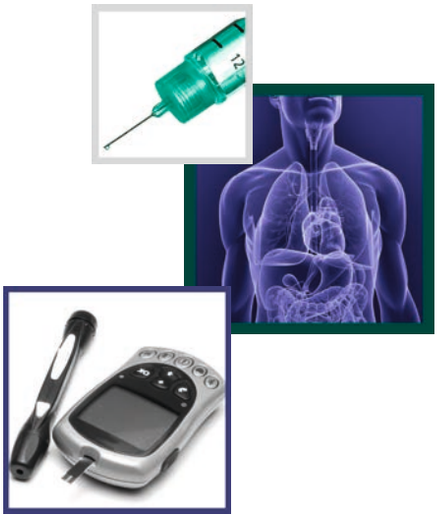
The future of diabetes prevention: a focus on the implications of the Diabetes Prevention Program Outcomes Study



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Q What were the main aims of the Diabetes Prevention Program?

Although the prevention of diabetes had been proposed occasionally in the past [1–3], evidence-based knowledge on the prevention of Type 2 diabetes (T2D) has only been gradually accumulated since the 1990s as the results from multiple proper prevention trials have been published. Both lifestyle interventions and pharmacologic intervention studies [4] have shown that the progression from prediabetes (primarily impaired glucose tolerance [IGT]) to overt diabetes can be halted very effectively. The US Diabetes Prevention Program (DPP) is the largest of these studies [5].

The DPP reported the effects of intervention on diabetes incidence, weight change and cardiovascular disease risk factors during an average 3-year trial period with a 58 and 34% relative risk reduction in the lifestyle and metformin arms, respectively [5]. The trial was prematurely closed based on these unequivocally positive results. It was then decided to follow the trial cohort as an observational study in order to obtain information on long-term outcomes, and 10 years of follow-up since DPP randomization [6]. Thus, the Diabetes Prevention Program Outcomes Study (DPPOS) is a long-term follow-up of the DPP to investigate whether the delay in the development of diabetes seen during the original DPP will be sustained, and to assess long-term effects of the interventions on health (i.e., interventions on the development of diabetes and its complications).

Q What were the eligibility criteria & how were 'prediabetic' subjects selected in the Diabetes Prevention Program Outcomes?

Participants eligible for inclusion in the DPPOS were those who were originally enrolled in the DPP and who survived until August 2002; at baseline they were overweight, 25 years of age or older, had IGT and a fasting plasma glucose of 5.3–7.7 mmol/l; and both genders and several ethnicities were included. Of these participants, 2766 (88% of the DPP participants) were recruited for the DPPOS with a follow-up of 5.7 years; 910, 924 and 932 of them were from the original lifestyle, metformin and placebo

groups, respectively [6]. People who had developed diabetes during the DPP were also included in the DDPOS.

Q What were the most striking conclusions? How do these compare to the findings of similar studies?

The most striking conclusions in each group were:

In the intensive lifestyle group: after an average of 10 years of follow-up aimed at modest weight loss, the intervention reduced the rate of developing T2D by 34% compared with the placebo group, and in people aged 60 years or older the risk of developing T2D was reduced by 49%. Lifestyle intervention delayed the onset of T2D by approximately 4 years, and it also reduced cardiovascular risk factors, hemoglobin A1C and fasting plasma glucose compared with placebo.

In the treatment with metformin group: after an average of 10 years of follow-up treatment, the rate of developing diabetes was reduced by 18% compared with placebo, diabetes was delayed by 2 years, and hemoglobin A1C and fasting glucose was reduced. Interestingly, a weight loss of approximately 2 kg remained steady with metformin over the 10-year period. This is probably the longest observation on weight in overweight people with metformin.

The findings on the prevention of diabetes with lifestyle intervention and metformin in the DPPOS are consistent with the results of two other studies. During the first 4-year follow-up of the Finnish Diabetes Prevention Study (DPS), lifestyle intervention reduced the incidence of T2D by 58% [7] – as in the DPP – and during the extended 3-year follow-up without intervention the effect remained, with an additional 39% reduction in diabetes incidence [8].

The Da Qing study reported results after a 20-year follow-up in 577 Chinese individuals with IGT [9]. After 6 years of lifestyle intervention, the cumulative incidence of diabetes was high (68% in the usual care group, 48% in the diet, 41% exercise and 46% in the diet more exercise). The incidence of T2D remained lower in the lifestyle groups than in the control group during the entire 20-year follow-up period since the intervention was stopped in its sixth year [10].

Q To what extent were intensive lifestyle changes more successful than oral medication?

Lifestyle modification effectively reduces the conversion from IGT to T2DM, but it is difficult to implement and maintain. Moreover, 40–50% of IGT subjects progress to T2DM in 10 years despite some weight loss. By contrast, pharmacological interventions that reverse known pathophysiological abnormalities (β-cell dysfunction and insulin resistance) uniformly prevent progression to T2DM. Metformin in the US DPP reduced the development of T2DM by 31%, thus less than the 58% achieved by lifestyle intervention [5].

Q Can these interventions result in long-term sustained effects?

Yes, they can. During the DPPOS, the incidence in the original metformin and placebo groups equaled to those in the original lifestyle group, and hence the 10-year cumulative incidence of diabetes remained lower in the lifestyle group. Prevention or delay of T2D with interventions based on lifestyle and metformin can persist for at least 10 years [6].

Q Are diet & exercise beneficial even after diabetes develops?

In many people who progress from prediabetes to T2D, this is due to limited lifestyle changes, as shown by the Finnish DPS [7]. These people should pay particular attention to their diet and exercise. Antidiabetic drug treatment alone in T2D has only a limited effect on glycemic control, which deteriorates in diabetic patients despite intensive treatment, as demonstrated in many prospective studies.

Q Should education efforts be targeted towards high-risk groups or specifically tailored for different cultures or communities?

Several studies have examined the effects of intensive lifestyle changes on

the reduction of T2D risk in people at high risk of developing diabetes (prediabetic). The landmark Finnish DPS showed that diet and exercise resulted in a risk reduction similar to that shown in the DPP/DPPOS. However, the Finnish trial only studied the effect of lifestyle intervention (not metformin), and did not study the effects of race/ethnicity on risk reduction. By contrast, DPP/DPPOS included diverse racial/ethnic groups (White–American, African–American, Native American, Pacific Islander and Hispanic individuals) [6]. Lifestyle changes are influenced by cultural factors, but trials conducted in China, India and Japan have shown that T2D can be prevented as well in non-Western populations [9–12]. The risk factors for T2D are the same in all human populations, and these factors form the basis for lifestyle management. Nevertheless, lifestyles are always closely related to social and cultural factors, and therefore it is necessary to tailor lifestyle interventions for different cultures and communities.

Q Does gene susceptibility limit the success of lifestyle interventions in preventing T2D?

In genetically predisposed individuals, the probability of developing T2D increases very significantly once exposed to unhealthy diet and physical inactivity. Genes themselves do not cause T2D. While we cannot change the genes, the only way to prevent T2D and its serious complications is the modification of lifestyle risk factors. Therefore, it is very important to understand the effects of different genetic profiles on the success of lifestyle intervention as the key strategy for T2D prevention. Such an approach to develop personalized medicine will become an important method of T2D prevention in the future.

The DPP has tested genetic associations with the risk of T2D [13,14] and between obesity-predisposing single nucleotide polymorphisms and weight loss/weight regain from 6 months to study end. Regardless of the intervention type (lifestyle or metformin), the *Ala12* allele at *PPARG* was associated with weight loss. By contrast, three single-nucleotide polymorphisms were associated with weight regain (*NEGR1* rs2815752, *BDNF* rs6265 and *PPARG* rs1801282), irrespective of treatment [15]. Therefore, genetic information may be important and may help to identify people who require additional support to maintain lifestyle intervention.

Q What is being done to inform the public & healthcare professionals about the results of clinical trials like this? How successfully have the findings from large clinical trials been translated into primary care?

In an attempt to stem the diabetes epidemic, the National Diabetes Education Program (NDEP) launched the first US comprehensive campaign that reached out to millions of Americans at high risk for T2D. The prevention initiative, known as 'Small Steps, Big Rewards. Prevent Type 2 Diabetes', aims to translate the results of the DPP into public health practices [101]. By delivering practical, real-world tools to those at risk, all individuals, from women with a history of gestational diabetes and their children to older adults, are encouraged to take the small steps needed to achieve the big reward of preventing or delaying the onset of T2D. NDEP also produces materials for the full healthcare team responsible for helping individuals at risk to prevent or delay the onset of this chronic disease [102].

Finland was the first country to implement a National Program for Diabetes Prevention. This program comprised three concurrent strategies for prevention: the population strategy, the high-risk strategy and the strategy of early diagnosis and management [16]. Several other community intervention programs have been created in order to implement the proven preventive strategies in real life situations. In Europe, the Diabetes in Europe: Prevention using Lifestyle, Physical Activity and Nutritional intervention (DE-PLAN) program is being implemented in 25 primary care centers in 17 European countries [17]. Many other countries, such as India, China, Canada and Australia, are now also developing national diabetes prevention programs.

Q What is the future for pharmacological diabetes prevention strategies?

New incretin-based therapies (dipeptidyl peptidase-4 inhibitors and GLP-1 agonists) have recently been approved, with evidence of efficacy when used alone or in combination with metformin in T2D patients, but there is still little evidence on the benefits of such treatments for T2D prevention.

New studies have been proposed and are being launched. For instance, in Europe and Australia the Early Prevention of Diabetes Complications in People with Hyperglycemia (ePREDICE) Study aims to assess the long-term effects of combined therapeutic regimens (different antidiabetic drugs plus lifestyle intervention) in the early prevention of diabetic complications in people with intermediate hyperglycemia (impaired fasting glucose or IGT) and screen-detected diabetes by the authors. In the USA, the NIH has launched a special call for trials aiming at searching for interventions that prevent and reverse the loss of the pancreatic β-cell function that is typical in T2D.

Q What challenges remain in this field? What progress do you foresee happening in the next 10 years?

Even though several trials in different countries have repeatedly reconfirmed that lifestyle intervention works extremely well for the prevention of T2D, and that the meta-analysis shows that for every six prediabetic people provided with lifestyle management for approximately 3 years, one case of T2D is prevented [18]. There is hardly any intervention that has such efficacy in the prevention of chronic diseases. The challenges that now remain for the prevention of T2D include:

- Translation of the trial results to become a part of regular primary care preventive medicine. This work is going on actively in many countries and does not happen automatically but requires a lot of work;
- Informing people worldwide about their individual risk of T2D. This can be carried out using the currently available simple diabetes risk scores, such as the Finnish Diabetes Risk Score (FINDRISC) [19], used worldwide and validated in different countries [17] and other projects to find out how to modify it for different populations;
- Prevention could also be aided by establishing proper population-based activities in other societal activities outside the health sector. T2D is not only a disease of some individuals, but its origin also includes many other aspects of life and living. In summary, actions that promote easy healthy choices (diet and physical activity) are preferred by people. Naturally, the list is much longer. We currently have very encouraging evidence from anti-smoking activities and actions to prevent cardiovascular disease at the population level. The next issue must be T2D prevention. We have the knowledge, but this is not enough (as we have learned from anti-smoking programs); we also have to apply it.

Over the next 10 years people will be increasingly aware of their T2D risk and will get increasingly better information about its prevention, especially if they are at high risk. Society should be preparing for the high human and economic cost of T2D, and starting to making decisions that improve the situation. The food industry will hopefully start producing less unhealthy food, and there will be increasing number of innovations on how to promote physical activity, particularly in situations where it is limited due to environment, culture or architectural design.

To achieve this, it is important that there are enough active spokesmen to promote anything that is helpful and, at the same, time to point out where the problems are. This is a key aim of the activities proposed to be carried out globally and historically agreed by all UN Member States at the UN Summit on noncommunicable diseases in September 2011 [20].

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