

# The prevention of type 2 diabetes mellitus

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**ABSTRACT** – There is a worldwide epidemic of type 2 diabetes, with numbers predicted to reach over 210 million by the year 2010. Important risk factors for type 2 diabetes are obesity, physical inactivity and dietary factors. Recent evidence shows that type 2 diabetes can certainly be delayed, and possibly prevented, by intensive lifestyle intervention, and therapies including acarbose, metformin, orlistat and the glitazones in selected populations. However, the UK has not had a successful record in trials which aim to prevent diabetes, and therefore implementation of effective and successful intensive lifestyle intervention to prevent diabetes may prove difficult in the UK. Other ‘non-glucose lowering’ agents, such as statins, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, may have a role to play in the prevention of diabetes.

**KEY WORDS:** acarbose, cardiovascular mortality, diet, impaired glucose tolerance, metformin, obesity, physical activity, prevention, type 2 diabetes mellitus

There is an emerging worldwide epidemic of type 2 diabetes, with numbers predicted to reach over 210 million by the year 2010.<sup>1</sup> The cost is huge: Diabetes UK have calculated that around £165 per second is spent on diabetes, and this is probably an underestimate. It is known that 50% of newly presenting patients with type 2 diabetes already have one or more complications at diagnosis, with around 21% having retinopathy and significant numbers with established macrovascular disease.<sup>2</sup>

The United Kingdom Prospective Diabetes Survey (UKPDS) showed that at the time of diagnosis there were marked pathophysiological abnormalities with 50% of  $\beta$ -cell function already having been lost. Extrapolating back, this means that the deterioration of  $\beta$ -cell dysfunction starts to occur from 12 years before a formal diagnosis of diabetes is made.<sup>3</sup>

## Modifiable risk factors for type 2 diabetes

The most important modifiable risk factors for type 2 diabetes are obesity, inactivity and dietary factors. Once body mass index (BMI) is over 35, the age-adjusted relative risk of diabetes is approximately 54-fold for men and 100-fold for women.<sup>4,5</sup> The International Obesity Taskforce found high prevalence of obesity in both men and women right across the world, particularly in North America, and huge increases in obesity reported in urban parts of developing countries.

Moving closer to home, in Europe England is in fifth place (behind Yugoslavia, Greece, Romania and the Czech Republic) in the league table of obesity, and the Health Survey for England showed a significant increase in prevalence of obesity between 1980 and 1998. More worrying is the increasing prevalence of obesity in children. In North America, between the 1970s and the mid-1990s there were significant increases in prevalence of obesity in adolescents aged from 12 to 17, with levels in boys increasing from around 5% up to 11%. This has been translated into increasing rates of type 2 diabetes in children in North America.<sup>6,7</sup>

The second important factor is change in diet. In the UK, from the 1940s until the mid-1990s the proportion of dietary energy taken from carbohydrates steadily decreased, while that from fat steadily increased. Other studies have shown a relationship between risk of type 2 diabetes and increased dietary fat, reduced dietary fibre and less fruit and vegetables in the diet.<sup>8-10</sup>

The last of this unhealthy triad is that of reduced physical activity. In the UK, the percentage of adult obesity closely mirrors both the number of cars per household and hours of television watched per week. In young people in the USA the percentage of high school students participating in physical activity decreased year on year through the 1990s.<sup>11</sup>

## Possible approaches to intervention

In terms of a public health approach, interventions to prevent type 2 diabetes include upstream, mid-stream and downstream approaches.<sup>12</sup> These can be evaluated by their effect on the risk factors, eg changing weight or increasing physical activity. Gold

### Trial acronyms

HOPE Study	Heart Outcomes Prevention Evaluation Study
LIFE Study	Losartan Intervention For Endpoint Study
STOP NIDDM Study	Study to Prevent Non insulin Dependent Diabetes
WOSCOPS Study	West of Scotland Coronary Prevention Study

standard outcomes would be reducing the risk of development of type 2 diabetes itself, and improving cardiovascular outcomes.

*Upstream approaches* are usually ambitious, involve whole communities, and in the past have mainly focused on cardiovascular risk reduction. The most famous and effective was the North Karelia Project in Finland in the 1970s which used an environment modification programme to lower cholesterol, reduce blood pressure, reduce smoking and improve cardiovascular outcomes. This was heralded as a huge success in terms of completely changing whole communities' risk profile for cardiovascular disease and did improve cardiovascular outcomes.<sup>13,14</sup>

Other upstream approaches, particularly in North America, have had little or no effect on the cardiovascular systems or on BMI.

*Midstream approaches* include community programmes particularly targeting people with risk factors. Most centred on weight loss programmes.<sup>15,16</sup> A number of school-based diabetes prevention programmes which increased knowledge and evidence of self-efficacy only had a short follow-up. The Bienstar Diabetes Risk Factor Prevention Programme which targeted 100 Mexican-American children showed evidence of reduced dietary fat increase, increased knowledge of diabetes and modest effect on body weight. Whether this will be translated to lessened risk of type 2 diabetes and cardiovascular disease in the future is awaited with interest.

### *Interventions to prevent diabetes targeted at those with impaired glucose tolerance (IGT)*

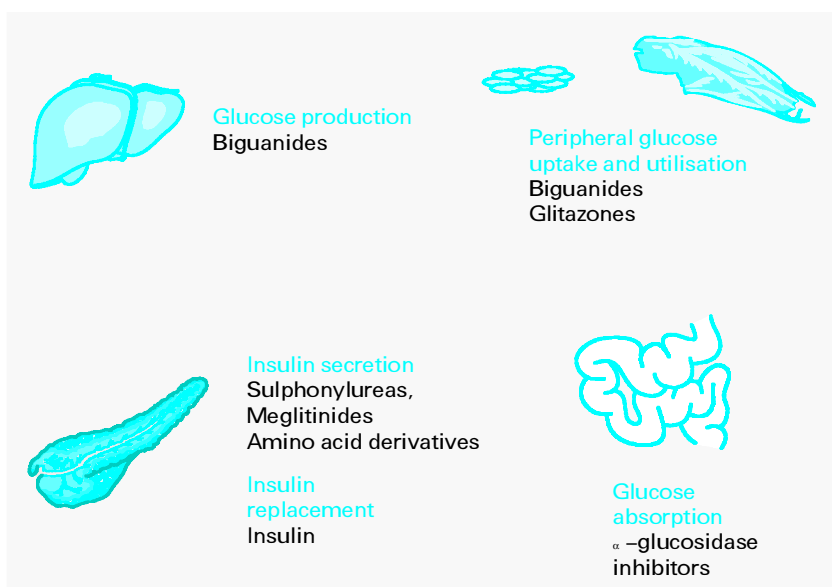
*Downstream approaches* focus mainly on people with impaired glucose tolerance (IGT) or the obese. Impaired glucose tolerance is associated with both an increased risk of developing diabetes itself, and also a higher risk of cardiovascular disease.

In the middle-aged population, the prevalence of IGT is 16% in the USA, 13% in Europeans, and 15% in South Asia.<sup>17,18</sup> Of particular note is that the majority of subjects with IGT have normal fasting glucose levels, and therefore will only be identified through an oral glucose tolerance test (OGTT).<sup>17</sup>

Targeted strategies for the prevention of diabetes in subjects with IGT have focused either on lifestyle and weight loss, particularly a hypocaloric low-fat diet of moderate intensity and moderate duration with assistance from an aerobic exercise training programme; or on pharmaceutical interventions with drugs that target insulin sensitivity such as metformin or the glitazones, or drugs that reduce glucose absorption, such as the alpha-glucosidase inhibitor acarbose, or drugs which promote insulin secretion, such as the sulphonylureas and meglitinides or the new amino acid derivatives (Fig 1). Prevention studies in people with IGT have focused on diet and exercise, so-called intensive lifestyle interventions, pharmaceutical interventions or a combination of both. In England, in the 1970s, neither the Bedford study nor the Whitehall Study showed any benefit. Swedish studies were more successful: they showed a lower incidence of diabetes after 10 years.

More recent interventions, mainly in subjects with IGT, are shown in Table 1. The Da Qing Study screened over 110,000 men and women in 33 health centres, which was effectively all those over 25 years.<sup>19</sup> There was a six-year follow-up with an OGTT every two years; the benefits are summarised in Table 2. However, whether these results could be obtained with other populations who may be older and more obese needed verification. In the Finnish Diabetes Prevention Study (FDPS) significantly more subjects in the intervention group than in the control group reached the lifestyle targets. For example, with exercise 86% of the intervention group, compared to 71% of the control group, managed to achieve more exercise than 4 hours per week, with benefits in outcome (see Table 2).<sup>20</sup>

The Diabetes Prevention Program (DPP) in the USA included



**Fig 1. Possible pharmaceutical interventions for diabetes and impaired glucose tolerance.**

**Table 1. Summary of the recent diabetes prevention trials.**

Study	Country	Glucose criteria for inclusion and number of subjects	Characteristics of subjects	Intervention
Da Qing <sup>19</sup>	China	IGT, 577	45 years, BMI 25.8 kg/m <sup>2</sup>	Diet, exercise or both
Finland DPS <sup>20</sup>	Finland	IGT, 522	55 years, BMI 31kg/m <sup>2</sup>	5% weight loss, fat intake <30%, saturated fat intake <10%, fibre >15g/1,000kcal, exercise 30 minutes/day
FHS <sup>23</sup>	UK	Fasting plasma glucose >5.5 mmol/l, 188	50 years, mean weight 81.7 kg	Healthy lifestyle or gliclazide
EDIT <sup>24</sup>	UK	IGT, 631	52 years, BMI 28.6 kg/m <sup>2</sup>	Metformin, acarbose or both
New Zealand <sup>25</sup>	New Zealand	IGT, 103	52 years, BMI 29 kg/m <sup>2</sup>	Low fat diet
DPP <sup>21</sup>	USA	IGT, 3,234	51 years, BMI 31kg/m <sup>2</sup>	Metformin or intensive lifestyle: 7% weight reduction, low fat diet, exercise 150 minutes/week
STOP-NIDDM <sup>22</sup>	Canada, Germany, Austria, the Nordic countries, Israel, Spain	IGT, 1,429	55 years, BMI 31 kg/m <sup>2</sup>	Acarbose

BMI = body mass index; DPP = Diabetes Prevention Program; DPS = Diabetes Prevention Study; EDIT = Early Diabetes Intervention Trial; FHS = Fasting Hyperglycaemia Study; IGT = impaired glucose tolerance; STOP-NIDDM = Study To Prevent Non Insulin Dependent Diabetes.

27 centres, where 45% of the subjects were from ethnic minority groups at high risk of diabetes.<sup>21</sup> The trial was stopped a year early with significant benefits reported (see Table 2). Further results from the DPP have since been presented which show that metformin and lifestyle were equally effective in the younger age group (under 44 years). One kilogram of weight loss equated to a 13% reduction in the risk of developing diabetes.

The STOP NIDDM Study was a multi-centre, placebo-controlled trial looking at an intervention with acarbose.<sup>22</sup> Acarbose appeared to have a better response in:

- the older age group
- those with a BMI greater than 30 kg/m<sup>2</sup>
- women
- those who were normotensive at baseline.

Further results recently presented also reported benefits in terms of cardiovascular outcomes, with a 35% risk reduction of new cases of hypertension, 33% risk reduction in new cases of myocardial infarction and 37% risk reduction in cardiovascular events.

### Practical implications for prevention programmes in the UK setting

Are interventions practical in UK health settings? In a recent survey in the UK, all GPs were aware of IGT as an entity but 47% were unaware of the risk of progression to type 2 diabetes, 62% were unaware of the link with coronary heart disease, and 38% underestimated the prevalence of IGT. Only 13% of 15,000 EU subjects perceived that weight loss was a benefit of exercise.<sup>28</sup> There was a huge variation across Europe in those who did not

participate in any physical activity: from less than 1% of the Finnish population to 49% in Portugal. The average was 11%, and the UK reported around 8%.

Body weight is consistently underestimated, particularly by men. Scandinavian men are less likely to underestimate their weight than men from other parts of Europe. These findings have considerable relevance when considering the implementation of lifestyle interventions to prevent diabetes, particularly in the UK setting.

The other target group in which to prevent diabetes is those with obesity. There have been two studies looking at surgical management of obesity. The Swedish Obese Subjects Study took 845 control subjects and 845 who underwent bariatric surgery. After a two-year follow-up there was significant weight loss of around 25% to 30% of body weight, with a significant improvement in cardiovascular risk, particularly in improvement in lipid profiles, and less risk of hypertension. The risk of diabetes was also significantly reduced.<sup>29</sup> In another study, less than 1% of those who had undergone bariatric surgery developed diabetes during a ten-year follow-up, whereas 22% of the control group did.

### Other approaches to diabetes prevention

It is interesting that there have been a number of reports of prevention of diabetes with non-glucose lowering agents in post-study analysis. The first was with pravastatin in the WOSCOPS Study, which involved over 5,900 men without diabetes, of whom 139 developed diabetes over the course of the five-year study. There was a 30% risk reduction in development of diabetes in those in the pravastatin group and, whilst pravastatin

Table 2. Summary of different interventions to prevent diabetes.

Study	Cumulative incidence of diabetes vs placebo (%)	Relative risk reduction (%)	NNT
Da Qing <sup>19</sup> 6 years ILS	66 vs 44	46	4.5
FDPS <sup>20</sup> 4 years ILS	23 vs 11	58	8
DPP <sup>21</sup> 3 years ILS	28.9 vs 14.4	58	7
STOPP NIDDM <sup>22</sup> 3 years acarbose	42 vs 32	24	11
TRIPOD <sup>29</sup> 2.5 years troglitazone	30.2 vs 13.5	55	6
DPP <sup>21</sup> 3 years metformin	28.9 vs 21.7	31	14
XENDOS 4 years orlistat	9.0 vs 6.0	37	36

DPP = Diabetes Prevention Program; FDPS = Finnish Diabetes Prevention Study; ILS = intensive lifestyle; NNT = Numbers needed to treat; TRIPOD = The Troglitazone in Prevention of Diabetes Study; XENDOS = Xenical in the prevention of Diabetes in Obese Subjects Study.

was not an independent risk factor, when triglyceride levels were included in the model this raised the role of statin therapy in the prevention of diabetes as an issue. However, it is of note that similar findings were not replicated in the Heart Protection Study.

In the HOPE Study, which included over 5,700 middle-aged subjects without known diabetes at baseline, treatment with ramipril compared to placebo showed a relative risk reduction of 34% in the development of diabetes. This was only on self-reported cases and therefore is potentially flawed. However, a 25% risk reduction was also noted in the LIFE Study with losartan. However, the control group had atenolol and one could argue about whether it was the losartan protecting against diabetes or atenolol increasing the risk of diabetes. Nevertheless, the role of angiotensin-converting enzyme and angiotensin receptor blocker in the prevention of diabetes needs further examination.

## Conclusion

In conclusion, type 2 diabetes can certainly be delayed, and possibly prevented, by intensive lifestyle intervention, acarbose, metformin and glitazones in selected populations. Only acarbose has so far been shown to be associated with improved cardiovascular outcomes. The profile of subjects responsive to metformin and acarbose appears to be quite different. Implementation of effective intensive lifestyles in particular may be difficult in some parts of Europe, including the UK. Obesity interventions with orlistat and surgery in the morbidly obese appear to be effective.

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