The potential of metformin for diabetes prevention

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SUMMARY

Well designed intervention trials, such as the Diabetes Prevention Program (DPP), have demonstrated the potential of lifestyle interventions or pharmacologic treatments for the prevention or delay of type 2 diabetes in subjects with impaired glucose tolerance (IGT). Lifestyle interventions are likely to form the cornerstone of the management of IGT in the future, as they do in the management of type 2 diabetes today. However, it remains to be seen whether the intensive lifestyle interventions employed in trials such as the DPP can be transferred successfully from the highly structured environment of a randomised trial to routine, day-to-day management within the primary care sector. Thus, pharmacologic treatment may provide an important additional option where subjects are unwilling or unable to improve their diet and levels of physical activity. Treatment with metformin significantly reduced the incidence of diabetes in subjects with IGT and high-normal fasting plasma glucose in the DPP. Moreover, metformin was well tolerated, and health economic analyses suggest that metformin treatment is cost-effective in the US and Europe. The DPP investigators found that the protective effect of metformin persisted beyond the end of the study, and estimated that only one quarter of the protection arose from a short-lived pharmacological effect. The results of the DPP identify metformin as an effective option for the prevention of diabetes in subjects with IGT and impaired fasting glucose.

Key-words: Impaired glucose tolerance · Diabetes prevention · Metformin · Type 2 diabetes · Impaired fasting glucose.

Facing up to the problem of impaired glucose tolerance

It is now clear that we face an explosive increase in the prevalence of type 2 diabetes, with its associated burdens of illness and loss of life expectancy on patients and on their families, and of spiralling costs to national healthcare systems [1-3]. Many more individuals, perhaps as many as one quarter of some populations, have impaired glucose tolerance (IGT), a pre-diabetic state that confers a markedly increased risk of developing type 2 diabetes [4]. Once type 2 diabetes is established, intensive life-long management is necessary to prevent the onset of the diabetic complications which herald disability and death. Indeed, many patients already have complications when they present for diagnosis [5]. Clearly, the pathogenesis of dysglycaemia begins long before the gross metabolic dysfunctions characteristic of clinical type 2 diabetes become apparent.

IGT precedes type 2 diabetes in most cases. IGT is defined as the presence of normal fasting plasma glucose (FPG) accompanied by elevated plasma glucose (7.8-11.1 mmol/L) 2 hours after a 75 g oral glucose tolerance test (OGTT) [6, 7]. IGT, like type 2 diabetes, is associated with poor cardiovascular outcomes: epidemiological studies have shown that elevated post-load plasma glucose levels in the diagnostic range for IGT are associated with increased all-cause and cardiovascular mortality (Fig 1) [8, 9]. We need to intervene earlier, at the stage of IGT, if we are to prevent the onset of diabetes and long-term diabetic complications.

Several well-designed clinical studies have investigated the potential of interventions to prevent or delay the conversion from IGT to type 2 diabetes. The landmark Diabetes Prevention Program [10] included treatment with metformin among its interventions. Metformin is of particular interest among the available options for pharmacological intervention as it is supported by a vast clinical database built up over several decades, and it remains the only agent proven to provide protection from macrovascular complications, including diabetes-related death, in patients with type 2 diabetes [11]. This review summarises the potential of metformin, and other interventions, to delay or prevent the onset of type 2 diabetes in individuals with IGT (Table I).

The potential of metformin to prevent or delay the onset of type 2 diabetes

The Diabetes Prevention Program

Study population

The DPP was the first large-scale trial designed to evaluate whether drug therapy with metformin, or an intensive lifestyle intervention, can prevent or delay the development of type 2 diabetes in individuals with IGT [10]. Moreover, the DPP remains the largest intervention study in subjects with IGT to date. All subjects eligible for the DPP had IGT at baseline, were non-diabetic according to the American Diabetes Association criteria of the time [12], and were at least 25 years old. Other inclusion criteria were designed to identify a study population at relatively high risk of developing diabetes. In particular, the study set out to recruit about half of its enrollees from ethnic groups who are at a higher risk of developing type 2 diabetes compared with white subjects. Accordingly, the DPP cohort contained strong representation of subjects whose backgrounds were African-American (20% of the overall DPP population), Hispanic (16%), Amer-
ican Indian (5%), or Asian-American (4%), and only 55% of the study population was white. Subjects were also required to have high-normal FPG (5.3-6.9 mmol/L [95-119 mg/dL]), although this criterion was not applied to American Indian enrollees, who were at high risk of converting from IGT to diabetes at any level of FPG. Finally, body mass index (BMI) had to be at least 24 kg/m² for all participants except Asian Americans (a lower cut-off value of 22 kg/m² and above was applied to this group, who are at greater risk of diabetes at lower values of BMI than western populations).

**Randomisation and treatment**

A total of 3,234 subjects were randomly assigned to receive an intensive lifestyle intervention, or standard lifestyle advice, together with metformin or placebo (Fig 2). The intensive lifestyle intervention arm was open, while the addition of metformin or placebo to standard lifestyle advice was carried out in a double-blind manner.

Standard lifestyle advice consisted of written information plus an annual 20-30 minute session with a lifestyle advisor. Intensive lifestyle intervention comprised a weight loss target of 7% of initial body weight, at least 150 min/week moderately vigorous exercise, and an individualised 16-lesson curriculum of diet, exercise and lifestyle advice.

<table>
<thead>
<tr>
<th><strong>Trials evaluating pharmacological treatment</strong></th>
<th><strong>Treatments</strong></th>
<th><strong>△ risk of diabetes vs control group</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Prevention Program (DPP) [10]</td>
<td>Metformin + standard lifestyle advice</td>
<td>– 31%</td>
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<tr>
<td></td>
<td>Intensive lifestyle intervention</td>
<td>– 58%</td>
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<tr>
<td>Wenying Study [17]</td>
<td>Metformin</td>
<td>– 88%</td>
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<tr>
<td></td>
<td>Acarbose</td>
<td>– 87%</td>
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<tr>
<td></td>
<td>Intensive lifestyle intervention</td>
<td>– 43%</td>
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<tr>
<td>STOP-NIDDM [18, 19]</td>
<td>Acarbose</td>
<td>– 25%</td>
</tr>
<tr>
<td>Finnish Diabetes Prevention Study (FDPS) [20]</td>
<td>Intensive lifestyle intervention</td>
<td>– 58%</td>
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<tr>
<td>Da Qing Study [21]</td>
<td>Diet</td>
<td>– 31%</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>– 46%</td>
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<tr>
<td></td>
<td>Diet + exercise</td>
<td>– 42%</td>
</tr>
</tbody>
</table>

*Control groups were: DPP placebo + standard lifestyle advice; Wenying standard lifestyle advice; STOP-NIDDM placebo; FDPS standard lifestyle advice; Da Qing no treatment.*
Incidence of type 2 diabetes

The study was terminated after a mean follow-up period of 2.8 years, 1 year earlier than planned, as it was found that the research questions posed by the study had already been answered. The annual incidence of diabetes in the placebo group was 11%, which confirms that the study population was indeed at a high risk of developing type 2 diabetes (Fig 3a). In contrast, the annual incidence of diabetes was 7.8% in the metformin group and 4.8% in the intensive lifestyle intervention group (Fig 3a), corresponding to reductions in the risk of developing type 2 diabetes, of 31% for metformin and 58% for the intensive lifestyle intervention, compared with placebo (p < 0.001 for each) (Fig 3b).

The effectiveness of metformin or the intensive lifestyle intervention did not differ according to race or gender, but marked variations were observed according to subjects’ age, BMI, or glycaemic status at baseline (Fig 4). Metformin was approximately as effective as the intensive lifestyle intervention in subjects aged ≤ 44 years (reductions in diabetes incidence of – 44% and – 48%, respectively, compared with placebo) and in severely obese subjects with BMI ≥ 35 kg/m² (reductions in diabetes incidence of – 53% and – 51%, respectively, compared with placebo). The effectiveness of metformin also approached that of the intensive lifestyle intervention in subjects with FPG 6.1-6.9 mmol/L (110-125 mg/dL) at baseline (reductions in diabetes incidence of – 48% and
– 63%, respectively, compared with placebo). This range of plasma glucose levels corresponds with the current definition of impaired fasting glucose (IFG) [4, 7]. Metformin was therefore most effective in subjects with combined IGT and IFG.

Prevention or delay of diabetes with metformin?

The results of the DPP demonstrated clearly that intervention either with metformin or an intensive lifestyle modification prevented or delayed the onset of type 2 diabetes in subjects at high risk of developing this disease. The main analysis of the DPP did not make clear, however, whether metformin was reducing the incidence of type 2 diabetes by changing the underlying pathophysiology of the disease, to prevent its onset, or merely suppressing the early stages of diabetic hyperglycaemia, to delay its onset. The DPP investigators have recently published the results of a washout study, which has begun to answer this important question [14].

A total of 1,274 subjects randomised to placebo or metformin participated in the washout study, which consisted of the withdrawal of study treatment for 1-2 weeks, followed by an evaluation of glycaemic status [14]. The risk of diabetes was significantly lower in the metformin group before the washout (odds ratio 0.66 [95% CI 0.54-0.82], p < 0.001), but not afterwards (odds ratio 1.49 [0.93-2.38], p = 0.098). However, the combined rate of conversions from IGT to diabetes from the double-blind and washout phases was still reduced by 25% in the metformin group relative to placebo (odds ratio 0.75 [0.62-0.92], p < 0.005). Neither age nor BMI at baseline influenced these findings. Overall, the investigators estimated that only about one quarter of the protective effect of metformin was due to a short-lived pharmacological effect that did not persist following the withdrawal of treatment. Thus, metformin was not ‘masking’ the presence of underlying diabetes simply by reducing plasma glucose to a level below the threshold value at which diabetes is diagnosed.

Cost-effectiveness of diabetes prevention in the Diabetes Prevention Program

Two analyses have evaluated the health economics of diabetes prevention using the active interventions from the DPP. The DPP investigators themselves have published a health economic analysis of the DPP interventions in the American setting [15]. Both active interventions were associated with modest increases in direct costs, from the perspective of healthcare providers, over and above those incurred in the placebo group ($2,463/subject for metformin and $2,701/subject for the intensive lifestyle intervention). A modelling approach was used to calculate the economic implications of the DPP interventions in the French, German and UK settings [16]. The intensive lifestyle intervention was cost-effective, as the cost/life-year gained was less than €28,000, the currently accepted definition of cost-effectiveness in health economic analyses (Table II). In the case of metformin, costs decreased relative to control, largely due to reduced costs associated with the management of complications, while life expectancy increased.

The Wenying Study

This randomised study evaluated the potential of metformin (750 mg/day), lifestyle intervention, and the α-glucosidase inhibitor, acarbose (150 mg/day), to delay or prevent type 2 diabetes in 321 Chinese men with IGT, aged > 25 years [17]. Conventional lifestyle advice served as a control intervention, and the follow-up period was 3 years. Fig 5 shows the annual incidences of type 2 diabetes, in each group, together with the relative risks of developing type 2 diabetes in the active treatment arms, compared with the control arm. Both pharmacological interventions markedly reduced the relative risk of developing type 2 diabetes.

Other intervention studies in subjects with IGT

The Study TO Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) study adds further evidence to support the potential of pharmacological intervention in subjects with IGT. STOP-NIDDM [18] randomised 1,429 participants with IGT (mean age of 55 years, mean BMI 31 kg/m²) to receive double-blind treatment with acarbose (300 mg/day) or placebo for a mean follow-up of 3.3 years. Acarbose treatment was associated with a 25% reduction in the risk of progression to diabetes, compared with placebo, irrespective of gender, or age or BMI at baseline. Acarbose was...
poorly tolerated, however, as roughly one third of patients in the acarbose group (31%) discontinued treatment prematurely, largely due to gastrointestinal side-effects, compared with 19% in the placebo group. In addition, the protective effect of acarbose was markedly reduced within 3 months of withdrawal of acarbose. Further follow-up of the STOP-NIDDM cohort showed that acarbose treatment was also associated with a significant reduction in the risk of a composite endpoint of cardiovascular events (p = 0.03), although these findings were based on a low event rate [19].

Other than the DPP, the Finnish Diabetes Prevention Study (FDPS) is the largest evaluation of an intensive lifestyle intervention in subjects with IGT. The 523 subjects in the FDPS were randomised to receive either standard lifestyle advice or an intensive diet and exercise program, including a target for weight loss of at least 5% of initial body weight [20], for an average follow-up of 3.2 years. The cumulative incidence of diabetes was 11% in the intensive lifestyle intervention group, and 23% in the control group, corresponding to a risk reduction of 58% (p < 0.001).

A second study, the Da Qing Study, was conducted in Chinese subjects with IGT [21]. This trial evaluated various combinations of diet and exercise on the risk of developing type 2 diabetes. This study was unusual in that the 35 participating clinics, rather than individual patients, were randomised to one of the four treatment arms: diet alone, exercise alone, diet plus exercise, or control. Significant reductions in the incidence of diabetes were observed in all active treatment arms. The magnitudes of the reductions were 33% in the diet group (p < 0.03), 47% in the exercise group (p < 0.0005) and 38% in the diet plus exercise group (p < 0.005).

**Lifestyle interventions or pharmacological treatments for diabetes prevention?**

Table I summarises the main results of the principal intervention trials in subjects with IGT. Apart from the small Wenying study, headline reductions in the risk of developing type 2 diabetes are larger in groups receiving intensive lifestyle interventions (the DPP and the FDPS), compared with pharmacological agents (the DPP and STOP-NIDDM). The American Diabetes Association (ADA) and the US National Institute of Diabetes, Digestive and Kidney Diseases (NIDDKD) have issued a joint position statement strongly promoting intensive lifestyle interventions as the therapy of choice for the initiation of treatment aimed at diabetes prevention on the basis of such observations [7]. Such an approach is reminiscent of standard care for type 2 diabetes, in which the use of diet and exercise to initiate therapy is strongly supported by current management guidelines [22, 23].

There is no doubt that obesity and lack of exercise contribute to the development of insulin resistance, IGT and, ultimately, type 2 diabetes. Indeed, a 10-year follow-up of almost 38,000 men in the US revealed a significant and independent association between the risk of developing diabetes and the length of time each week spent watching television [24]. So, we should always encourage our sedentary patients to modify their lifestyle by improving their diet and taking more exercise, and structured interventions covering a range of risk factors have provided promising improvements in risk factors [25], or actual clinical outcomes [26] in dysglycaemic patients. However, a serious question remains over the practicability of intensive lifestyle interventions, as used in the

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**Figure 5**

Diabetes prevention in the Wenying Study [17].
DPP and the FDPS, to deliver real improvements in clinical outcomes in western populations. The intensive lifestyle intervention in the DPP relied on an individualised, 16-lesson curriculum of diet, exercise and lifestyle advice, involving access to support from healthcare professionals within these areas. Extending this level of support to the millions of people within the general population who are believed to have IGT provides a major challenge to healthcare systems, in terms of the resources required, and to the patients themselves, as such treatments are not currently reimbursable.

Not surprisingly, experience with lifestyle interventions beyond the period of active intervention is mixed so far. The Activity Counseling Trial provided patients with three levels of support over a period of 24 months: standard lifestyle advice similar to that used in the control group of the DPP, this intervention plus regular contact by mail and active counselling at the clinic, and the interventions received by the second group plus regular telephone counselling and behavioural classes [27]. While some improvement in an index of cardiorespiratory fitness was observed in the most intensive vs least intensive groups in women, there were no significant improvements in this parameter in men, and no significant change in total physical activity in women or men. A further study evaluated the effects of two diet regimens on a range of metabolic parameters. Improvements in weight and BMI were observed during the 1-year active intervention period, but these parameters, and glycaemia, worsened steadily over the following 4 years (Fig 6). Finally, an internet-based self-management programme designed to improve fitness in sedentary diabetic subjects found that patients’ commitment to the intervention declined substantially over time, and concluded that sustaining involvement with the programme will be a key factor in the success of future initiatives of this type [29]. Pharmacological intervention may prove to be a more practicable therapeutic option for patients who are unwilling or unable to comply with intensive lifestyle interventions.

Beyond the Diabetes Prevention Program

The DPP had a number of features in common with the UKPDS: both were randomised, parallel group studies, both included a head-to-head comparison of the effects of metformin and conventional lifestyle advice, and improved clinical outcomes were observed in the metformin group in either study. However, the DPP left some important questions unanswered, especially with regard to the effects of metformin on the risk of adverse cardiovascular outcomes, and the potential utility of intensive lifestyle advice and metformin in combination. About 95% of the original DPP cohort is currently being followed up in the DPP Outcome Study (DPPOS), which may bridge the gap between diabetes prevention and long-term cardiovascular prognosis. The DPPOS will not, however, combine metformin with intensive lifestyle intervention. This question is being addressed by the Indian DPP (IDPP), which is currently randomising subjects with IGT to four arms, in which they receive a lifestyle intervention, or no intervention, with and without metformin in each case. The IDDP is expected to report within 5 years.
Conclusions

Both intensive lifestyle interventions and pharmacological treatments have been shown to significantly reduce the risk of developing type 2 diabetes in high-risk populations within the highly structured framework of a randomised clinical trial. The most suitable way to transfer these benefits into the general population remains to be determined. Intensive lifestyle interventions may be particularly difficult to apply in the primary care setting, due to the difficulty of maintaining adequate long-term adherence to diet and exercise programmes. Pharmacological therapy may be appropriate where lifestyle interventions are ineffective or impracticable. Metformin has been proven to protect from the development of diabetes in the DPP and from life-threatening macrovascular complications in the UKPDS and is likely to play an important part in initiatives to prevent diabetes in the future.

References