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Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. Lancet Diabetes Endocrinol. 2015 Nov;3(11):866-75.

What We Know, Think We Know, or Are Starting to Know

The core pathophysiology of type-2 diabetes [T2D] is the progressive decline, and and eventual termination of function, in the capacity of the beta-cells [β-cells] of the pancreas to produce insulin, and maintain blood glucose levels in normal range ['normoglycaemic'] [(1)]. While insulin resistance in peripheral tissues develops first, it is the loss of function of β-cells that characterises the progressive severity of the disease [(1)]. Thus, it is important to recognise that diabetes is a spectrum of levels of glucose* and insulin control, from impaired glucose tolerance [IGT] and pre-diabetes, to a diagnosis of T2D.

The crucial point is that defects in glucose metabolism emerge often long before the diagnosis of a disease [(2)]. For example, people who are clinically normoglycaemic that progress to IGT may already have lost half of their β-cell function by the time they progress to IGT, and subjects with IGT and an oral glucose tolerance test [OGTT] result near the cutoff for diagnosis of T2D will have lost at least 80% of their β-cell function [(2)]. And, Roy Roy Taylor' s research group, in their very-low-calorie liquid diet studies for diabetes remission, have demonstrated that the capacity of β-cells to recover function may be contingent on duration of disease, i.e., individuals still within a few years of diagnosis may have a greater odds of recovering function than individuals with longer duration of disease [(3)].

The progressive deterioration in glucose tolerance and β-cell function indicates that time is a crucial factor in diabetes prevention, and large scale diabetes prevention programs in a number of countries have focused on intervening at the earlier stages of IGT [(4-6)]. Peripheral insulin resistance is a modifiable risk factor, with both diet and exercise exerting beneficial effects on insulin sensitivity [(7)]. The drug metformin also enhances glucose uptake in skeletal muscle, but its primary mechanism of action is enhancing insulin action in the liver to reduce the rate of hepatic glucose production [(8)].

Thus, a combination of pharmacotherapy with metformin and/or diet and exercise may have potential to reduce rates of progression from IGT to T2D. In the Diabetes Prevention Program [DPP], subjects with IGT and BMI >34kg/m2 were randomly assigned to either metformin, diet+exercise, or placebo [(9)]. Progression to TD2 was reduced by 58% in the lifestyle group, compared to 31% in the metformin group, over 3yrs [(9)]. The present study was the 15yr follow-up of the DPP.

*Geek Box: Diabetes Definitions

There are a number of markers used in the assessment of blood glucose regulation. The following table sets out the various blood glucose ranges used in the UK, note that these ranges may differ slightly in other countries. The table has the ranges for each stage of glucose tolerance [left hand column], for both fasting glucose levels [middle column] and the 2hr postprandial glucose response to an oral glucose tolerance test [right hand column].

Glucose Tolerance State	***Fasting Plasma Glucose***	***2hr Plasma Glucose (OGTT)***
Normoglycaemic	*4.0–5.4mmol/L [72–99mg/dL]*	*Up to 7.8mmol/L (140mg/dL)*
Impaired Fasting Glucose [IFG]	*5.5–6.9mmol/L [100-125mg/dL]*	*7.8–11.0mmol/L [140–199mg/dL]*
Impaired Glucose Tolerance [IGT]	*<7.0mmol/L [<126mg/dL]*	*7.8–11.0mmol/L [140–199mg/dL]*
Combined IFG/IGT	*5.5–6.9mmol/L [100-125mg/dL]*	*7.8–11.0mmol/L [140–199mg/dL]*
Type 2 Diabetes [T2D]	*>7.0 mmol/L [>126mg/dL]*	*>11.1 mmol/L [200mg/dL]*

The levels for IFG and IGT are considered to be 'pre-diabetes'. There is also glycated haemoglobin A1c [HbA1c], a marker for when red blood cells are exposed to glucose levels in plasma. HbA1c reflects longer-term blood glucose regulation over the period of the previous 3-months, and is expressed as a percentage. Currently, 6.5% is considered the threshold for a diagnosis of T2D, and the range of 6.0–6.4% is considered 'high-risk' according to World Health Organisation guidelines. However, there is evidence which suggests that HbA1c may be less sensitive to identifying at-risk patients compared to the plasma glucose measures. In the US National Health and Nutrition Examination Survey [NHANES], fasting glucose identified twice as many individuals as in the prediabetes range compared to HbA1c [(10)]. Thus, while HbA1c is a useful clinical tool for diabetes management, in the prognosis and identification of individuals earlier in the glucose intolerance continuum it may lack the specificity of OGTT results, which reflect the actual pathophysiology of elevated glucose levels and the ability of the β-cells and insulin to return blood glucose levels into normal range. HbA1c may miss diagnoses at an earlier stage which could be identified by an OGTT [(11)]. It is helpful to have an idea of the various levels of glucose tolerance, given the continuum of glucose tolerance. Although attention tends to be put on the diagnosis of a disease itself, in this case T2D, in reality the underlying pathophysiology precedes diagnosis by years. This explains the need for early intervention in the natural history of the disease.

The Study

The initial Diabetes Prevention Program [DPP] was a randomised controlled trial across 27 study centres in the US. Participants were randomly assigned to one of three groups:

- Metformin - 850mg twice per day
- Placebo - [resembling metformin in appearance and dosing regimen]
- Lifestyle - targeting 7% weight loss, low-fat/low-calorie diet, and 150min/week moderate intensity physical activity

The lifestyle group received 16 individual sessions of behavioural counselling, which developed to include group sessions from 24-weeks of the intervention. Both the metformin and placebo groups were double-blinded, however, the lifestyle group was not due to the behavioural sessions.

The DPP Outcomes Study [DDPOS] began 1yr after conclusion of the initial intervention, to examine the long-term effects of the interventions on further diabetic and cardiovascular risk factors. In the 1yr period between the end of the DPP and the DPPOS, all participants were offered the lifestyle program.

Following enrolment to the DPPOS, the original metformin group continued with metformin, and the lifestyle group were offered group behavioural programs and individual check-ins, each provided twice per year. The primary outcomes of the DPPOS were development of T2D and microvascular disease.

Results: Of the 2,776 participants in the DDPOS, 609 were diagnosed with T2D during the DDP study period and a further 941 diagnosed during the DDPOS follow-up period. The annual incidence of diagnosis over the entire 15yr study period was 7%, 5.7%, and 5.2% in the placebo, metformin, and lifestyle groups, respectively.

The absolute number of cases, and the cumulative prevalence of T2D incidence in each group, were 560 (62%), 499 (56%), and 480 (55%) in the placebo, metformin, and lifestyle groups, respectively.

- ***>T2D - Lifestyle vs. Placebo:*** The lifestyle intervention significantly reduced T2D incidence by 27% [HR 0.73, 95% CI 0.65–0.83], compared to placebo.

- ***>T2D - Metformin vs. Placebo:*** Metformin treatment significantly reduced T2D incidence by 18% [HR 0.82, 95% CI 0.72–0.93], compared to placebo.

- ***>T2D - Lifestyle vs. Metformin:*** There was no significant difference between these groups in T2D incidence at 15yrs follow-up.

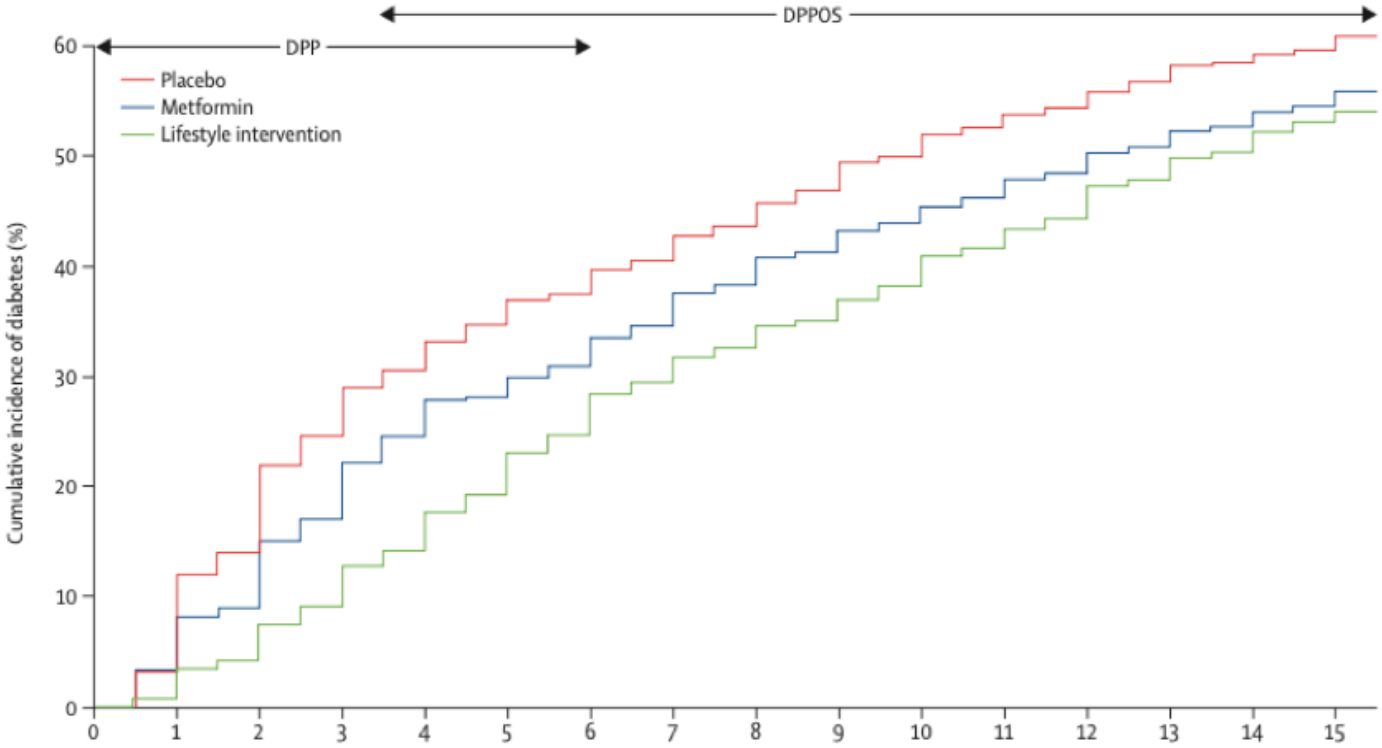


Figure *from paper illustrating the cumulative incidence in diabetes over the time period of 15yrs [horizontal X-axis] in the placebo group* ***[red]****, metformin group* ***[blue]****, and lifestyle group* ***[green]****. At years 3-5, there was a 58% reduction in incidence of T2D in the lifestyle group, and 31% in the metformin group, compared to placebo. At 15yrs follow up the difference was reduced to 27% and 18%, respectively.*

- ***Microvascular Outcomes:*** There was no significant difference in microvascular outcomes between the three groups, although the prevalence of such outcomes was 58% higher in men than in women. Irrespective of treatment group, participants who did not develop T2D had a 28% [HR 0.72, 95% CI 0.63–0.83] lower risk of developing microvascular disease compared to participants who were diagnosed with T2D. In women only, the lifestyle intervention reduced microvascular disease by 21% [HR 0.79, 95% CI 0.62–0.98] compared to placebo, and 22% [HR 0.78, 95% CI 0.62–0.96] compared to the metformin group.

The Critical Breakdown

Pros: The DPP was a large-scale study with a diverse representative sample for the US population, 68% women, 54% White, 20% African-American, 15% Hispanic, 6% Native American, and 5% Asian American [including Pacific Islanders]. The study included 3,234 participants in the initial DPP, of which 2,776 were enrolled into the DPPOS. The DDPOS included both 10yr and 15yr follow-ups, providing insight into long-term outcomes beyond T2D, in particular cardiovascular health outcomes. Both of the primary outcomes were analysed according to the intention-to-treat principle which is a form of analysis which includes all participants that were randomised in the study, irrespective of whether they dropped out or not. To do this, the investigators take the last value recorded for that participant forward into the analysis, as if that value represented the data point the participant finished the trial with. Intention-to-treat is recommended in any trials comparing the effects of a treatment, because if the intervention and control arm are not balanced, it may lead to bias in the results. The study had high levels of retention - 87% of enrolment in the DDPOS - and completion rates were similar between groups.

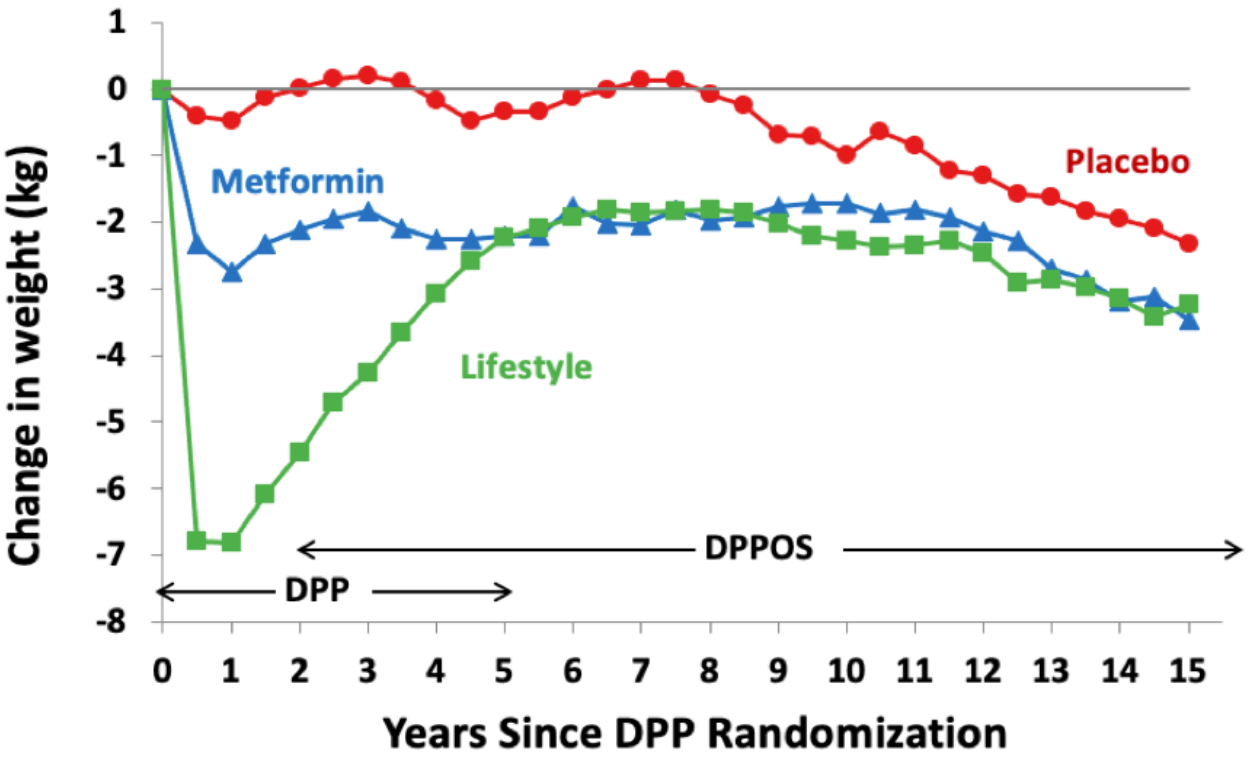
Cons: The discrepancy in behavioural counselling may have been an unavoidable aspect of the study design, however, we do know from other diabetes prevention studies that number of practitioner contacts is a strong predictor of successful outcomes. This may have biased the initial intervention toward the lifestyle group. The fact that all three groups were offered the lifestyle program during the 1yr bridge period between the DPP and DPPOS means that any continued health-promoting behaviours in the metformin/placebo groups may have reduced the relative effects of the lifestyle intervention. Conversely, the use of metformin in the lifestyle and placebo groups may have reduced the relative effects of metformin alone.

Key Characteristic

The duration of follow-up provided important insight into the potential effect of lifestyle interventions over the long-term. There have been some findings from diabetes prevention programs which suggested that diet and exercise could prevent progression from IGT to T2D [4-6]. However, these effects appear to be most evident in the 2-6yr periods of an intervention, and longer-term follow-ups have not yielded optimistic findings. For example, in the Chinese Da Qing IGT and Diabetes Study, participants with a BMI of >25-30kg/m2 in the lifestyle intervention group had a 43% progression to diagnosis of T2D, compared to 72% of the control [no diet or exercise] group [4]. At 20yrs follow-up, however, progression to T2D was 80% in the intervention group compared to 93% of controls [12]. Thus, while lifestyle interventions may yield greater prevention in the short-term, progression to T2D may still be high in the long-term. The DDPOS 15yr follow-up suggests similar long-term results. At years 3-5, there was a 58% reduction in incidence of T2D in the lifestyle group, and 31% in the metformin group, compared to placebo. Over time, the significant difference between the lifestyle intervention and the metformin intervention groups which was evident during the initial DPP study dissipated, such that at 15yrs follow-up there was no significant difference between these two groups. The potential reason for this is elaborated on in the next section.

Interesting Finding

What could explain the erosion of effect over time in the diabetes prevention studies? One clue lies in the DPP itself. In a follow-up analysis of the respective contributions of weight loss, diet and exercise in the DPP lifestyle group, weight loss averaging 5kg over 3.2yrs was the strongest factor associated with a 55% reduction in risk, independent of exercise and diet composition [13]. See the ***Figure***, below: at the end of the first year of the DPP, mean weight loss was 0.4kg, 2.3kg, and 6.7kg in the placebo, metformin, and lifestyle groups, respectively. By the end of the 3yr initial intervention, mean weight loss was 1.8kg and 4.2kg in the metformin and lifestyle groups, respectively. By year 5 the difference in weight loss between metformin and lifestyle groups was abolished, and it remained equivocal for the duration of follow-up.



In the DPP, participants who progressed to T2D had evidence of impaired glycaemic control at baseline, in particular fasting glucose of 7.4mmol/L vs. 5.7mmol/L in participants who did not progress to T2D. Now, look at the above graph - the left Y-axis shows the change in weight as a percentage of baseline starting weight: over the first year of the intervention, the lifestyle group lost an average of 7% bodyweight. During this period, fasting glucose significantly declined and was associated with the 7% reduction in bodyweight. However, by 3.5yrs fasting glucose had returned to baseline levels in the lifestyle group and was associated a weight reduction of just 4% below baseline at that point. Cumulatively, the data suggests that weight loss and maintenance of minimum of 5% bodyweight is required to prevent progression [13-15].

Relevance

The DPP and DPPOS have provided a substantial wealth of data to the evidential puzzle of diabetes prevention. And while the results of the diet+exercise intervention may not have been superior to treatment with metformin over the long-term, the total body of data derived from this study is highly instructive.

First, it is possible to achieve significant improvements in blood glucose regulation without pharmacotherapy, however, the effects of these lifestyle interventions appear to be contingent on the magnitude of weight loss in higher risk individuals. A recent meta-analysis specifically focusing on glycaemic control in IGT found that diet and physical activity improve blood glucose regulation, including FPG and OGTT, over a median follow-up period of 4.8-years [(16)]. So yes, diet and exercise alone may improve the underlying metabolic complications associated with IGT [(7,16).]

Second, however, while diet and exercise may both be necessary, they may not alone be sufficient. This is because continued decline in β-cell function is a hallmark of the progression from IGT to T2D. Carr et al. found that a 2yr diet and lifestyle intervention resulted in 2.6kg weight loss average and increased insulin sensitivity, but failed to restore β-cell function [(14)]. In the Finnish Diabetes Prevention Study [DPS], incidence of progression to T2D was reduced by 58% over 3yrs in subjects with IGT and BMI >25kg/m2 [(6)]. The reduction in risk in the intervention group corresponded to an average weight loss of 3.5kg, compared to 0.8kg in the control group [(15)].

On the other end of the spectrum from diabetes prevention is diabetes remission, and a similar theme is observed in that literature. Taylor et al. demonstrated that a very-low-calorie liquid diet resulted in restoration of beta-cell function and liver insulin sensitivity, following significant reduction in liver fat content [(17)]. This pilot study was followed by the Diabetes Remission Clinical Trial (DiRECT), in which 86% of participants achieving weight loss of ~15kg achieved remission of T2D [(18)]. However, only 57% of participants achieving 10-15kg weight loss achieved remission.

The DPP and DPPOS corroborate the crucial modifying effect of a minimum of 5% initial bodyweight loss in the prevention of progression from a state of impaired glucose tolerance to a diagnosis of diabetes, and the importance of diet and exercise in facilitating that risk reduction.

Application to Practice

A review of nine intervention studies found that the primary driver of prevention of progression from IGT to T2D was weight loss, achieved through achievement of dietary and physical activity targets [(7)]. Weight loss is thus an effective intervention to prevent progression from IGT to T2DM. The limitations are the degree of weight loss required and the need to maintain that weight loss in the context of continued declining β-cell function. While at present the interventions are effective, achieving long-term adherence in a real-world setting remains a challenge. Another diabetes prevention program, the Look AHEAD trial, may give practitioners an important clue in facilitating positive outcomes: those participants who maintained >10% weight loss over 8yrs were those who had significantly more recorded contacts with their study practitioner than those who regained their baseline weight [(19)].

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