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Can Leukocyte Glucose Consumption Explain the HbA1c Reduction After BCG Vaccination in Long-Standing Type 1 Diabetes? A Quantitative Plausibility Analysis

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Abstract

Introduction: Trials of Bacillus Calmette-Guérin (BCG) vaccination in long-standing type 1 diabetes mellitus reported HbA1c reductions of more than 10% at 3 years and 18% at 4 years, attributed to increased leukocyte glucose consumption. The glucose disposal this requires has not been quantified.

Objective: To test whether leukocyte glucose consumption is quantitatively sufficient to explain these reductions.

Methods: We built a Monte Carlo bounding model. HbA1c reductions of 10% and 18% (baseline 7.36%) were converted to mean glucose with the A1C-Derived Average Glucose equation and to required extra glucose disposal, bounding the glucose-dependent disposal share (φ) at 0.3 and 1.0. Immune capacity combined immune mass, resting uptake from 18F-fluorodeoxyglucose positron emission tomography, reprogrammed fraction, and per-cell fold increase from adenosine triphosphate-yield stoichiometry, in three scenarios: T cell/regulatory T cell (Treg) only, trained myeloid lineage, and whole immune system.

Results: Required extra disposal was 6.5 to 11.6 mg/min (φ = 0.3) and 21.5 to 38.8 mg/min (φ = 1.0). For an 18% reduction, median capacity-to-demand ratios at φ = 0.3 were 0.006 (T cell/Treg), 0.17 (myeloid), and 0.57 (whole immune system), with sufficiency probabilities of 0%, 5.7%, and 28%; at φ = 1.0, 0.002, 0.05, and 0.17 (0%, 0.2%, 3.2%). Only a 10% reduction at φ = 0.3 with the whole immune system reprogrammed had a median ratio above 1 (1.03; 51%).

Conclusion: Leukocyte glucose consumption could explain the reported reductions only under permissive assumptions and widespread immune reprogramming, and is unlikely to do so if reprogramming is limited to T cells or the myeloid lineage.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease characterized by the loss of insulin-producing beta cells, and its burden is large and growing. Approximately 8.4 million people worldwide lived with T1DM in 2021, and prevalent cases are projected to reach 13.5 to 17.4 million by 2040.[1] Glycemic control, measured by glycated hemoglobin (HbA1c), remains the cornerstone of care because it reduces long-term complications. In the Diabetes Control and Complications Trial, intensive therapy lowered the risk of incident retinopathy by 76% but increased severe hypoglycemia two- to threefold.[2] Interventions that lower HbA1c without insulin-related hypoglycemia are therefore of considerable clinical interest.

Bacillus Calmette-Guérin (BCG), a live attenuated tuberculosis vaccine, has been tested as an immunomodulator in long-standing T1DM. A double-blind, placebo-controlled trial randomized six adults with long-standing T1DM to BCG or placebo and reported a transient modification of autoimmunity, with no reduction in HbA1c at the end of the 20-week follow-up.[3,4] In a subsequent long-term follow-up, investigators reported HbA1c reductions of more than 10% at year 3 and 18% at year 4, sustained

thereafter.[4] They attributed this effect to a systemic shift in glucose metabolism from oxidative phosphorylation to aerobic glycolysis, supported by metabolomic, transcriptomic, and glucose-uptake assays.[4] This proposal parallels trained immunity, in which monocytes trained in vitro with beta-glucan display high glucose consumption and lactate production through an Akt-mTOR-HIF-1α pathway (mTOR, mechanistic target of rapamycin; HIF-1α, hypoxia-inducible factor 1α).[5] In humans, BCG vaccination induces a persistent transcriptional program related to myeloid development in bone marrow hematopoietic stem and progenitor cells (HSPCs),[6] and single-cell analyses showed that gene expression changes occurred mainly in uncommitted stem cells, whereas chromatin accessibility changes predominated in differentiated progenitors.[7]

Whether increased leukocyte glucose consumption can quantitatively explain the reported HbA1c reductions remains unknown. The clinical observations derive principally from trials conducted by a single research group in very small cohorts, with three BCG-treated participants in the 8-year analysis,[3,4] and the proposed mechanism has been supported by cellular assays and murine data rather than by a whole-body glucose balance. Lowering mean glucose by the reported magnitude would require a sustained increase in glucose disposal, yet the immune system of a reference 73-kg adult comprises approximately 1.8×10^{12} cells weighing 1.2 kg.[8] To our knowledge, the additional glucose this tissue would need to consume has not been estimated. Without such an estimate, the physiological plausibility of leukocyte glucose consumption as the dominant mechanism cannot be judged, and alternative explanations cannot be prioritized.

We aimed to test whether increased leukocyte glucose consumption is quantitatively sufficient to explain the HbA1c reductions reported after BCG vaccination in long-standing T1DM. Secondary objectives were to estimate the additional glucose disposal required for HbA1c reductions of 10% and 18%, to compare it with the glucose-consuming capacity of the immune system under three reprogramming scenarios (T cell/regulatory T cell only, trained myeloid lineage, and whole immune system), and to identify the parameters that most influence this comparison.

METHODS

Study design

We conducted a quantitative plausibility analysis using a Monte Carlo bounding model. The question was whether the additional glucose disposal required to explain the HbA1c reductions reported after BCG vaccination in long-standing T1DM[4] is attainable by the glucose-consuming capacity of the human immune system. The model has two layers: a demand layer, which converts an HbA1c reduction into the required extra whole-body glucose disposal, and a capacity layer, which estimates the extra glucose the immune system can consume under defined reprogramming scenarios. Each input was specified as a probability distribution based on published values where available and on explicit assumptions

otherwise (Table 1). The model assumes steady state and does not simulate daily glycemic dynamics or insulin dosing.

Target effects

The target effects were derived from the long-term BCG follow-up by Kühtreiber et al.[4] The primary report followed six participants from the original randomized Phase I trial for up to 8 years, including three BCG-treated and three placebo-treated participants. HbA1c was assessed at enrollment before BCG administration and subsequently during longitudinal follow-up. The BCG-treated group had a mean baseline HbA1c of 7.36%, which declined to 6.65% during long-term follow-up. The reported relative reduction was greater than 10% after year 3 and approximately 18% at year 4, with the lower HbA1c maintained through year 8.[4]

Because the primary report provides the observed baseline HbA1c, we no longer infer baseline HbA1c from the final value. The observed BCG-group baseline value of 7.36% was therefore used as the reference HbA1c for the primary demand calculation. The 10% and 18% relative reductions were analyzed separately to reproduce the two clinically reported effect magnitudes. The year-8 HbA1c value of 6.65% represents the mean of the three BCG-treated participants followed for the full 8-year period and should not be interpreted as an independent year-4 endpoint.

Layer A: required extra glucose disposal

Mean glucose was estimated from HbA1c with the A1C-Derived Average Glucose (ADAG) Eq. 9:

$eAG\ (mg/dL) = 28.7 \times HbA1c - 46.7$

The fractional fall in mean glucose was $r_G = 1 - eAG(H_1)/eAG(H_0)$, where H_0 is the baseline HbA1c (7.36%) and $H_1 = H_0 \times (1 - d)$, with d the relative reduction. Whole-body glucose turnover (Ra) was sampled from a normal distribution (mean 2.3, SD 0.25 mg/kg/min), truncated to 1.7 to 3.0 mg/kg/min, consistent with postabsorptive turnover measured in healthy volunteers (2.2 ± 0.1 mg/kg/min).[10] The reference body weight was 73 kg.[8]

We assumed steady state with constant glucose appearance and a fraction φ of basal disposal that depends on glucose concentration in a first-order manner (the remainder, including much of cerebral uptake, is glucose-independent). A new glucose sink must then compensate for the disposal lost by glucose-dependent tissues as glucose concentrations fall, so the required extra disposal is:

$R\ (mg/min) = \varphi \times r \times Ra \times BW$

The glucose-dependent fraction of basal glucose disposal (φ) was treated as a model sensitivity parameter rather than as a directly measured physiological constant. Glucose effectiveness represents the ability of glucose to promote its own disposal independently of changes in insulin and accounts for a substantial component of glucose disposal in humans, although estimates vary according to the experimental and modeling approach.[11,12] Because published estimates of glucose effectiveness are not directly equivalent to the φ parameter used in the present steady-state formulation, we did not assign an empirical probability distribution to φ. Instead, the model was evaluated under two prespecified boundary scenarios: φ = 0.3, the bound most favorable to the hypothesis because only a limited fraction of basal disposal is glucose-dependent and the required extra disposal is therefore lowest, and φ = 1.0, the least favorable bound, in which all basal disposal is treated as glucose-dependent. This approach allowed the dependence of the inferred glucose-disposal requirement on φ to be evaluated explicitly rather than obscured by an unsupported probability distribution.

Layer B: capacity of the immune system

The extra glucose uptake attainable by reprogrammed immune cells was calculated as:

$$E\ (mg/min) = M \times 10 \times MR_0 \times p \times (F - 1) \times 0.18016$$

where M is the immune cell mass (kg), MR_0 the resting glucose metabolic rate of immune tissue (μmol/100 g/min), p the fraction of immune mass reprogrammed, F the fold increase in glucose uptake per reprogrammed cell, and 0.18016 the mass of glucose per μmol (mg). The factor of 10 converts kilograms to units of 100 g.

- Immune mass (M): log-normal, median 1.2 kg (log-scale SD 0.22), approximating the published 95% confidence interval (0.8 to 1.9 kg) for a reference 73-kg adult.[8]
- Resting uptake (MR_0): log-normal, median 2.0 μmol/100 g/min (log-scale SD 0.6). This was anchored to the organ-level 18F-fluorodeoxyglucose (FDG) metabolic rates measured by dynamic total-body positron emission tomography (PET) in healthy volunteers, which ranged from 0.59 μmol/100 g/min in the lung to 23.2 μmol/100 g/min in the parietal cortex.[13] FDG metabolic rate was used as a proxy for glucose metabolic rate, without lumped-constant correction. The median was varied from 1 to 8 μmol/100 g/min in a sensitivity analysis.
- Fold increase per cell (F): derived from adenosine triphosphate (ATP)-yield stoichiometry, taking glycolysis to yield 2 ATP and oxidative phosphorylation about 30 ATP per glucose molecule. Glucose use per ATP produced is g/2 + (1 − g)/30, where g is the fraction of ATP derived from glycolysis. The baseline fraction g_0 was sampled uniformly from 0.1 to 0.6, and the post-reprogramming fraction g_1 was drawn between g_0 and 1. An ATP-demand multiplier A (uniform, 1 to 2) represented the higher biosynthetic demand of activated cells.

$$F = [g/2 + (1 - g)/30] / [g/2 + (1 - g)/30] \times A$$

Scenarios

Three reprogramming scenarios differed in the fraction p of immune mass affected: (1) T cell/regulatory T cell (Treg) only (p uniform, 0.002 to 0.02); (2) trained myeloid lineage (p uniform, 0.05 to 0.65); and (3) whole immune system (p = 1). Scenario 3 is a deliberately favorable upper bound rather than a physiological expectation. The p ranges are assumptions that span plausible shares of immune mass for T cell/Treg subsets and for myeloid-lineage cells; because scenario 3 sets p = 1, conclusions about the upper bound do not depend on them, and alternative ranges were examined in a sensitivity analysis.

Simulation and outcomes

For each combination of HbA1c reduction (10% and 18%), φ (0.3 and 1.0), and scenario, 200,000 independent iterations were run. The primary outcome was the capacity-to-demand ratio Q = E/R, summarized as median and 5th to 95th percentiles, and the probability of sufficiency, P(Q ≥ 1). We also computed resting immune glucose use, $M \times 10 \times MR_0 \times 0.18016$, as a share of whole-body turnover, and the fold increase in glucose uptake that would be required across all immune cells, $F_{req} = 1 + R/(M \times 10 \times MR_0 \times 0.18016)$.

Sensitivity analysis

For the trained myeloid scenario with an 18% reduction and φ = 0.3, we computed Spearman rank correlations between each input and log(Q) to identify the parameters that most influence the result. We also varied the median resting glucose uptake (1, 2, 4, and 8 μmol/100 g/min) and the ranges of the reprogrammed fraction (Table 3).

Software and reproducibility

The model was implemented in Python 3.12.3 using the open-source libraries NumPy 2.4.4, SciPy 1.17.1, and Matplotlib 3.10.8, with a fixed random seed (42). All distributions and their sources are listed in Table 1. The complete script is available as Supplementary Material and in a public repository.

Table 1
Model inputs and sources

Parameter	Distribution / value	Source or basis
Baseline HbA1c	7.36% (fixed)	Observed BCG-group baseline in the primary report[4]
HbA1c reduction	10% and 18%	Reported effects[4]
Mean glucose conversion	eAG = 28.7 × HbA1c − 46.7 (mg/dL)	ADAG Eq. 9
Whole-body glucose turnover	Normal (2.3, 0.25), truncated 1.7–3.0 mg/kg/min	Tracer studies[10]
Glucose-dependent share of disposal (φ)	Boundary values, 0.3 and 1.0	Assumption, bounded using glucose-effectiveness literature[11,12]
Body weight	73 kg	Reference adult[8]
Immune cell mass	Log-normal, median 1.2 kg (95% CI 0.8–1.9)	[8]
Resting immune glucose uptake	Log-normal, median 2.0 μmol/100 g/min	Anchored to FDG-PET range[13]; assumption (varied from 1 to 8 in sensitivity analysis)
Reprogrammed fraction (p)	Scenario-specific	Assumption; alternative ranges examined in sensitivity analysis
Baseline glycolytic ATP share (g_0)	Uniform, 0.1–0.6	Assumption
Post-reprogramming glycolytic ATP share (g_1)	Uniform, between g_0 and 1	Assumption
ATP-demand multiplier (A)	Uniform, 1–2	Assumption

ADAG, A1C-Derived Average Glucose; ATP, adenosine triphosphate; eAG, estimated average glucose; FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; HbA1c, glycated hemoglobin. φ, glucose-dependent share of basal glucose disposal. Superscript numbers refer to the reference list.

Ethics

This study used only published aggregate data and involved no human participants or identifiable information. In accordance with Article 1, sole paragraph, items II, III, V, and VI of Resolution No. 510/2016 of the Brazilian National Health Council, research that uses public-access or public-domain information, aggregated databases without individual identification, or exclusively published scientific texts is not registered or evaluated by the CEP/CONEP system; institutional ethics review was therefore not required.

RESULTS

Required extra glucose disposal

Converting the reported HbA1c reductions to mean glucose with the ADAG equation, a 10% reduction (to 6.62%) lowered estimated mean glucose by 12.8% and an 18% reduction (to 6.04%) by 23.1%. The median additional glucose disposal required was 6.5 mg/min (10% reduction) and 11.6 mg/min (18% reduction) at φ = 0.3, and 21.5 and 38.8 mg/min at φ = 1.0. These correspond to approximately 9 and 17 g of glucose per day at φ = 0.3 and 31 and 56 g per day at φ = 1.0, against a reference whole-body glucose turnover of 168 mg/min (2.3 mg/kg/min in a 73-kg adult).

Resting immune glucose use and per-cell fold increase

Resting immune tissue was estimated to consume 4.3 mg/min of glucose, or 2.6% of whole-body turnover. Under ATP-yield stoichiometry, the fold increase in glucose uptake per reprogrammed cell had a median of 2.5, a 95th percentile of 5.9, and a maximum of 12.0 across 200,000 iterations.

Capacity relative to demand

In the T cell/Treg-only scenario, median extra uptake was 0.06 mg/min, and no iteration reached the required disposal at either target or at either value of φ (probability of sufficiency, 0%). In the trained myeloid scenario, median extra uptake was approximately 2.0 mg/min, and in the whole immune system scenario it was approximately 6.6 mg/min (Table 2). At φ = 0.3, the median capacity-to-demand ratio for an 18% reduction was 0.006 (5th to 95th percentile, 0.001 to 0.03) for T cell/Treg, 0.17 (0.02 to 1.07) for the myeloid lineage, and 0.57 (0.10 to 2.74) for the whole immune system, with probabilities of sufficiency of 0%, 5.7%, and 28.2%. For a 10% reduction at φ = 0.3, the median ratios were 0.010, 0.31, and 1.03, with probabilities of 0%, 15.2%, and 51.0%. At φ = 1.0, the median ratios for an 18% reduction were 0.002, 0.05, and 0.17 (probabilities of 0%, 0.2%, and 3.2%), and for a 10% reduction 0.003, 0.09, and 0.31 (0%, 1.4%, and 11.2%). Figure 1 shows the φ = 0.3 case.

Table 2
Immune glucose capacity relative to the required extra disposal

HbA1c reduction (φ)	Scenario	Required (mg/min)	Capacity (mg/min)	Capacity/demand, median (5th–95th pct)	P(capacity ≥ demand)
10% (φ = 0.3)	T cell/Treg only	6.5	0.06	0.010 (0.001–0.06)	0.0%
10% (φ = 0.3)	Trained myeloid lineage	6.5	2.01	0.312 (0.038–1.93)	15.2%
10% (φ = 0.3)	Whole immune system	6.5	6.59	1.026 (0.184–4.93)	51.0%
18% (φ = 0.3)	T cell/Treg only	11.6	0.06	0.006 (0.001–0.03)	0.0%
18% (φ = 0.3)	Trained myeloid lineage	11.6	2.01	0.173 (0.021–1.07)	5.7%
18% (φ = 0.3)	Whole immune system	11.6	6.59	0.570 (0.102–2.74)	28.2%
10% (φ = 1.0)	T cell/Treg only	21.5	0.06	0.003 (< 0.001–0.02)	0.0%
10% (φ = 1.0)	Trained myeloid lineage	21.5	2.01	0.094 (0.011–0.58)	1.4%
10% (φ = 1.0)	Whole immune system	21.5	6.59	0.308 (0.055–1.48)	11.2%
18% (φ = 1.0)	T cell/Treg only	38.8	0.06	0.002 (< 0.001–0.01)	0.0%
18% (φ = 1.0)	Trained myeloid lineage	38.8	2.01	0.052 (0.006–0.32)	0.2%
18% (φ = 1.0)	Whole immune system	38.8	6.59	0.171 (0.031–0.82)	3.2%

Required and capacity values are medians of 200,000 Monte Carlo iterations for each combination of HbA1c reduction and φ; P(capacity ≥ demand) is the proportion of iterations in which capacity met or exceeded demand. pct, percentile.

Fold increase required across all immune cells

Explaining an 18% reduction with the whole immune system would require a median 3.7-fold increase in glucose uptake across all immune cells at φ = 0.3 (5th to 95th percentile, 1.9 to 8.8) and a 9.9-fold increase at φ = 1.0 (4.1 to 26.9). For a 10% reduction, the corresponding medians were 2.5-fold (1.5 to 5.3) and 5.9-fold (2.7 to 15.4).

Sensitivity to the glucose-dependent disposal fraction

Because the glucose-dependent fraction of basal disposal could not be measured from the available clinical data, the demand layer was evaluated at two boundary values of φ. The lower bound (φ = 0.3) reduced the required disposal by 70% relative to the upper bound (φ = 1.0), and the capacity-to-demand ratio rose accordingly (Table 2). The conclusion therefore depended on φ: at φ = 1.0, the probability of sufficiency did not exceed 11.2% in any scenario, whereas at φ = 0.3 the whole immune system met or exceeded demand in 51.0% (10% reduction) and 28.2% (18% reduction) of iterations. The upper bound (φ = 1.0) is thus the less favorable assumption for the hypothesis, and the lower bound (φ = 0.3) the more permissive one.

Sensitivity analysis

In the trained myeloid scenario with an 18% reduction at φ = 0.3, the capacity-to-demand ratio correlated most strongly with the per-cell fold increase (Spearman ρ = 0.62), followed by the reprogrammed fraction (ρ = 0.51) and resting tissue glucose uptake (ρ = 0.49). Immune mass showed a weaker association (ρ = 0.18), and the required disposal was weakly inversely associated (ρ = −0.09).

Sensitivity to resting glucose uptake and reprogrammed fraction

Raising the median resting glucose uptake from 1 to 8 μmol/100 g/min increased the median capacity-to-demand ratio for an 18% reduction at φ = 0.3 from 0.09 to 0.69 in the myeloid scenario (probability of sufficiency, 1.2% to 37.6%) and from 0.29 to 2.28 in the whole immune system scenario (9.8% to 79.4%) (Table 3). Varying the reprogrammed fraction in the myeloid scenario from 0.05–0.30 to 0.65–0.90 increased the median ratio from 0.09 to 0.44 (1.1% to 19.9%), whereas a T cell/Treg fraction of 0.01 to 0.05 gave a median ratio of 0.016, with no iteration reaching sufficiency.

Table 3
Sensitivity of the capacity-to-demand ratio to resting glucose uptake and the reprogrammed fraction (18% reduction, φ = 0.3)

Varied input	Setting	Myeloid: median ratio	Myeloid: P(≥ 1)	Whole system: median ratio	Whole system: P(≥ 1)
Resting uptake, median (μmol/100 g/min)	1	0.086	1.2%	0.285	9.8%
Resting uptake, median (μmol/100 g/min)	2 (base case)	0.173	5.7%	0.570	28.2%
Resting uptake, median (μmol/100 g/min)	4	0.345	17.4%	1.142	55.3%
Resting uptake, median (μmol/100 g/min)	8	0.691	37.6%	2.283	79.4%
Myeloid reprogrammed fraction (p)	0.05–0.30	0.091	1.1%	–	–
Myeloid reprogrammed fraction (p)	0.30–0.65	0.264	8.9%	–	–
Myeloid reprogrammed fraction (p)	0.65–0.90	0.439	19.9%	–	–

*The base case uses a median resting uptake of 2.0 μmol/100 g/min and a myeloid reprogrammed fraction of 0.05–0.65 (*Table 2*). –, not applicable (p = 1). P(≥ 1), probability that capacity met or exceeded demand.*

DISCUSSION

The principal finding of this quantitative plausibility analysis is that whether increased leukocyte glucose consumption can account for the glycemic improvement reported after BCG vaccination in long-standing T1DM depends strongly on the assumptions adopted. When reprogramming was restricted to T cells and regulatory T cells or to the myeloid lineage, the estimated glucose-consuming capacity fell short of the required disposal in most simulations under both bounds of the glucose-dependent share of disposal. Capacity approached demand only when the entire immune system was assumed to be reprogrammed and the glucose-dependent share was low, a combination that represents a deliberately favorable upper bound. These findings do not challenge the evidence that BCG induces immunometabolic remodeling; rather, they indicate that cellular evidence of enhanced glucose utilization should not be equated with a quantitatively sufficient systemic glucose-lowering mechanism.

The proposed mechanism is biologically plausible. BCG vaccination has been associated with increased glucose utilization and metabolic reprogramming in immune cells from individuals with diabetes.[14] Independent experimental studies have shown that BCG induces metabolic remodeling characteristic of trained immunity, including enhanced glycolytic activity and altered intermediary metabolism.[15]

Mechanistically, activation of the mTOR-HIF-1α axis promotes aerobic glycolysis and contributes to the metabolic phenotype associated with trained immunity.[5,16] These observations support the existence of a BCG-responsive metabolic program in leukocytes, but they do not establish that the resulting glucose flux is sufficient to account for systemic glycemic changes.

The persistence of the clinical response is also compatible with the biology of trained immunity. Long-term observations in individuals with advanced T1DM have linked BCG vaccination with sustained changes in glucose metabolism and aerobic glycolysis.[4,17] Human studies subsequently demonstrated that BCG vaccination can induce persistent transcriptional remodeling of hematopoietic progenitor compartments, with downstream effects on myeloid-cell development and function.[6] Trained-immunity responses differ among BCG strains,[18] which limits extrapolation from one BCG formulation to another; the long-term clinical analysis used the Connaught strain.[4] More recent single-cell analyses have further shown that BCG modifies the gene-expression and epigenetic landscapes of human hematopoietic stem and progenitor cells.[7] Thus, durable immunological reprogramming provides a plausible framework for prolonged biological effects, although persistence of this cellular state does not establish its contribution to whole-body glucose disposal.

An important distinction is therefore required between cellular glucose uptake and net systemic glucose disposal. Activated immune cells use glucose for ATP generation, biosynthesis, redox regulation, nucleotide production, and other cellular functions. Immunometabolic remodeling consequently represents a broader reorganization of cellular physiology rather than a simple increase in glucose oxidation. Trained immunity involves coordinated changes in glycolysis, glutamine metabolism, mitochondrial pathways, and lipid metabolism, which interact with epigenetic regulation.[19,20] Metabolic intermediates generated through these pathways can themselves influence chromatin remodeling and inflammatory gene expression.[21] Increased glucose uptake may therefore be functionally important for immune-cell reprogramming without producing a proportional increase in systemic glucose clearance.

The hematopoietic component of trained immunity further complicates a simple glucose-sink interpretation. BCG can reprogram hematopoietic stem and progenitor cells in mice and humans and subsequently alter the phenotype of circulating myeloid cells, extending the biological consequences of vaccination beyond mature leukocytes present at the time of exposure.[6,22] The magnitude of any systemic metabolic effect, however, would depend on the size, distribution, persistence, and functional state of the reprogrammed cellular compartment. Myeloid remodeling is also not restricted to glycolysis: monocytes and macrophages undergo broad metabolic changes after training,[23] and glutaminolysis, fumarate accumulation, and the mevalonate pathway contribute to epigenetic reprogramming.[24,25] These changes vary over time and across the induction and maintenance phases of the trained state,[26] which supports the view that metabolic remodeling functions partly as an intracellular regulatory process rather than simply as a mechanism for removing circulating glucose.

The clinical evidence should therefore be interpreted within the broader literature. A systematic review and meta-analysis found evidence of an association between BCG intervention and improved glycemic measures in T1DM, while also emphasizing the need for better-designed studies to establish the magnitude and durability of these effects.[27] Evidence from a five-year phase II trial in juvenile-onset T1DM, which assessed HbA1c, time in range, and insulin use, is so far available only as a conference abstract.[28] Alternative explanations for the HbA1c reductions, such as improved insulin sensitivity, reduced hepatic glucose production, changes in insulin dosing or behavior, regression to the mean, and attrition in small long-term cohorts, cannot be distinguished by the present analysis. Trained immunity is increasingly recognized as a distributed biological phenomenon involving immune cells, hematopoietic progenitors, metabolic pathways, and epigenetic regulation,[29] and its relevance to diabetes may involve interactions between metabolic and inflammatory pathways that are not reducible to immune-cell glucose uptake.[30] The original randomized trial provided early evidence of biological activity of BCG in long-standing T1DM, but the clinical findings should be interpreted in the context of the study design and subsequent literature,[3,31] and recent reviews of BCG-induced trained immunity describe interconnected metabolic, epigenetic, and hematopoietic mechanisms.[32] Within this framework, leukocyte glucose consumption may represent one component of a larger biological response rather than an isolated systemic glucose sink.

Some limitations should be acknowledged. The model relied on published aggregate physiological parameters rather than direct longitudinal measurements of glucose flux in BCG-treated individuals, and the clinical targets derive from a very small cohort. Several key variables, including the glucose-dependent share of disposal, the reprogrammed fractions, and the per-cell fold increase, therefore required assumptions and uncertainty distributions or boundary values. In particular, φ could not be measured and was evaluated at two boundary values, and the conclusion changed materially between them. Resting immune glucose uptake was anchored to organ-level FDG-PET metabolic rates without lumped-constant correction, tissue-specific rates for spleen, bone marrow, and lymph nodes were not available, and the sensitivity analysis showed that a higher assumed resting uptake substantially increased the probability of sufficiency in the whole-immune-system scenario. Immune populations also differ substantially in anatomical distribution and metabolic phenotype. The representation of the glycolytic shift simplifies substrate flexibility and does not fully capture lactate recycling, biosynthetic glucose utilization, or mitochondrial adaptation. In addition, the model is a steady-state analysis that does not simulate daily glycemic dynamics or insulin dosing, whole-body glucose turnover was taken from healthy volunteers rather than from people with T1DM, and the reported percent reductions are not directly comparable with the mean raw HbA1c values. The wide uncertainty intervals, including whole-immune-system intervals that span a capacity-to-demand ratio of 1, indicate that the conclusions are probabilistic rather than definitive. Nevertheless, the analysis has an important strength: it explicitly separates the glucose disposal required to account for the clinical observation from the estimated metabolic capacity of the immune compartment and evaluates the proposed mechanism, including a deliberately favorable upper-bound scenario.

Future studies should directly measure whole-body glucose turnover (for example, with glucose tracers or clamps) together with immune-cell glucose flux (for example, with dynamic FDG-PET of lymphoid tissue and bone marrow), continuous glucose monitoring, insulin requirements, and endogenous insulin secretion before and after BCG vaccination. Integration with single-cell transcriptomic, epigenomic, and metabolomic approaches could determine whether the magnitude of immune metabolic remodeling correlates with glycemic improvement and identify the cellular populations responsible for any clinically relevant metabolic effect. Such studies would help distinguish direct glucose disposal from indirect effects mediated through immune, hematopoietic, hepatic, or peripheral metabolic pathways. Randomized, blinded designs would also help separate a metabolic effect from nonspecific factors.

CONCLUSION

In conclusion, this analysis indicates that increased leukocyte glucose consumption could explain the reported glycemic improvement after BCG vaccination in long-standing T1DM only under permissive assumptions that combine a low glucose-dependent share of disposal with reprogramming of most of the immune system, and it is unlikely to be sufficient if reprogramming is limited to T cells or the myeloid lineage. BCG-induced immunometabolic and epigenetic remodeling remains biologically plausible and potentially relevant, but the present analysis cannot identify which other mechanisms contribute, and a broader multifactorial model of glucose regulation should be tested. Direct metabolic studies are needed to determine whether immune-cell reprogramming contributes materially to the clinical response and through which mechanisms.

Declarations

Conflict of Interest:

None declared

References

1. Gregory GA, Robinson TIG, Linklater SE, Wang F, Colagiuri S, de Beaufort C et al (2022) Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. Lancet Diabetes Endocrinol. ;10(10):741–760. doi: 10.1016/S2213-8587(22)00218-2. Erratum in: Lancet Diabetes Endocrinol. 2022;10(11):e11. 10.1016/S2213-8587(22)00280-7
2. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O et al (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329(14):977–986. 10.1056/NEJM199309303291401
3. Faustman DL, Wang L, Okubo Y, Burger D, Ban L, Man G et al (2012) Proof-of-concept, randomized, controlled clinical trial of Bacillus-Calmette-Guerin for treatment of long-term type 1 diabetes. PLoS

ONE 7(8):e41756. 10.1371/journal.pone.0041756

4. Kühtreiber WM, Tran L, Kim T, Dybala M, Nguyen B, Plager S et al (2018) Long-term reduction in hyperglycemia in advanced type 1 diabetes: the value of induced aerobic glycolysis with BCG vaccinations. NPJ Vaccines 3:23. 10.1038/s41541-018-0062-8
5. Cheng SC, Quintin J, Cramer RA, Shepardson KM, Saeed S, Kumar V et al (2014) mTOR- and HIF-1α-mediated aerobic glycolysis as metabolic basis for trained immunity. Science 345(6204):1250684. 10.1126/science.1250684
6. Cirovic B, de Bree LCJ, Groh L, Blok BA, Chan J, van der Velden WJFM et al (2020) BCG vaccination in humans elicits trained immunity via the hematopoietic progenitor compartment. Cell Host Microbe 28(2):322–334e5. 10.1016/j.chom.2020.05.014
7. Sun SJ, Aguirre-Gamboa R, de Bree LCJ, Sanz J, Dumaine A, van der Velden WJFM et al (2024) BCG vaccination alters the epigenetic landscape of progenitor cells in human bone marrow to influence innate immune responses. Immunity 57(9):2095–2107e8. 10.1016/j.immuni.2024.07.021
8. Sender R, Weiss Y, Navon Y, Milo I, Azulay N, Keren L et al (2023) The total mass, number, and distribution of immune cells in the human body. Proc Natl Acad Sci U S A 120(44):e2308511120. 10.1073/pnas.2308511120
9. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ et al (2008) Translating the A1C assay into estimated average glucose values. Diabetes Care 31(8):1473–1478. 10.2337/dc08-0545
10. Møller N, Rizza RA, Ford GC, Nair KS (2001) Assessment of postabsorptive renal glucose metabolism in humans with multiple glucose tracers. Diabetes 50(4):747–751. 10.2337/diabetes.50.4.747
11. Best JD, Kahn SE, Ader M, Watanabe RM, Ni TC, Bergman RN (1996) Role of glucose effectiveness in the determination of glucose tolerance. Diabetes Care 19(9):1018–1030. 10.2337/diacare.19.9.1018
12. Cobelli C, Man CD, Sparacino G, Magni L, De Nicolao G, Kovatchev BP (2009) Diabetes: Models, Signals, and Control. IEEE Rev Biomed Eng 2:54–96. 10.1109/RBME.2009.2036073
13. Liu G, Xu H, Hu P, Tan H, Zhang Y, Yu H et al (2021) Kinetic metrics of ^{18}F-FDG in normal human organs identified by systematic dynamic total-body positron emission tomography. Eur J Nucl Med Mol Imaging 48(8):2363–2372. 10.1007/s00259-020-05124-y
14. Kühtreiber WM, Takahashi H, Keefe RC, Song Y, Tran L, Luck TG et al (2020) BCG vaccinations upregulate Myc, a central switch for improved glucose metabolism in diabetes. iScience 23(5):101085. 10.1016/j.isci.2020.101085
15. Arts RJW, Carvalho A, La Rocca C, Palma C, Rodrigues F, Silvestre R et al (2016) Immunometabolic pathways in BCG-induced trained immunity. Cell Rep 17(10):2562–2571. 10.1016/j.celrep.2016.11.011
16. Schlüter T, van Elsas Y, Priem B, Ziogas A, Netea MG (2025) Trained immunity: induction of an inflammatory memory in disease. Cell Res 35(11):792–802. 10.1038/s41422-025-01171-y

17. Shpilsky GF, Takahashi H, Aristarkhova A, Weil M, Ng N, Nelson KJ et al (2021) Bacillus Calmette-Guerin's beneficial impact on glucose metabolism: evidence for broad based applications. iScience 24(10):103150. 10.1016/j.isci.2021.103150
18. Xu JC, Chen ZY, Huang XJ, Wu J, Huang H, Niu LF et al (2024) Multi-omics analysis reveals that linoleic acid metabolism is associated with variations of trained immunity induced by distinct BCG strains. Sci Adv 10(14):eadk8093. 10.1126/sciadv.adk8093
19. Kim HG, Rincon JC, Efron PA, Maile R (2025) DAMP-driven trained immunity: metabolic and epigenetic reprogramming in critical illness and chronic inflammation. Front Immunol 16:1669054. 10.3389/fimmu.2025.1669054
20. Riksen NP, Netea MG (2021) Immunometabolic control of trained immunity. Mol Aspects Med 77:100897. 10.1016/j.mam.2020.100897
21. Ferreira AV, Domínguez-Andrés J, Merlo Pich LM, Joosten LAB, Netea MG (2024) Metabolic regulation in the induction of trained immunity. Semin Immunopathol 46(3–4):7. 10.1007/s00281-024-01015-8
22. Kaufmann E, Sanz J, Dunn JL, Khan N, Mendonça LE, Pacis A et al (2018) BCG educates hematopoietic stem cells to generate protective innate immunity against tuberculosis. Cell 172(1–2):176–190e19. 10.1016/j.cell.2017.12.031
23. Mulder WJM, Ochando J, Joosten LAB, Fayad ZA, Netea MG (2019) Therapeutic targeting of trained immunity. Nat Rev Drug Discov 18(7):553–566. 10.1038/s41573-019-0025-4
24. Arts RJ, Novakovic B, Ter Horst R, Carvalho A, Bekkering S, Lachmandas E et al (2016) Glutaminolysis and fumarate accumulation integrate immunometabolic and epigenetic programs in trained immunity. Cell Metab 24(6):807–819. 10.1016/j.cmet.2016.10.008
25. Bekkering S, Arts RJW, Novakovic B, Kourtzelis I, van der Heijden CDCC, Li Y et al (2018) Metabolic induction of trained immunity through the mevalonate pathway. Cell 172(1–2):135–146e9. 10.1016/j.cell.2017.11.025
26. Jarit-Cabanillas A, Dunphy G, Virga F, Van den Bossche J, Sancho D (2026) Metabolic support of trained immune responses in myeloid cells. eLife 15:e108814. 10.7554/eLife.108814
27. Korde SB, Pillewan SR, Dumbre SR, Bandgar AR, Shinde PS, Gairola S et al (2024) Significance of Bacillus Calmette-Guerin (BCG) vaccine intervention for patients with type 1 diabetes (T1D): a systematic review and meta-analysis. Diabetes Metab Syndr 18(8):103102. 10.1016/j.dsx.2024.103102
28. Faustman DL, Braley J, Hullavarad N, Bulczynski E, Dorsey J, Kartsounis N et al (2026) Phase II clinical trial of BCG immunotherapy for type 1 diabetes with juvenile onset: five-year analysis of safety, HbA1c, time in range, and insulin use [abstract]. Diabetes 75(Suppl 1):2862–LB. 10.2337/db26-2862-LB
29. Das S, Lavine KJ (2025) Role of trained immunity in health and disease. Curr Cardiol Rep 27(1):18. 10.1007/s11886-024-02167-7

30. Liu Y, Lei Y, Dai Z, Luo C, Gong Q, Li Y et al (2025) Trained immunity: novel perspectives in diabetes and associated complications. Front Immunol 16:1613602. 10.3389/fimmu.2025.1613602
31. Faustman DL, Hashiguchi S, Davis M, Kuhtreiber W (2026) Diabetic immunotherapy advances with BCG: metabolic and immune reprogramming. Cells 15(17):1604. 10.3390/cells15171604
32. Chen J, Gao L, Wu X, Fan Y, Liu M, Peng L et al (2023) BCG-induced trained immunity: history, mechanisms and potential applications. J Transl Med 21(1):106. 10.1186/s12967-023-03944-8

Figures

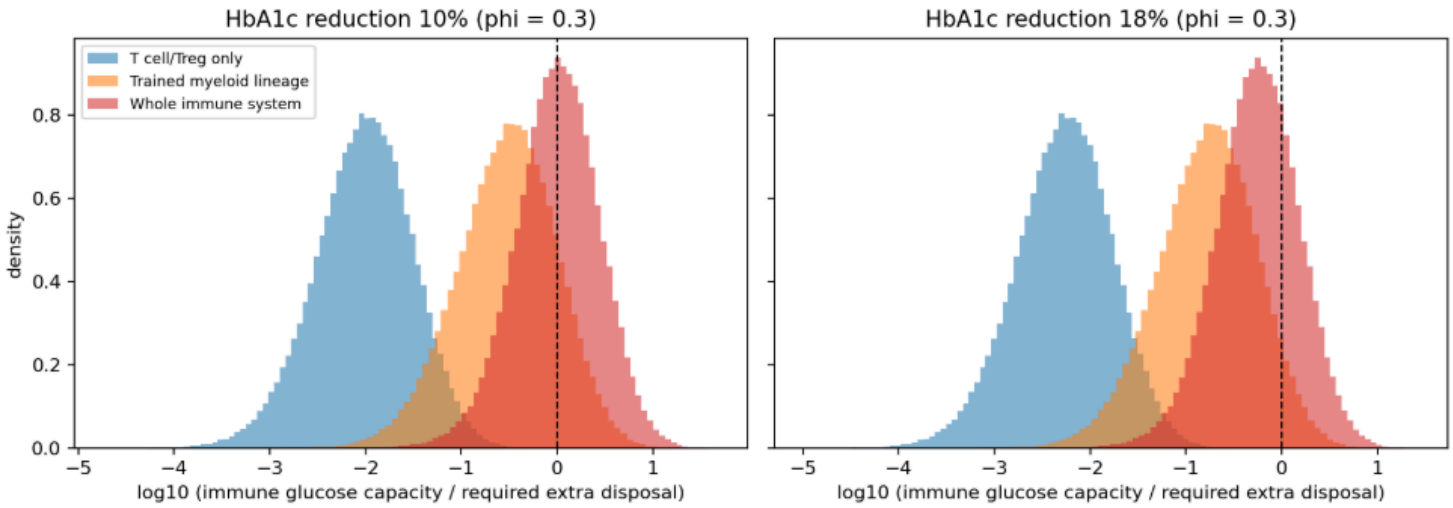


Figure 1

Distribution of the capacity-to-demand ratio (log10 scale) for each scenario at HbA1c reductions of 10% and 18% with φ = 0.3. The dashed line marks equality (ratio = 1). Colors indicate scenarios (blue, T cell/Treg only; orange, trained myeloid lineage; red, whole immune system); each histogram represents 200,000 iterations.