Evidence and strategies for the primary prevention of type 2 diabetes

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Article points

1. There is substantial evidence showing that there are health benefits to be gained from primary prevention of type 2 diabetes.
2. Both lifestyle changes and drug interventions have proven efficacy in preventing progression to type 2 diabetes in people with impaired glucose tolerance.
3. Prevention of type 2 diabetes requires a screening programme to be in place.
4. There are practical and economic issues to be considered in the implementation of prevention strategies.

Key words

- Cost implications
- Impaired glucose tolerance
- Lifestyle changes
- Type 2 diabetes
- Prevention
- Screening

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Diabetes is increasing in prevalence at an alarming rate worldwide. Approximately 2.5 million people in the UK have been diagnosed with diabetes. Impaired glucose tolerance (IGT) precedes the development of type 2 diabetes. There is now substantial evidence from clinical trials around the world that lifestyle changes and drug interventions can significantly reduce the rate of progression to type 2 diabetes in high-risk individuals with IGT. This article examines the evidence for primary prevention of type 2 diabetes and possible prevention strategies that may be used to achieve this goal.

The global burden of diabetes is increasing as prevalence of the condition soars. In the UK alone, approximately 2.5 million people have been diagnosed with diabetes (The Information Centre, 2008; Department of Health Social Services and Public Safety, 2008; The Information Services Division, 2008; Welsh Assembly Government, HSA1, 2008), many of whom are from ethnic minorities (Chowdhury et al, 2003).

This article considers the evidence for the primary prevention of type 2 diabetes, and possible prevention strategies that can be implemented to achieve this goal.

Screening

The recent observed increase in diabetes has occurred too quickly for it to have a genetic cause, emphasising the importance of environmental factors such as obesity and lack of exercise in the development of the condition. Other associated factors include gender (female predominance), ethnicity (non-European origin) and a positive family history (American Diabetes Association [ADA], 2000; Arslanian, 2002).

In the authors' opinion, identifying and preventing the onset of type 2 diabetes is of crucial importance, as it will reduce the incidence of complications that are responsible for much of the excess mortality seen in people with diabetes. Universal screening on the basis of age alone is time-consuming and not cost-effective (Lawrence et al, 2001). A screening programme that targets people at high risk of cardiovascular disease is of greater value.

The ADA (2004) and Diabetes UK (2006) recommend that screening for type 2 diabetes should be performed in adults who are over 40 years of age and overweight (BMI >25 kg/m^2) (ADA and National Institute of Diabetes, Digestive and Kidney Diseases, 2002; Diabetes UK, 2006). People with other risk factors, such as impaired glucose tolerance (IGT) or impaired fasting glucose, a family history of diabetes, previous gestational diabetes,

hypertension or hyperlipidaemia, should also be screened for diabetes.

A 2-hour oral glucose tolerance test and fasting plasma glucose test have been used to test this target group, and have demonstrated adequate levels of sensitivity and specificity (ADA, 2000). So, who will do this screening and how will it be funded? It is likely that the burden of screening for diabetes will fall upon general practice, along with screening for the myriad of other diseases that general practice is currently trying to prevent. IGT may become yet another condition that has the ability to label the well as "at risk".

Prevention of type 2 diabetes

IGT precedes the development of type 2 diabetes. One study found that the risk of developing type 2 diabetes was increased six-fold in people with IGT (Pan et al, 1997), whereas another study showed it to be increased 23-fold (Tuomilehto et al, 2001).

IGT is not only a risk factor for diabetes, it is also a risk factor for cardiovascular disease (Lowe et al, 1997). Consequently, interventions should be put in place to target people with IGT to prevent type 2 diabetes and cardiovascular diseases (Simpson et al, 2003)

Several clinical trials from around the world have provided evidence that intensive lifestyle intervention or pharmacological treatment can reduce progression to type 2 diabetes in high-risk individuals with IGT. Some of these trials are discussed below.

Clinical trials

Lifestyle interventions

The Finnish Diabetes Prevention Study (Tuomilehto et al, 2001), and the Diabetes Prevention Program (DPP [Knowler et al, 2002]) in the USA, provide promising evidence that diet and exercise can cause a 50% reduction in the progression from IGT to type 2 diabetes. Earlier studies, including the Da Qing IGT and Diabetes Study (Pan et al, 1997) and the Malmö Study (Eriksson et al, 1991), also demonstrated the beneficial effects of lifestyle intervention in reducing the risk of diabetes in people with IGT.

Table 1 summarises the results of these clinical trials of lifestyle interventions, such as weight loss and physical exercise, in the prevention of type 2 diabetes.

Pharmacological treatments

Alongside studies of diet and exercise, trials of pharmacological treatments have been undertaken to establish whether medications have any effect on the prevention of type 2 diabetes.

The STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) showed that acarbose reduced the development of diabetes by 25%, despite there being a 25% discontinuation rate among those on the drug (Chiasson, 2006).

The 6-year Early Diabetes Intervention Trial compared the effects of acarbose 50 mg three times daily with those of placebo and metformin 500 mg three times a day (Holman et al, 2003). The study showed positive effects of acarbose compared with placebo in the prevention of type 2 diabetes. Acarbose can be used – either as an alternative to, or in addition to lifestyle changes – to delay the progression from IGT to type 2 diabetes (Scheen, 2003).

Another smaller study, the Chinese Diabetes Prevention Study (Pan et al, 2003), compared the effects of acarbose, metformin and conventional education in the prevention of type 2 diabetes in people with IGT. Over a 3-year period, 6.9%, 12.4% and 34.9% of each group, respectively, progressed to type 2 diabetes.

The DPP (Knowler et al, 2002) investigated the efficacy of metformin, troglitazone

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1. Impaired glucose tolerance (IGT) precedes the development of type 2 diabetes.
2. IGT is a risk factor for cardiovascular disease as well as diabetes.
3. Clinical trials have shown that intensive lifestyle or drug interventions can reduce progression to type 2 diabetes in high-risk individuals with IGT.
4. In Study to Prevent Non-Insulin-Dependent Diabetes Mellitus, acarbose reduced the development of diabetes by 25%, despite a 25% discontinuation rate among those on the drug.

Table 1. Trials of lifestyle intervention to prevent type 2 diabetes.

Study	Control group: % developing diabetes	Intervention group: % developing diabetes
Swedish Malmö Study*	28%	10.6%
Chinese Da Qing IGT and Diabetes study†	15.7%	8%
Finnish Diabetes Prevention Study¶	25%	11%
USA Diabetes Prevention Program‡	11%	5%

*Eriksson and Lindgärde, 1991; †Pan et al, 1997; ¶Tuomilehto et al, 2001; ‡Knowler et al, 2002; IGT=impaired glucose tolerance.

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1. Clinical trial findings present clinicians with a difficult choice, as the cost of 8 mg rosiglitazone per day, for 3 years would be nearly £1330, whereas the cost of 850 mg twice daily of metformin (as per Diabetes Prevention Program) would cost less than £20 for 3 years, resulting in a 60% and 31% decrease in the incidence of diabetes, respectively.
2. In the Xenical in the Prevention of Diabetes in Obese Subjects study, orlistat (an anti-obesity agent) plus lifestyle changes resulted in a 37% greater reduction in type 2 diabetes compared with lifestyle changes alone in obese people with IGT.
3. The findings of clinical trials highlight the important role of prevention of diabetes in reducing the global diabetes epidemic.
4. Before any intervention can be implemented, economic studies are needed to answer two key questions: how much does it cost and is it good value?

(thiazolidinedione), diet and exercise in the prevention of type 2 diabetes in people with IGT. However, the troglitazone arm of the study had to be discontinued after 2 years because of the significantly increased risk of liver damage and fatal hepatotoxicity caused by the drug.

Furthermore, the trial found that metformin reduced the risk of developing type 2 diabetes by 31% compared with placebo. However, this effect was not seen in all participants: for example, metformin had no effect in people over 60 years of age and those with a BMI < 30 kg/m^2 (Knowler et al, 2002). This trial also showed that the cumulative incidence of type 2 diabetes was significantly reduced in the metformin and lifestyle intervention groups compared with the placebo group throughout the follow-up period.

Although the DPP discontinued the use of troglitazone, a more recent study, DREAM (Diabetes Reduction Approaches with Ramipril and Rosiglitazone Medication [DREAM Trial Investigators et al, 2006]), compared the effects of an angiotensin-converting enzyme (ACE) inhibitor or thiazolidinediones, or both, on the development of diabetes or death, and on regression to normoglycaemia, in people with impaired fasting glucose or IGT or both. This study reported that after a mean follow-up of 3 years there was no significant reduction in the incidence of diabetes or death with ramipril, but there was a significant increase in regression to normoglycaemia. In contrast, rosiglitazone decreased the incidence of diabetes by almost 60% and the likelihood of regression to normoglycaemia by 70%.

Clinical trial findings present clinicians with a difficult choice, as the cost of 8 mg rosiglitazone per day, for 3 years would be nearly £1330 (DREAM Trial Investigators et al, 2006), whereas the cost of 850 mg twice daily of metformin (as per DPP) would cost less than £20 for 3 years (Knowler et al, 2002), resulting in a 60% and 31% decrease in the incidence of diabetes, respectively. On the other hand, the cost of lifestyle intervention in the DPP study is $2269 per person over 3 years, resulting in a 58% reduction in the progression of diabetes (Knowler et al, 2002).

Apart from anti-diabetes treatments, another pharmacological agent used to prevent diabetes is the anti-obesity agent orlistat. One study in particular, the XENDOS (Xenical in the Prevention of Diabetes in Obese Subjects), compared the effects of orlistat (Xenical) and lifestyle intervention with lifestyle intervention alone in people with normoglycaemia or IGT. In this study there was a 37% reduction in the development of diabetes in the orlistat and lifestyle intervention group compared with the group that used lifestyle intervention alone (Torgerson et al, 2004).

Cost implications

It is clear from the above findings that prevention of diabetes has an important role in reducing the global diabetes burden. However, like all prevention schemes, there are cost implications. Economic studies are therefore needed to answer two key questions about any intervention to prevent diabetes: how much does it cost and is it good value?

In the DPP, the cost of identifying people with IGT was $139, and the cost of the metformin and lifestyle interventions over a 3-year period, compared with the placebo intervention, was $2191 and $2269, respectively. In the metformin intervention, most of the additional cost relative to the placebo intervention was accounted for by the cost of metformin, and in the lifestyle intervention it was accounted for by staff time used for counselling and adherence monitoring (Knowler et al, 2002).

Herman et al (2005) used a model based on the DPP and the UKPDS (UK Prospective Diabetes Study) to assess the effects of lifestyle intervention and metformin in people with IGT. This study estimated that, compared with the placebo intervention, the lifestyle and metformin interventions delayed the development of type 2 diabetes by 11 years and 3 years, respectively, reduced the absolute incidence of diabetes by 20% and 8%, respectively, and improved survival by 0.5 years and 0.2 years, respectively.

The study found that the cost per quality adjusted life year (QALY) was approximately $1100 for lifestyle intervention and $31 300

for metformin intervention, compared with the placebo intervention. It also confirmed that lifestyle intervention was cost-effective in all age groups and cost-saving in people aged 25–44 years, whereas metformin was not cost-effective in people over the age of 65 years ($173 593 per QALY). *Table 2* summarises the results of various published economic studies.

Herman et al also found that the cumulative incidence of diabetes complications was reduced; blindness was reduced by 39% with lifestyle modification and by 16% with metformin; end-stage renal disease by 38% and 17%, respectively; amputation by 35% and 16%, respectively; stroke by 9% and 3%, respectively; and coronary heart disease by 8% and 2%, respectively.

Table 2. Summary of published economic studies*.

Study and setting(s)	Year of costs	Methods	Findings
Quilici et al (2005) **Sweden**	2003 (SEK)	Within trial cost-effectiveness analysis of acarbose, based on STOP-NIDDM, 40-month time horizon, projected total direct costs based on progression to type 2 diabetes or cardiovascular disease.	Acarbose dominant to placebo for high-risk groups.
Caro et al (2004) **Canada**	2000 ($CD)	Markov model, based on DPP, DPS and STOP-NIDDM, projected LE, diabetes-free years, and total direct lifetime costs, 10-year time horizon.	Acarbose and metformin dominant vs. control, ILC cost-effective to control (ICER $749 per life year gained).
DPP Research Group (Tuomilehto et al, 2001) **USA**	2000 ($US)	Within trial cost-effectiveness of DPP interventions (3 years), direct and indirect costs, extensive sensitivity analyses.	ILC cost-effective vs. placebo. Significant improvement in economic benefits if implementation costs reduced.
Herman et al (2005) **USA**	2000 ($US)	Markov model, DPP and UKPDS data adapted to US setting, projected LE, QALE and total direct medical costs, lifetime time horizon, healthcare payer and societal perspectives taken.	ILC dominant vs. metformin. Metformin not cost-effective for over 65 years of age, outcome sensitive to pricing of treatments.
Palmer et al (2004a) **Australia, France Germany, Switzerland, UK**	2002 (€)	Markov model, based on DPP, projected LE, years free of diabetes and total direct costs, lifetime time horizon, extensive sensitivity analyses and subgroup analyses on age and BMI.	ILC and metformin dominant vs. control except UK (ICER €6381 and €5400 per life year gained, respectively).
Mantavani et al (2004) **Italy**	2004 (€)	Markov model, based on DPP, adapted to Italian setting, projected LE, years free of diabetes and total direct costs, lifetime time horizon.	ILC and metformin cost-effective vs. control (ICER €11 234 and €11 556 per life year gained, respectively).
Palmer et al (2004b) **Spain**	2004 (€)	Markov model, based on DPP, adapted to Spanish setting, projected LE, years free of diabetes and total direct cost, lifetime time horizon.	Metformin cost-effective vs. control (ICER €5080 per life year gained). ILC costs prohibitive due to personnel costs.
Eddy et al (2005) **USA**	2005 ($US)	Archimedes model, based on ILC intervention from DPP, projected LE, total direct costs, 30-year time horizon.	ICER $62 602 and $35 523 for ILC and metformin vs. control, respectively.

*Reproduced with permission from the International Diabetes Federation website; BMI = body mass index; DPP = Diabetes Prevention Program; DPS = Diabetes Prevention Study; ICER = incremental cost-effectiveness ratio; ILC = intensive lifestyle change; LE = life expectancy; QALE = quality-adjusted life expectancy; STOP-NIDDM = Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; UKPDS = UK Prospective Diabetes Study

"The case for reducing the burden of diabetes is becoming ever more urgent. Lifestyle modification and various pharmacological agents, including anti-diabetes drugs such as metformin, acarbose and rosiglitazone, and anti-obesity agents such as orlistat, have proven efficacy in preventing diabetes."

Conclusion

The case for reducing the burden of diabetes is becoming ever more urgent. Lifestyle modification and various pharmacological agents, including anti-diabetes drugs such as metformin, acarbose and rosiglitazone, and anti-obesity agents such as orlistat, have proven efficacy in preventing diabetes.

By screening high-risk groups, it is possible to identify those with diabetes or IGT and start them on appropriate treatment, which would primarily include education for lifestyle intervention. This could further be supported by dietitians, access to local health centres or gyms at a reduced price, support groups, and possible pharmacological treatment, although the cost of such interventions has not been calculated. Reducing the number of people progressing to diabetes will also help reduce the incidence of cardiovascular events. ■

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