DIABETES

BCG vaccination for type 1 diabetes mellitus

New research by Denise Faustman and colleagues demonstrates that the Bacillus Calmette–Guérin (BCG) vaccine, developed to protect against tuberculosis, can lower blood levels of glucose to a range that is near normal (<6%) in patients with established type 1 diabetes mellitus (T1DM), a change that was sustained long-term.

The authors previously conducted a short phase I trial that included six patients with T1DM who received standard care plus either two doses of BCG vaccine or placebo. After 20 weeks, those treated with BCG vaccine showed increased numbers of regulatory T (T_{reg}) cells, which are important for immune balance; however, there was no overall clinical response. "Owing to the increasing amount of data on the BCG vaccine working in other autoimmune diseases, we re-opened this study and started following-up the participants from the original phase I trial and enrolled additional patients with T1DM who had received the BCG vaccine," explains Faustman.

In the current study, 52 participants with T1DM received standard care or standard care with either BCG vaccine or placebo. The original phase I trial participants were followed-up for 8 years and the second group were followed-up for 5 years. The initial serum levels of HbA_{1c} in the BCG group were 7.36% and dropped to 6.18% after 5 years, while the placebo and standard-care-only groups showed no decrease. At 8 years, serum levels of HbA_{1c} held steady at ~6.65% in the BCG group.

The researchers showed that BCG vaccination demethylated T_{reg} genes and increased their expression. Additionally, the authors demonstrated that BCG vaccination improved glucose metabolism by systemically switching from oxidative phosphorylation to aerobic glycolysis (a high glucose consumption state) in diabetic mouse models. "These data reveal a new mechanism for BCG-induced lowering of blood sugars," concludes Faustman.

Ivone Leong

ORIGINAL ARTICLE Kühtreiber, W. M. et al. Long-term reduction in hyperglycemia in advanced type 1 diabetes: the value of induced aerobic glycolysis with BCG vaccinations. *npj Vaccines* **3**, 23 (2018)

NUTRITION

DBM is common during adolescence

Double burden of malnutrition (DBM) is characterized by the simultaneous existence of undernutrition and overweight or obesity, which is common in low-income and middle-income countries (LMICs). Now, a new study by Rishi Caleyachetty and colleagues shows that DBM during adolescence is common in LMICs and the differences in prevalence across LMICs could be caused by large-scale factors, such as internal conflict in a country.

"Despite adolescence being a period of rapid growth with increased nutritional demands, the global health community has largely neglected the nutritional needs of this population," explains Caleyachetty. Comprehensive data on the cause of DBM in adolescents living in LMICs are needed to guide global efforts in solving this problem; however, this information is lacking, which prompted the authors to quantify DBM in adolescents and uncover the large-scale factors associated with the varying burden of adolescent malnutrition.

The authors performed meta-analyses on the height and weight data of 129,276 adolescents (mean age of 14.3 years) from surveys taken from 57 LMICs. Undernutrition was defined as stunting, thinness or both, and overnutrition was characterized as overweight or obese. The analysis showed that in LMICs the prevalence of undernutrition in adolescents was 15.6% and overnutrition was 21.6%. There was a 38–59% difference in prevalence of adolescent malnutrition across the different LMICs, which could be explained by internal conflict in the country, lack of democracy, the gross domestic product of the country, food insecurity, year of the survey and urbanization.

"This deeper understanding of adolescent malnutrition in LMICs will have a pivotal role, not only for the development and nutrition community, but also for policy makers and governments," concludes Caleyachetty.

Ivone Leong

ORIGINAL ARTICLE Caleyachetty, R. et al. The double burden of malnutrition among adolescents: analysis of data from the Global School-Based Student Health and Health Behavior in School-Aged Children surveys in 57 low- and middle-income countries. *Am. J. Clin. Nutr.* https://doi.org/10.1093/ajcn/nqy105 (2018)

CIRCADIAN RHYTHMS

Shift work causes insulin resistance

New research by Patrick Schrauwen and colleagues shows that circadian misalignment, which is seen in people who undertake shift work, causes a substantial reduction in muscle insulin sensitivity. Furthermore, they demonstrate that the peroxisome proliferator-activated receptor (PPAR) pathway has a role in this effect.

Previous epidemiological studies found that people who work night shifts have an increased risk of developing type 2 diabetes mellitus. Additionally, animal models with liver-specific or muscle-specific disruption of clock genes (genes that regulate circadian rhythms) develop insulin resistance. However, the metabolic effect of circadian misalignment in skeletal muscle in humans is still unknown, which led the authors to investigate this effect.

Schrauwen and his team recruited 14 healthy lean young men, who underwent a 3-day circadian alignment (control) protocol and a 3.5-day circadian misalignment protocol where their behavioural cycle was shifted by 12 hours. Plasma levels of glucose and free fatty acids were measured after each protocol, which showed that both levels increased during the misalignment. "Importantly, we found that rapid day–night shift resulted in a ~23% reduction of insulin sensitivity, which was mainly accounted for by muscle insulin resistance," explains Schrauwen.

Next, the researchers analysed mRNA expression levels from muscle biopsy samples taken after each protocol and demonstrated that during circadian misalignment the expression of core clock genes (*BMAL1*, *CRY1* and *PER2*) kept the same expression pattern as in the control condition. This result suggested that the molecular clock in skeletal muscle is misaligned relative to behavioural conditions. Finally, further analyses revealed that genes with protein products involved in fatty acid metabolism and PPAR signalling had increased expression, suggesting that circadian misalignment upregulated lipid metabolism in the muscle.

As the current study is on healthy participants, the authors are interested in whether similar effects would be observed in people with metabolic disorders (such as diabetes mellitus and obesity).

Ivone Leong

ORIGINAL ARTICLE Wefers, J. et al. Circadian misalignment induces fatty acid metabolism gene profiles and compromises insulin sensitivity in human skeletal muscle. *Proc. Natl Acad. Sci. USA* https://doi.org/10.1073/pnas.1722295115 (2018)