

Milestone 15

Better living (not) through chemistry

Obesity and overweight are the major risk factors for the development of type 2 diabetes (T2D). The explosion in T2D prevalence over the past half century has paralleled that of the obesity epidemic, thought to be driven by changes in lifestyles associated with increased availability of calorie-dense foods, as well as decreased physical activity and the emergence of urban obesogenic environments. Left unchecked, by 2050, as many as 750 million people will have T2D worldwide.

While new therapeutics aimed at tackling excess adiposity and elevated HbA_{1c} levels are highly effective for managing T2D, the best strategy to reduce the global burden is undoubtedly prevention – in part through identification and early treatment of individuals at high risk of developing T2D.

Prediabetes is defined by an elevated level of blood glucose that does not meet the threshold for a definitive T2D diagnosis and it is considered an intermediary stage towards development of clinical T2D. Generally characterized by a higher than normal BMI, the debate regarding whether and how to treat individuals with prediabetes with pharmaceutical interventions is contentious. However, the concept that prediabetes is reversible and therefore T2D is preventable in at-risk populations (and more

broadly) is widely accepted by the medical community – and the evidence is strong.

In 1986, the first large-scale, randomized controlled trial aimed at reducing incidence of T2D through behavioural interventions – healthy diet and/or exercise – was initiated in Da Qing, China. Investigators leading the Da Qing IGT and Diabetes Study screened >100,000 men and women, enrolling 577 individuals with impaired glucose tolerance, irrespective of BMI. Participants were randomized to either a no-intervention control group or one of three interventional groups: diet only, exercise only, or diet-plus-exercise, with regular follow-up visits with a physician over the course of the study. At 6 years, the cumulative incidence of T2D was 67.7% in the control group compared with 43.8% (diet only), 41.1% (exercise only) and

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46% (diet-plus-exercise) in the interventional groups, demonstrating a statistically significant reduction in T2D incidence associated with diet and/or exercise over the course of the study.

A post hoc 30-year follow-up of the Da Qing study, including 540 of the original participants, compared outcomes between the control group and the interventional groups combined. Participants in the healthy diet and/or exercise group had a median delay in onset of T2D of almost 4 years, fewer cardiovascular events and lower incidence of microvascular complications and reduced all-cause and cardiovascular deaths.

Clinical trials in other settings have affirmed these beneficial effects in individuals with impaired glucose tolerance. The Diabetes Prevention Program (DPP) in the USA found that a lifestyle modification intervention was more effective than metformin for reducing T2D incidence in a diverse, at-risk population; and the Finnish Diabetes Prevention Study reported similar findings. Long-term follow-up over 15 years and 7 years, respectively, demonstrated sustained effects of the diet/exercise interventions and, in the case of DPP, demonstrated cost-effectiveness.

Extending the work of prevention studies, in 2018, the DiRECT trial showed that T2D in patients with a recent diagnosis (<6 years) was reversed in 46% of participants in the low-calorie diet intervention group. These findings were confirmed in the DAIDEM-1 trial, reporting significant reductions in weight, and with diabetes remission observed in 61% of participants in the low-calorie diet intervention group, in a population from the Middle East and North Africa region with a diagnosis of T2D within the past 3 years.

The evidence supporting prevention and remission of T2D provides a strong case for expanding support for dietary and physical interventions in clinical practice. However, further research is urgently needed to understand patient acceptability and ways to prevent weight regain when normal diets resume after the initial phase, and to determine the optimal settings in which to deliver the interventions.

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Nature Medicine

Milestone study

Pan, X.-R. et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. *Diabetes Care* **20**, 537–544 (1997)

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