

Benefits of BCG-induced metabolic switch from oxidative phosphorylation to aerobic glycolysis in autoimmune and nervous system diseases

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The most commonly used vaccine worldwide, bacillus Calmette-Guérin (BCG), appears to have the ability to restore blood sugar control in humans with early onset but long-duration type 1 diabetes when a repeat vaccination strategy is used. This is a process that may be driven by a metabolic switch from overactive oxidative phosphorylation to accelerated aerobic glycolysis and a reset of the immune system. BCG is a live, attenuated strain of *Mycobacterium bovis*, a cousin of *M. tuberculosis*. Humans and *Mycobacterium*, which are found in the environment and in warm-blooded hosts, share a long coevolutionary history. In recent times,

humans have had fewer exposures to these and other microorganisms that historically helped shape the immune response. By ‘re-introducing’ an attenuated form of *Mycobacterium* via BCG vaccination, humans might benefit from an immunological perspective, a concept supported by a growing body of data in autoimmunity and robust data on the nonspecific immune effects of BCG related to protection from diverse infections and early mortality. New findings of immune and metabolic defects in type 1 diabetes that can be corrected with repeat BCG vaccination suggest that this therapeutic strategy may be applicable in other diseases with inadequate aerobic glycolysis, including Parkinson’s disease, dementia, depression and other disorders affecting the nervous system.

Keywords: BCG vaccine, autoimmunity, diabetes mellitus, type 1, nervous system diseases, aerobic glycolysis, mycobacterium.

Introduction

The bacillus Calmette-Guérin (BCG) vaccine is the most commonly used vaccine worldwide, administered primarily for the prevention of tuberculosis since its introduction in 1921. Recent clinical trials show that repeat administration of the BCG vaccine may have clinical benefits in autoimmunity, most notably in clinically isolated syndromes (CIS) [1]/ multiple sclerosis (MS) [2, 3] and in type 1 diabetes [4].

Aerobic glycolysis, one of the two key metabolic pathways through which cells obtain energy, is associated with high glucose utilization by immune

cells. In individuals with type 1 diabetes, aerobic glycolysis is suppressed and oxidative phosphorylation, a metabolic pathway in which low glucose utilization, high ketone production and high Krebs cycle utilization is instead predominant [5, 6].

Repeat vaccination with BCG (i.e. ≥ 2 vaccinations) appears to address these immune defects through a ‘reset’ of the immune system achieved by the induction of beneficial regulatory T cells (Tregs) and the killing of cytotoxic T lymphocytes (CTLs) [4]. BCG also resets cellular metabolism; namely, by augmenting aerobic glycolysis and decreasing oxidative phosphorylation in the immune system [5].

Resetting the metabolism of immune cells in type 1 diabetes appears to control and regulate blood sugars in a clinically significant way. In a randomized, placebo-controlled clinical trial, BCG treatment led to long-term improvement of blood sugars, without hypoglycaemia, in adult subjects with long-standing type 1 diabetes (~20 years disease duration) [5]. Not only was there a statistically significant lowering of HbA1c for ≥ 1 year with BCG ($P = 0.02$), but blood sugar lowering was maintained for 5 continuous years ($P = 0.0002$).

These findings in type 1 diabetes suggest that the therapeutic strategy of repeat BCG vaccination may have broader applications to other diseases with inadequate aerobic glycolysis, including a number of nervous system diseases. Here, we discuss the recent findings with BCG in type 1 diabetes and the potential for using this *Mycobacteria*-based vaccine to reset immunometabolism in novel disease settings.

Lessons from *Mycobacteria*: The interplay of immunity and metabolism with BCG introduction in adults

BCG is a live, attenuated strain of *Mycobacterium bovis*. This avirulent *Mycobacterium* is related to the pathogenic *M. tuberculosis* strain, the causative agent of tuberculosis in humans, and to other strains in the *M. tuberculosis* complex. The *M. tuberculosis* complex shares a long coevolutionary history with humans, with phylogenetic analysis suggesting that it has been infecting humans for thousands of years [7].

Throughout this long coevolution, this microorganism – which can be found free-living in soil and water, as well as in the tissue of warm-blooded hosts – has helped to shape the human immune system. Yet, in recent history, improvements in sanitation and food safety, the movement away from occupations and living conditions that keep humans in close interaction with animals and the soil, and advancements in medicine leading to fewer infections have meant that many humans are growing up bereft of the wider exposure to microorganisms that helped shape our evolutionary history. How has loss of exposure to these ancient “partners” potentially affected the human immune system?

One possible answer may be found in the ‘hygiene hypothesis’ [8] and similar theories (e.g. ‘biome depletion model’ [9], ‘early immune challenge

hypothesis’ [10], ‘old friends hypothesis’ [11]). Broadly, these concepts suggest that the increased incidences of allergies and autoimmune diseases in humans may be due to fewer exposures to the microbes that traditionally trained the immune system to respond appropriately to pathogens. Thus, the introduction (or, from an evolutionary perspective, ‘re-introduction’) of an attenuated form of *Mycobacteria* into humans via BCG vaccination might be beneficial to immune system function.

Indeed, BCG is already known to have protective and therapeutic effects beyond the prevention of infection with tuberculosis. These effects include reduced susceptibility to nonmycobacterial infections [12–14], therapeutic effects in bladder cancer (when administered as an intravesical infusion) [15], and a reduced incidence of early mortality [16, 17]. These effects appear to be mediated through both adaptive immunity and innate immune responses known as ‘trained immunity’. This latter immune response is triggered through postvaccination epigenetic changes that shape the immune system by creating beneficial commensalism at the gene level [18].

Further, alterations in immunometabolism are closely linked to infections, including infection with *M. tuberculosis*. In murine lung tissue, infected monocytes in tuberculosis granulomas predominantly utilize serum sugar through a shift towards glycolysis [19]. In a parallel fashion, these monocytes exhibit downregulation of enzymes participating in the Krebs cycle and oxidative phosphorylation [19]. In the human, too, infected immune cells respond to *M. tuberculosis* by increasing glucose uptake through a shift to predominant aerobic glycolysis [20].

Similar findings related to central glucose metabolism and aerobic glycolysis have been observed by our group after *in vivo* administration of repeat BCG vaccinations in adults with type 1 diabetes [5, 6]. These findings are discussed in more detail in further sections.

Significance of immunity to tuberculosis in diverse human disease states: The broader value of BCG vaccination

Over the past two decades, multiple clinical trials have been launched to evaluate the effects of BCG vaccination in autoimmunity, allergy and childhood infections [1–6, 16, 17, 21–27]. The findings

from these studies have been promising and show the potential benefits of 're-introducing' beneficial immune-modulating bacteria – in the form of BCG vaccination – in the human.

For example, BCG vaccination has been shown to confer a survival advantage in low-birthweight infants by offering protection from infections unrelated to tuberculosis, and to confer a long-term survival advantage in healthy populations [16, 17, 24, 28, 29].

In a double-blind, placebo-controlled study in adults with multiple sclerosis, BCG administration prevented progression to clinically definite disease when given after a first demyelinating event (clinically isolated syndrome [CIS]), thereby halting new-onset disease in the early period (6 months) after vaccination [1]. Follow-up during the trial showed that the clinical effect of BCG was even more pronounced at 5 years.

In a retrospective study in type 1 diabetes, receipt of two or more BCG vaccinations in childhood was associated with a lower incidence of type 1 diabetes by age 12 [25].

A randomized, double-blind, placebo-controlled Phase I trial in adults with long-standing type 1 diabetes showed that two doses of intradermal BCG increased beneficial Tregs, killed pathogenic CTLs and temporarily restored production of a small amount of pancreatic insulin, but that these favourable biomarker responses did not translate into lowering of glycated haemoglobin (HbA1c) values, a standard measure of blood sugar control, at the end of the 20-week trial [4]. Long-term follow-up, however, showed that, at 8 years, elevated HbA1c values in BCG-treated subjects were reduced to the near-normal range (6.65%; $P < 0.002$) after an onset delay of three years [5]. These reductions in HbA1c were not seen in either the placebo control group nor in a matched reference group of patients with type 1 diabetes who were receiving the standard of care alone. HbA1c reductions appeared to be permanent for the next five years after onset of clinical effect, without further administration of BCG vaccination. Unlike the expectation with insulin alone, BCG-driven reductions to near-normal blood sugar levels in this trial were not associated with hypoglycaemic events [5].

In the same study, a closer look at Tregs from BCG-treated subjects showed that BCG also

demethylated Treg signature genes [5]. This was clinically significant, since increased mRNA expression of the same genes from demethylation correlated with the change in methylation [5, 30]. Similar to *M. tuberculosis* and *M. leprae*, which create granulomas encircled with Tregs [31], BCG systemically induces Tregs [4]. Epigenetic reprogramming of the host by *M. tuberculosis* and other infections occurs at key checkpoints, including methyltransferases, and at key steps in aerobic glycolysis, such as HIF1 α [30, 32–34]. Patients with long-standing type 1 diabetes who received repeated BCG vaccinations had both immune and metabolic changes related to the genes involved in the reestablishment of tolerance and glucose utilization [5]. These changes in receptor-controlled glucose utilization appear to have therapeutic utility for lowering blood sugar in type 1 diabetes. All subjects with type 1 diabetes in this trial had classic, juvenile-onset diabetes (i.e. early age of onset), but long disease duration (>15 years).

BCG restores balance in cellular energy production and accelerates glucose uptake

The impact of BCG on human blood sugars in type 1 diabetes appears to be driven through immune and immunometabolic effects, similar to those observed with *M. tuberculosis* infection. Mechanistic data demonstrate that BCG can reset the immune system on the cellular level by inducing suppressive Tregs [5, 35, 36] and killing the autoreactive CTLs that attack insulin-secreting pancreatic islet cells [4, 37]. *M. tuberculosis* similarly induces or 'turns on' Tregs through a beneficial host-microbe interaction at the DNA level with changes in methylation [30, 32–34].

Beyond the immune effects of BCG, recent human data on BCG vaccination in type 1 diabetes show BCG's ability to regulate blood sugar through changes in metabolism [5]. The systemic metabolic shift in glucose metabolism moves from oxidative phosphorylation, a low cellular glucose state, towards accelerated and early aerobic glycolysis, a high glucose utilization state [5]. At baseline, subjects with type 1 diabetes exhibit a derangement in lymphoid system sugar metabolism. Both T cells and monocytes show overzealous oxidative phosphorylation, possibly linked to prior poor prior host-microbe interactions. The introduction of BCG gradually restores this imbalance towards normal levels. Using mRNA sequencing methods, we have been able to demonstrate that serial BCG

vaccination in adults with type 1 diabetes increased key early glycolytic enzymes, upregulated glucose uptake leading to systemic lowering of blood sugars, shunted the accelerated glucose utilization through the pentose phosphate pathway, decreased utilization of late glycolytic steps (including the Krebs cycle) and decreased oxidative phosphorylation (Figure 1).

The impact of administering BCG to normal (nonautoimmune) mice has been studied in relation to sugar utilization patterns [5]. When BCG pretreated nonautoimmune mice were chemically made diabetic using streptozocin, these mice experienced hyperglycaemia at significantly lower levels than untreated mice that were similarly given streptozocin to induce diabetes. Therefore, even in animals that are not prone to autoimmunity, BCG appears to be even able to boost aerobic glycolysis levels after chemical induction of diabetes, assisting to reduce blood glucose levels.

Why is hypoglycaemia avoided with BCG vaccination in type 1 diabetes?

Upregulation of aerobic glycolysis with BCG vaccination may elucidate the finding of minimal to no hypoglycaemia in the Phase I trial subjects who achieved stable, near-normal blood sugars with long-term follow-up [5].

Patients with long-standing type 1 diabetes who received two serial BCG vaccinations as part of an eight-year study experienced a correction in blood sugars that was near-normal after year 3.5, an effect that persisted for at least five additional years [5]. The insulin requirements for these patients were reduced, and BCG-related correction of

HbA1c to the 5.7–6.0% range was not associated with any increase in hypoglycaemia. For glycolysis regulated at the natural cell level, glucose transporters are sensitive to ambient sugar and turn off when serum sugar falls. This appears to be seen after serial BCG vaccination and stands in contrast to standard insulin therapy (i.e. insulin pumps, continuous glucose monitors), where increasing insulin use to achieve tight blood sugar control can also increase the risk of hypoglycaemia.

Additionally, in patients with type 1 diabetes, overutilization of oxidative phosphorylation for cellular metabolism likely results the overproduction of ketones. It has been known for years that patients with type 1 diabetes, but not type 2 diabetes, are susceptible to ketosis, even when at the same level of glucose dysregulation. The mystery behind this phenomenon might be explained by the baseline defects in lymphoid metabolism in type 1 diabetes. With BCG therapy, accelerated and regulated glucose transport occurs early at the cell membrane, the pentose phosphate shunt is turned on, and fewer metabolites are funnelled through the Krebs cycle. This suggests that BCG-treated patients with type 1 diabetes may be less prone to ketone production, since it occurs at later stages of glycolysis (Figure 1).

BCG findings in type 1 diabetes support the validity of the hygiene hypotheses and related theories

Aerobic glycolysis is a metabolic state with high cellular glucose utilization and rapid ATP production. In contrast, oxidative phosphorylation, which utilizes the mitochondria and Krebs cycle for energy production, is associated with lower cellular glucose use.

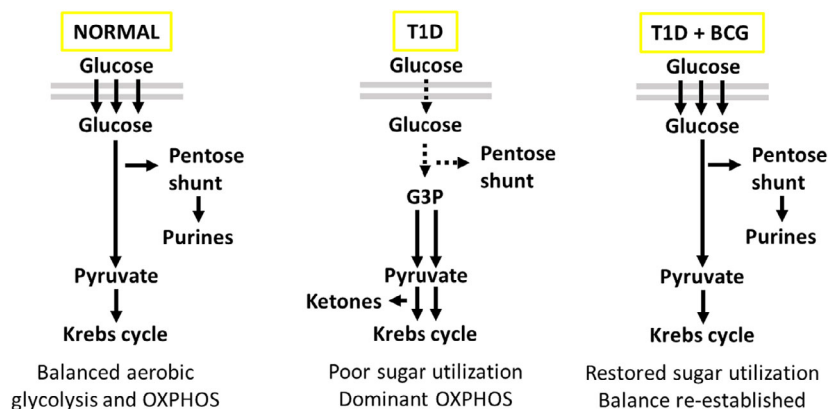


Fig. 1 Lymphocyte aerobic glycolysis and oxidative phosphorylation (OXPHOS) in normal white blood cells (left), in untreated type 1 diabetic lymphocytes (middle), and in treated lymphocytes from human subjects receiving the BCG vaccine (right).

Individuals with type 1 diabetes have a baseline deficiency in aerobic glycolysis with diminished glucose uptake; a reciprocal augmentation of oxidative phosphorylation is instead present [5]. After BCG vaccinations, the metabolism of the immune system gradually shifts from overactive oxidative phosphorylation to regulated glucose transport through aerobic glycolysis [5].

This metabolic data support the hygiene hypothesis and related theories as a mechanistic insight into autoimmunity and allergies. These theories suggest that lack of proper childhood microbial exposures, that is lack of interactions between the host immune system and microorganisms, leads to defects in immune tolerance. Our new data on deficient aerobic glycolysis in type 1 diabetes that can be augmented by BCG vaccination [5] support these hypotheses and also suggest that the lack of adequate exposure to microbes not only leads to defects in the immune system, but also leads to defects in metabolism.

Microbes within infected cells often try to convert cells at sites of infections to aerobic glycolysis, an easy source of sugars for energy. The use of antibiotics to eliminate immune system-boosting infections and the use of vaccines and sanitation measures related to food, water and living environments to prevent infectious diseases might diminish the set point for a better balance of aerobic glycolysis with oxidative phosphorylation. In animal models, human cells in culture, and human clinical trials, BCG or a similar approach (i.e. administration of Complete Freund's adjuvant [CFA] or of tumour necrosis factor [TNF, which is induced by BCG]) shows efficacy in diverse autoimmune diseases, including type 1 diabetes, multiple sclerosis and others [1–5, 37–41]. Therefore, we would predict that similar states of overzealous oxidative phosphorylation might be present at baseline in many of these diseases, beyond just type 1 diabetes. Further, many autoantibodies can, at times, be directed against glycolytic enzymes in the aerobic glycolysis pathway that is interrupted in autoimmunity. These autoantibodies could directly interrupt this pathway or may form in autoimmune hosts from lack of proper synthesis of enzymes that appear foreign with subsequent re-expression in life. To date, autoantibodies have been found to diverse enzymes in the glycolytic pathway, including enolase, GADPH, aldolase pyruvate kinase and others [42].

Our type 1 diabetes findings strongly show that infection with an avirulent strain of *Mycobacterium* can produce a therapeutic effect on a systemic basis, lasting greater than 8 years [5], whilst the collective data on BCG's heterologous benefits leads to a new appreciation of the evolutionary synergy of reintroducing avirulent *Mycobacterium* into modern humans through BCG vaccination. In adults with type 1 diabetes, this synergy is illustrated through the systemic immunometabolic changes after repeat BCG vaccination that appear to re-establish both blood sugar control and self-tolerance through induction of Tregs [5, 6].

Why do the clinical effects of BCG vaccination take several years to manifest in type 1 diabetes?

Our clinical trials do not yet answer the question of why the clinical effect of HbA1C reduction after BCG vaccination is delayed by three years in humans [5]. However, a human clinical trial that evaluated BCG in multiple sclerosis had a similar finding, where BCG's effects were more pronounced with longer (5 year) follow-up time periods [1]. In addition, in our study of mice with streptozotocin (STZ)-induced diabetes, a lag time of at least 6 weeks was needed to see a reduction in HbA1c [5]. Given the 2.5-year lifespan of a mouse, this translates into approximately 3.5 years in the human. With a live vaccine like BCG, it may be that the effects of BCG – such as the initial Treg induction that occurs approximately 6 weeks after receipt of the second BCG vaccination in our trials – may need time to become systemic for the correction of HbA1c. Further, the shift to aerobic glycolysis may involve additional cells and organs beyond those we have examined.

Pancreatic islet regeneration vs correction of immunometabolism in type 1 diabetes: Which is key?

BCG-induced lowering of HbA1C in type 1 diabetes appears to be permanent for at least 8 years [5]. In our study, pancreatic islet regeneration was not obligatory for correction of blood sugars. The underlying mechanism, immunometabolism, was sufficient to regulate cellular glucose transport, at least in adult patients with long-standing type 1 diabetes and no significant residual C-peptide at the trial start. It is appreciated that the human lymphoid system, based on overall cell numbers, is the third largest organ in the human, so systemic conversion of this organ system to higher glucose utilization may be enough for a clinical effect. Still

lacking in the human data is whether BCG can induce increased sugar utilization through augmented aerobic glycolysis in muscle, liver, fat and other nonlymphoid cells to contribute to the therapeutic effects. In humans with type 1 diabetes, aerobic glycolysis is deficient at baseline, and BCG appears to restore the balance between aerobic glycolysis and oxidative phosphorylation to normal levels. At this time, however, although some murine type 2 diabetes data suggest that intravenous BCG administration may be therapeutic in relation to weight reduction, lowering of blood sugars and prevention of fatty liver [43], the efficacy of BCG in humans with type 2 diabetes has not yet been generated through clinical trials.

We have previously shown that BCG or the BCG-equivalent (CFA) treatment of NOD mice results in restored normoglycemia through regeneration of pancreatic islets [40, 41]. However, in our current human studies of adults with long-standing type 1 diabetes and negligible C-peptide secretion from the pancreas at baseline, this does not seem to be the primary mechanism. Although HbA1c was stably corrected to the normal range for over 5 years, stimulated C-peptide remained at almost undetectable levels and was not high enough to account for the observed lowering of HbA1c [5].

In paediatric populations, this might not be the case. Since the recent BCG trials in type 1 diabetes have been limited to adults [4, 5], it is possible that any BCG-driven restoration of normoglycemia in paediatric populations could be driven by both pancreatic islet regeneration/ preservation and regulation of immunometabolism. A paediatric trial is currently planned.

Are timing of BCG administration, number of doses and strain important?

The timing of BCG administration relative to disease onset, the number of BCG doses given, and the strain of BCG used for vaccination appear to be significant factors in determining the efficacy of BCG treatment in autoimmunity.

In murine models, permanent reversal of type 1 diabetes is observed in nonobese 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 [40, 41, 44, 45].

However, giving a single injection of BCG at birth in diabetes-prone humans or NOD mice has no observable benefits [44–48]. Thus, it appears that the disease must be apparent for BCG to be effective and also suggests that multi-dosing might be the correct strategy [25, 49]. Indeed, a retrospective study in humans who received BCG vaccination in childhood has shown that a single dose of BCG is not associated with a reduced incidence of developing type 1 diabetes by age 12, but having at least two doses appears to have a protective effect [25].

Studies in the human and mouse also reveal the variable efficacy of different BCG substrains. The TICE substrain of BCG is known to have poor immunoregulatory properties in the NOD mouse and in humans [50]. In an early human type 1 diabetes trial, a single dose of the *Connaught* substrain did appear to prevent progression to new-onset disease [50, 51], whilst subsequent early trials testing less potent BCG strains, such as TICE, showed no clinical effect in humans within the short follow-up windows of these studies [50–52].

In recent decades, a trend towards a higher incidence of immune-mediated diseases, including type 1 diabetes [53], allergy [54] and multiple sclerosis [54], has been observed in the developed world. In contrast, there is a low prevalence of type 1 diabetes in regions where tuberculosis mycobacteria are found [55], and there is a negative association between tuberculosis and multiple sclerosis [56]. In Turkey, retrospective data suggest that receipt of two or more BCG vaccinations in childhood is protective against the development of type 1 diabetes, but receipt of only one BCG vaccination is not [25]. In Sweden, receipt of multiple vaccinations of BCG (at birth, 7 years and 14–15 years) was mandatory until 1965, when the 7 year booster was stopped, followed by the 14–15 year booster in 1979 and the vaccination of newborns in 1986 [57]. Today, Sweden has amongst the highest reported incidences of type 1 diabetes in the world, with an accelerated trend in total cases that started in the 1990s [57]. When looked at in the context of the gradual reduction in BCG vaccination in Sweden, the acceleration of new type 1 diabetes diagnoses begins only a few years after the final (newborn) BCG vaccination was stopped, and incidence was typically highest amongst younger children, which correlates with those with the fewest BCG vaccination exposures [57].

Can central nervous system diseases benefit from increased aerobic glycolysis?

If BCG boosts aerobic glycolysis, what other disease states might benefit?

Human diseases that exhibit poor sugar uptake in affected tissues are well documented in the ^{18}F -fluorodeoxyglucose (^{18}F FDG) PET/CAT literature. This radiographic imaging method utilizes a radioactive sugar to determine the rate of sugar uptake as a measure of aerobic glycolysis in various tissues or regions of various tissues. Low glucose uptake is observed in many central nervous system (CNS) diseases early in the disease process and is associated with select localized regions of the brain having diminished glucose uptake and loss of function associated with the clinical symptoms. Indeed, developing neurons predominantly use aerobic glycolysis, whilst with senescence older neurons have a diminished ability to use sugar [58].

Table 1 summarizes sugar uptake defects in the CNS as measured by ^{18}F FDG PET/CAT. Although not all CNS diseases are associated with diminished aerobic glycolysis, the data show that Parkinson's disease, Huntington's disease, Alzheimer's disease, multiple sclerosis, depression and ageing all have CNS regions with diminished sugar utilization or diminished aerobic glycolysis early in the disease process [59–81].

It is interesting to speculate whether BCG, by augmenting aerobic glycolysis, could correct these low glucose uptake states in the CNS to restore neuron health and perhaps induce broader clinical benefits beyond the already promising multiple sclerosis data [1–3]. Augmented sugar utilization in the CNS may perhaps be an additional reason – beyond the potential protective effects against neuroinflammation provided by the BCG vaccine [27] – why BCG administered to new-onset multiple sclerosis patients is associated with marked clinical improvement in Phase II clinical trials [1].

Interestingly, a review of the literature by Raison and colleagues has suggested that lack of contact with previously available triggers of anti-inflammatory and immunoregulatory signalling through increased sanitation is associated with the possible pathophysiology and onset of major depressive disorder [82]. This perhaps implies that greater microbial exposure through BCG vaccination is needed to augment aerobic glycolysis, similar to the developing autoimmune data in human clinical trials.

Concluding remarks

In type 1 diabetes, microbial exposure through repeat BCG vaccination appears to systemically trigger a switch from oxidative phosphorylation, a state of poor cellular glucose utilization, to increased aerobic glycolysis, a state of high cellular

Table 1 Altered glucose metabolism in central nervous system (CNS) disorders

Disease	Glucose Metabolism	Location	References
Parkinson's disease	Deficient	Disease regions	[59–64]
Huntington's disease	Deficient	Striatum	[65, 66]
Dementia	Deficient	Disease regions	[67]
Alzheimer's disease	Deficient	Disease regions	[68–71]
Multiple sclerosis	Deficient	Disease regions	[72]
Depression	Deficient	Cortical regions	[73, 74]
Ageing/Development	Deficient	Young brains high glucose, old brains low glucose	[58, 75]
Obsessive Compulsive Disorder	Accelerated	Bilateral caudate nuclei, Orbital frontal cortex	[76]
Schizophrenia ^a	Accelerated	Cortico-striato-thalamic frontal lobe	[77–80]

Low glucose uptake is observed in many central nervous system (CNS) disorders early in the disease process, including in Parkinson's, Huntington's and Alzheimer's diseases as well as in dementia, multiple sclerosis and depression. Might BCG vaccination be able to correct glucose metabolism – and therefore provide a therapeutic effect – by augmenting aerobic glycolysis to restore metabolic balance, similar to the developing data in human autoimmunity?

^aSome studies have shown the opposite, finding deficient glucose transport in the low frontal lobe [81].

glucose utilization. Correction of this metabolic defect in type 1 diabetes using the BCG vaccine results in white blood cells using more serum sugar and appears to drive clinically important effects; namely, the stable, long-term lowering of HbA1c for > 5 years without hypoglycaemia after an initial onset delay of three years. These findings support the hygiene hypothesis and suggest that early-life exposure to microbes that promote aerobic glycolysis is both beneficial to immune system development and could even be corrective later in life as a treatment approach to diverse diseases. Since certain CNS diseases are also known to be associated with too little lymphoid sugar utilization, this raises the intriguing hypothesis that BCG vaccination or a similar intervention to reset cell metabolism could be an attractive therapeutic strategy in these disorders. Taken with other known benefits of BCG benefits related to reduced mortality [16, 17] and reduced susceptibility to infection [12–14], these findings also support reconsideration of vaccine policy in nations that no longer mandate BCG vaccination due to low tuberculosis incidence. *Mycobacteria*, at least in the form of the attenuated BCG strain, are indeed ‘old friends’ that we may want to welcome back.

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Conflict of interest statement

None to report.

References

- Ristori G, Romano S, Cannoni S *et al*. Effects of Bacille Calmette-Guérin after the first demyelinating event in the CNS. *Neurology* 2014; **82**: 41–8.
- Ristori G, Buzzi MG, Sabatini U *et al*. Use of Bacille Calmette-Guérin (BCG) in multiple sclerosis. *Neurology* 1999; **53**: 1588–9.
- Paolillo A, Buzzi MG, Giugni E *et al*. The effect of Bacille Calmette-Guérin on the evolution of new enhancing lesions to hypointense T1 lesions in relapsing remitting MS. *J Neurol* 2003; **250**: 247–8.
- Faustman DL, Wang L, Okubo Y *et al*. Proof-of-concept, randomized, controlled clinical trial of Bacillus-Calmette-Guerin for treatment of long-term type 1 diabetes. *PLoS One* 2012; **7**: e41756.
- Kühtreiber WM, Tran L, Kim T *et al*. Long-term reduction in hyperglycemia in advanced type 1 diabetes: the value of induced aerobic glycolysis with BCG vaccinations. *NPJ Vaccines* 2018; **3**: 23.
- Kühtreiber WM, Faustman DL. BCG Therapy for type 1 diabetes: Restoration of balanced immunity and metabolism. *Trends Endocrinol Metab* 2019; **30**: 80–92.
- Comas I, Coscolla M, Luo T *et al*. Out-of-Africa migration and Neolithic coexpansion of *Mycobacterium tuberculosis* with modern humans. *Nat Genet* 2013; **45**: 1176–82.
- Strachan DP. Family size, infection and atopy: the first decade of the “hygiene hypothesis”. *Thorax* 2000; **55**(Suppl 1): S2–10.
- Bilbo SD, Wray GA, Perkins SE *et al*. Reconstitution of the human biome as the most reasonable solution for epidemics of allergic and autoimmune diseases. *Med Hypotheses*. 2011; **77**: 494–504.
- Kramer A, Bekeschus S, Bröker BM, Schleibinger H, Razavi B, Assadian O. Maintaining health by balancing microbial exposure and prevention of infection: the hygiene hypothesis versus the hypothesis of early immune challenge. *J Hosp Infect* 2013; **83**(Suppl 1): S29–34.
- Rook GA, Adams V, Hunt J, Palmer R, Martinelli R, Brunet LR. *Mycobacteria* and other environmental organisms as immunomodulators for immunoregulatory disorders. *Springer Semin Immunopathol* 2004; **25**: 237–55.
- De Castro MJ, Pardo-Seco J, Martínón-Torres F. Nonspecific (heterologous) protection of neonatal BCG vaccination against hospitalization due to respiratory infection and sepsis. *Clin Infect Dis* 2015; **60**: 1611–9.
- Moorlag SJCFM, Arts RJW, van Crevel R, Netea MG. Non-specific effects of BCG vaccine on viral infections. *Clin Microbiol Infect* 2019; **25**: 1473–1478.
- Butkeviciute E, Jones CE, Smith SG. Heterologous effects of infant BCG vaccination: potential mechanisms of immunity. *Future Microbiol* 2018; **13**: 1193–208.
- Rentsch CA, Derré L, Dugas SG *et al*. Building on a solid foundation: Enhancing bacillus Calmette-Guérin therapy. *Eur Urol Focus* 2018; **4**: 485–493.
- Higgins JP, Soares-Weiser K, López-López JA *et al*. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. *BMJ* 2016; **355**: i5170.
- Biering-Sørensen S, Jensen KJ, Monterio I, Ravn H, Aaby P, Benn CS. Rapid protective effects of early BCG on neonatal mortality among low birth weight boys: Observations from randomized trials. *J Infect Dis* 2018; **217**: 759–66.
- Netea MG, van Crevel R. BCG-induced protection: Effects on innate immune memory. *Semin Immunol* 2014; **26**: 512–7.
- Shi L, Salamon H, Eugenin EA, Pine R, Cooper A, Gennaro ML. Infection with *Mycobacterium tuberculosis* induces the Warburg effect in mouse lungs. *Sci Rep* 2015; **5**: 18176.
- Gleeson LE, Sheedy FJ, Palsson-McDermott EM *et al*. Cutting edge: *Mycobacterium tuberculosis* induces aerobic glycolysis in human alveolar macrophages that is required for control of intracellular bacillary replication. *J Immunol* 2016; **196**: 2444–9.
- Goodridge HS, Ahmed SS, Curtis N *et al*. Harnessing the beneficial heterologous effects of vaccination. *Nat Rev Immunol* 2016; **16**: 392–400.

- 22 Arnoldussen DL, Linehan M, Sheikh A. BCG vaccination and allergy: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2011; **127**: 246–253.e1–21.
- 23 Shann F. The nonspecific effects of vaccines and the expanded program on immunization. *J Infect Dis* 2011; **204**: 182–4.
- 24 Kristensen I, Aaby P, Jensen H. Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa. *BMJ* 2000; **321**: 1435–8.
- 25 Karaci M. The protective effect of the BCG vaccine on the development of type 1 diabetes in humans. In: Faustman D, ed. *The Value of BCG and TNF in Autoimmunity*, 1st ed. Cambridge, MA: Academic Press, 2014; 52–62.
- 26 Kiraly N, Allen KJ, Curtis N. BCG for the prevention of food allergy – exploring a new use for an old vaccine. *Med J Aust* 2015; **202**: 565–6.
- 27 Ristori G, Faustman D, Matarese G, Romano S, Salvetti M. Bridging the gap between vaccination with Bacille Calmette-Guérin (BCG) and immunological tolerance: the cases of type 1 diabetes and multiple sclerosis. *Curr Opin Immunol* 2018; **55**: 89–96.
- 28 Rieckmann A, Villumsen M, Sørup S *et al*. Vaccinations against smallpox and tuberculosis are associated with better long-term survival: A Danish case-cohort study 1971–2010. *Int J Epidemiol* 2017; **46**: 695–705.
- 29 Pollard AJ, Finn A, Curtis N. Non-specific effects of vaccines: plausible and potentially important, but implications uncertain. *Arch Dis Child* 2017; **102**: 1077–81.
- 30 Morikawa H, Ohkura N, Vandenbon A *et al*. Differential roles of epigenetic changes and Foxp3 expression in regulatory T cell-specific transcriptional regulation. *Proc Natl Acad Sci U S A* 2014; **111**: 5289–94.
- 31 Parente JN, Talhari C, Schettini AP, Massone CT. regulatory cells (TREG) (TCD4+ CD25+ FOXP3+) distribution in the different clinical forms of leprosy and reactional states. *Anais Bras Dermatol* 2015; **90**: 41–7.
- 32 Scott-Browne JP, Shafiani S, Tucker-Heard G *et al*. Expansion and function of Foxp3-expressing T regulatory cells during tuberculosis. *J Exp Med* 2007; **204**: 2159–69.
- 33 Yadav V, Dwivedi VP, Bhattacharya D *et al*. Understanding the Host Epigenetics in Mycobacterium tuberculosis Infection. *J Genet Genome Res* 2015; **2**: 016.
- 34 Yaseen I, Kaur P, Nandicoori VK, Khosla S. Mycobacteria modulate host epigenetic machinery by Rv1988 methylation of a non-tail arginine of histone H3. *Nat Commun* 2015; **6**: 8922.
- 35 Okubo Y, Mera T, Wang L, Faustman DL. Homogeneous expansion of human T-regulatory cells via tumor necrosis factor receptor 2. *Sci Rep* 2013; **3**: 3153.
- 36 Okubo Y, Torrey H, Butterworth J, Zheng H, Faustman DL. Treg activation defect in type 1 diabetes: correction with TNFR2 agonism. *Clin Transl Immunol* 2016; **5**: e56.
- 37 Ban L, Zhang J, Wang L, Kuhlreiter W, Burger D, Faustman DL. Selective death of autoreactive T cells in human diabetes by TNF or TNF receptor 2 agonism. *Proc Natl Acad Sci USA* 2008; **105**: 13644–9.
- 38 Faustman DL. TNF, TNF inducers, and TNFR2 agonists: a new path to type 1 diabetes treatment. *Diabetes Metab Res Rev* 2018; **34**: e2941.
- 39 Tran SD, Kodama S, Lodde BM *et al*. Reversal of Sjogren's-like syndrome in non-obese diabetic mice. *Ann Rheum Dis* 2007; **66**: 812–4.
- 40 Ryu S, Kodama S, Ryu K, Schoenfeld DA, Faustman DL. Reversal of established autoimmune diabetes by restoration of endogenous beta cell function. *J Clin Invest* 2001; **108**: 63–72.
- 41 Kodama S, Kuhlreiter W, Fujimura S, Dale EA, Faustman DL. Islet regeneration during the reversal of autoimmune diabetes in NOD mice. *Science* 2003; **302**: 1223–7.
- 42 Adamus G. Impact of autoantibodies against glycolytic enzymes on pathogenicity of autoimmune retinopathy and other autoimmune disorders. *Front Immunol* 2017; **8**: 505.
- 43 Inafuku M, Matsuzaki G, Oku H. Intravenous *Mycobacterium bovis* bacillus calmette-guérin ameliorates nonalcoholic fatty liver disease in obese, diabetic *ob/ob* mice. *PLoS One* 2015; **10**: e0128676.
- 44 McInerney MF, Pek SB, Thomas DW. Prevention of insulinitis and diabetes onset by treatment with complete Freund's adjuvant in NOD mice. *Diabetes* 1991; **40**: 715–25.
- 45 Sadelain MW, Qin HY, Lauzon J, Singh B. Prevention of type I diabetes in NOD mice by adjuvant immunotherapy. *Diabetes* 1990; **39**: 583–9.
- 46 Harada M, Kishimoto Y, Makino S. Prevention of overt diabetes and insulinitis in NOD mice by a single BCG vaccination. *Diabetes Res Clin Pract* 1990; **8**: 85–9.
- 47 McDevitt H, Munson S, Ettinger R, Wu A. Multiple roles for tumor necrosis factor-alpha and lymphotoxin alpha/beta in immunity and autoimmunity. *Arthritis Res* 2002; **4**: S141–152.
- 48 Huppmann M, Baumgarten A, Ziegler AG, Bonifacio E. Neonatal Bacille Calmette-Guérin vaccination and type 1 diabetes. *Diabetes Care* 2005; **28**: 1204–6.
- 49 Shehadeh N, Etzioni A, Cahana A *et al*. Repeated BCG vaccination is more effective than a single dose in preventing diabetes in non-obese diabetic (NOD) mice. *Isr J Med Sci* 1997; **33**: 711–5.
- 50 Pozzilli P. BCG vaccine in insulin-dependent diabetes mellitus. IMDIAB Group. *Lancet* 1997; **349**: 1520–1.
- 51 Shehadeh N, Calcinaro F, Bradley BJ, Bruchim I, Vardi P, Lafferty KJ. Effect of adjuvant therapy on development of diabetes in mouse and man. *Lancet* 1994; **343**: 706–7.
- 52 Allen HF, Klingensmith GJ, Jensen P, Simoes E, Hayward A, Chase HP. Effect of bacillus calmette-guérin vaccination on new-onset type 1 diabetes. A randomized clinical study. *Diabetes Care* 1999; **22**: 1703–7.
- 53 Onkamo P, Väänänen S, Karvonen M, Tuomilehto J. Worldwide increase in incidence of Type I diabetes—the analysis of the data on published incidence trends [published correction appears in *Diabetologia* 2000 May; 43(5):685]. *Diabetologia* 1999; **42**: 1395–403.
- 54 Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med* 2002; **347**: 911–20.
- 55 Airaghi L, Tedeschi A. Negative association between occurrence of type 1 diabetes and tuberculosis incidence at population level. *Acta Diabetol* 2006; **43**: 43–5.
- 56 Andersen E, Isager H, Hyllested K. Risk factors in multiple sclerosis: tuberculin reactivity, age at measles infection, tonsillectomy and appendectomy. *Acta Neurol Scand* 1981; **63**: 131–5.
- 57 Dahlquist GG, Nyström L, Patterson CC, Swedish childhood diabetes study group; Diabetes Incidence in Sweden Study Group. Incidence of type 1 diabetes in Sweden among individuals aged 0–34 years, 1983–2007: an analysis of time trends. *Diabetes Care* 2011; **34**: 1754–9.

- 58 Zheng X, Boyer L, Jin M *et al*. Metabolic reprogramming during neuronal differentiation from aerobic glycolysis to neuronal oxidative phosphorylation. *eLife* 2016; **5**: e13374.
- 59 Walker Z, Gandolfo F, Orini S *et al*. Clinical utility of FDG PET in Parkinson's disease and atypical parkinsonism associated with dementia. *Eur J Nucl Med Mol Imaging* 2018; **45**: 1534–45.
- 60 Berti V, Polito C, Borghammer P *et al*. Alternative normalization methods demonstrate widespread cortical hypometabolism in untreated de novo Parkinson's disease. *Q J Nucl Med Mol Imaging* 2012; **56**: 299–308.
- 61 Borghammer P. Perfusion and metabolism imaging studies in Parkinson's disease. *Dan Med J* 2012; **59**: B4466.
- 62 Borghammer P, Chakravarty M, Jonsdottir KY *et al*. Cortical hypometabolism and hypoperfusion in Parkinson's disease is extensive: probably even at early disease stages. *Brain Struct Funct* 2010; **214**: 303–17.
- 63 Dunn L, Allen GF, Mamais A *et al*. Dysregulation of glucose metabolism is an early event in sporadic Parkinson's disease. *Neurobiol Aging* 2014; **35**: 1111–5.
- 64 Xu Y, Wei X, Liu X *et al*. Low cerebral glucose metabolism: a potential predictor for the severity of vascular parkinsonism and Parkinson's disease. *Aging Dis* 2015; **6**: 426–36.
- 65 Gouarné C, Tardif G, Tracz J *et al*. Early deficits in glycolysis are specific to striatal neurons from a rat model of huntington disease. *PLoS One* 2013; **8**: e81528.
- 66 Powers WJ, Videen TO, Markham J *et al*. Selective defect of in vivo glycolysis in early Huntington's disease striatum. *Proc Natl Acad Sci USA* 2007; **104**: 2945–9.
- 67 Shivamurthy VK, Tahari AK, Marcus C, Subramaniam RM. Brain FDG PET and the diagnosis of dementia. *AJR Am J Roentgenol* 2015; **204**: W76–85.
- 68 Chen Z, Zhong C. Decoding Alzheimer's disease from perturbed cerebral glucose metabolism: implications for diagnostic and therapeutic strategies. *Prog Neurobiol* 2013; **108**: 21–43.
- 69 Cunnane S, Nugent S, Roy M *et al*. Brain fuel metabolism, aging, and Alzheimer's disease. *Nutrition* 2011; **27**: 3–20.
- 70 Cunnane SC, Courchesne-Loyer A, St-Pierre V *et al*. Can ketones compensate for deteriorating brain glucose uptake during aging? Implications for the risk and treatment of Alzheimer's disease. *Ann N Y Acad Sci* 2016; **1367**: 12–20.
- 71 Costantini LC, Barr LJ, Vogel JL, Henderson ST. Hypometabolism as a therapeutic target in Alzheimer's disease. *BMC Neurosci* 2008; **2**: S16.
- 72 Kindred JH, Tuulari JJ, Bucci M, Kalliokoski KK, Rudroff T. Walking speed and brain glucose uptake are uncoupled in patients with multiple sclerosis. *Front Hum Neurosci* 2015; **9**: 84.
- 73 Fu C, Zhang H, Xuan A, Gao Y, Xu J, Shi D. A combined study of 18F-FDG PET-CT and fMRI for assessing resting cerebral function in patients with major depressive disorder. *Exp Ther Med* 2018; **16**: 1873–81.
- 74 Kumar A, Newberg A, Alavi A, Berlin J, Smith R, Reivich M. Regional cerebral glucose metabolism in late-life depression and Alzheimer disease: a preliminary positron emission tomography study. *Proc Natl Acad Sci USA* 1993; **90**: 7019–23.
- 75 Goyal MS, Vlassenko AG, Blazey TM *et al*. Loss of brain aerobic glycolysis in normal human aging. *Cell Metab* 2017; **26**: 353–360.e3.
- 76 Newberg AB, Moss AS, Monti DA, Alavi A. Positron emission tomography in psychiatric disorders. *Ann N Y Acad Sci* 2011; **1228**: E13–25.
- 77 Shinto AS, Kamaleshwaran KK, Srinivasan D *et al*. "Hyperfrontality" as seen on FDG PET in unmedicated schizophrenia patients with positive symptoms. *Clin Nucl Med* 2014; **39**: 694–7.
- 78 Volkow ND, Brodie JD, Wolf AP, Angrist B, Russell J, Cancro R. Brain metabolism in patients with schizophrenia before and after acute neuroleptic administration. *J Neurol Neurosurg Psychiatr* 1986; **49**: 1199–202.
- 79 Resnick SM, Gur RE, Alavi A, Gur RC, Reivich M. Positron emission tomography and subcortical glucose metabolism in schizophrenia. *Psychiatry Res* 1988; **24**: 1–11.
- 80 Buchsbaum MS, Potkin SG, Siegel BV *et al*. Striatal metabolic rate and clinical response to neuroleptics in schizophrenia. *Arch General Psychiatr* 1992; **49**: 966–74.
- 81 McGuire P, Quested D, Spence S, Murray R, Frith C, Liddle P. Pathophysiology of 'positive' thought disorder in schizophrenia. *Br J Psychiatry* 1998; **173**: 231–5.
- 82 Raison CL, Lowry CA, Rook GA. Inflammation, sanitation, and consternation: loss of contact with coevolved, tolerogenic microorganisms and the pathophysiology and treatment of major depression. *Arch Gen Psychiatr* 2010; **67**: 1211–24.

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