can make permanent, beneficial changes to the immune system and lower blood sugars in type 1 diabetes."

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Used for almost a century to prevent tuberculosis, BCG has been known for more than 30 years to boost production of a cytokine called tumor necrosis factor (TNF), which may be beneficial in autoimmune diseases both by eliminating the auto reactive T cells that attack an individual's tissues - in the case of type 1 diabetes, pancreatic islets - and by inducing production of regulatory T cells (Tregs) that could prevent an autoimmune reaction. Faustman's team first reported in 2001 that inducing TNF production could cure type 1 diabetes in mice, but since TNF dosing is toxic in humans, clinical trials have utilized BCG for its ability to elevate TNF levels safely.

Initial clinical trial results, published in a 2012 *PLOS One* paper, reported that two doses of BCG spaced four weeks apart led to reductions in auto reactive T cells, an increase in Tregs and what turned out to be a transient increase in insulin production.

But by the end of that short 20-week trial, there was no reduction in HbA1c, the established measure of blood sugar levels over time. An extension and expansion of that trial with long term follow-up has found significant clinical benefits, including restoration of near blood sugar levels. The current results are based on data from 282 human study participants - 52 with type 1 diabetes who participated in the BCG clinical trials and 230 who contributed blood samples for mechanistic studies.

Regular monitoring of clinical trial participants found that HbA1c levels of those receiving BCG had dropped by more than 10 percent at three years after treatment and by more than 18 percent at four years. That reduction was maintained over the next four years, with treated participants having an average HbA1c of 6.65, close to the 6.5 considered the threshold for diabetes diagnosis, and with no reports of severe hypoglycemia. Participants in the placebo group and in a comparison group of patients receiving no treatment experienced consistent HbA1c elevations over the same eight-year time period.

In investigating how BCG administration produces its beneficial effects, the research team identified a mechanism never previously seen in humans in response to treatment with any drug - a shifting of the process of glucose metabolism from oxidative phosphorylation, the most common pathway by which cells convert glucose into energy, to aerobic glycolysis, a process that involves significantly greater glucose consumption by cells. The researchers also found that BCG could reduce blood sugar elevations in mice that were caused by means other than autoimmune attack, raising the possibility that BCG vaccines could also be beneficial against type 2 diabetes.

Mihai G. Netea, PhD, professor in the Department of Internal Medicine at Radboud University Medical Center in the Netherlands, says of this study, "The clinical effects and the proposed mechanism demonstrated are exciting and add to the emerging consensus that the BCG vaccine can have a lasting and valuable impact on the immune system. We know, and this study shows, that BCG vaccination induces epigenetic reprogramming at the chromatin architecture level and functional alterations indicative of a permanent change in immunity. The MGH trials and other, larger prevention and intervention trials underway around the globe may lead to a major shift in the prevention and treatment of infections and autoimmunity." Netea was not involved in the current study.

The results are published in npj vaccines.