

Potential mechanism by which BCG vaccine lowers blood sugar levels to near normal in type 1 diabetes discovered

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Previous research has shown that the bacillus Calmette-Guerin (BCG) vaccine, used to prevent tuberculosis, can reduce blood sugar levels in people with advanced type 1 diabetes in the long term. New research being presented at this year's European Association for the Study of Diabetes (EASD) Annual Meeting in Berlin, Germany (1-5 October) reveals the mechanism through which the vaccine can make durable, beneficial changes to the immune system and lower blood sugars.

The new findings suggest that the immune-metabolic imbalance in type 1 [diabetes](#) could stem from too few microbial (ie, germ) exposures that have been eliminated in today's more sterile environments, and that reintroduction of a bacterium (BCG) might reset abnormal metabolic functions boosting the immune system to consume [sugar](#) and reduce blood glucose levels over time.

"It has long been believed that the move to cleaner and more urban environments is involved in not only how type 1 diabetes develops, but increased incidence of the disease", explains Dr. Faustman, Director of the Massachusetts General Hospital Immunobiology Laboratory, who led the study. "In particular, reduced exposures to certain microbes, the consequence of better sanitation, greater use of antibiotics, smaller family sizes, cleaner houses, less daily exposures to the soil, and less exposure to domesticated animals, appears to have changed the modern metabolic function."

The BCG vaccine, based on a harmless strain of bacteria related to the one that causes tuberculosis, appears to have the effect of safely mimicking the microbial exposures modern societies have lost.

In an earlier phase 1 randomised trial, two injections of the BCG vaccine 2 weeks apart reduced average blood sugar to near normal levels by the 3-year mark in people with advanced type 1 diabetes, an improvement that was sustained for 5 more years. [1] Faustman and colleagues from Massachusetts General Hospital in the USA also identified that the BCG vaccine uses a novel mechanism to change the way the body consumes glucose—from oxidative phosphorylation (the most common pathway by which cells convert glucose to energy) to aerobic glycolysis, a state that speeds up the rate cells turn glucose into energy, leading to reduced [blood sugar levels](#) over time.

These new findings show that type 1 diabetics have metabolism consistent with less microbial exposure. As a result, type 1 diabetic patients have [white blood cells](#) that use minimal blood sugar compared to non-diabetics control subjects. Exposing the patients to microbes in the BCG vaccine seems to result in the white blood cells using more blood sugar by increasing aerobic glycolysis.

"BCG is an organism that needs a lot of energy sources. It lives inside white [blood](#) cells and elevates the sugar utilisation", explains Dr. Faustman.

The findings support the hygiene hypothesis which suggests that early life exposure to microbes that promote [aerobic glycolysis](#) is actually beneficial to the development of the immune system and is an important determinant of sensitivity to autoimmune diseases such as type 1 diabetes.

"The BGC vaccinations like tuberculosis itself, convert a depressed

lymphatic system deficient in sugar utilisation into a highly efficient process, a restoration similar to normal subjects without diabetes", says Dr. Faustman.

"Our discovery that type 1 diabetic patients have too little lymphoid sugar utilisation opens the door for more clinical trials using the BCG vaccine, even in advanced type 1 diabetes, to permanently lower [blood sugar](#) with the potential to reduce the substantial illness and mortality associated with this disease."

The authors note some limitations including that this is an early, small study, and a large 5-year phase 2 trial of 150 type 1 diabetic subjects approved by the US Food and Drug Administration is currently underway to test whether repeat BCG [vaccine](#) can clinically improve type 1 diabetes in adults with existing disease.

More information: [1] The June 2018 Nature study of 282 participants—52 with type 1 diabetes and 230 who contributed blood samples for mechanistic studies (211 with type 1 diabetes and 71 non-diabetic controls) showed that 3 years after BCG vaccination, blood sugar levels had dropped on average by more than 10%, and by over 18% after 4 years. This reduction was maintained after 8 years in the BCG treated six participants, who had an average HbA1c score of 6.65—close to the 6.5 threshold for diabetes diagnosis, and with no reports of hypoglycemia (low blood sugar). BCG-treated patients were also able to reduce their insulin intake. In contrast, average blood sugar levels of participants in the placebo group continued to rise over the study period.

Provided by Diabetologia

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