Preventing type 2 diabetes: can we make the evidence work?

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Preventing type 2 diabetes: can we make the evidence work?

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ABSTRACT

Type 2 diabetes is associated with many serious comorbidities and is one of the leading causes of mortality globally. Type 2 diabetes is preceded by a condition called prediabetes, which is characterised by elevated glucose concentrations resulting from peripheral and/or hepatic insulin resistance. Individuals with prediabetes have been the traditional target of diabetes prevention programmes; these have consistently shown that lifestyle modification can significantly reduce the risk of developing type 2 diabetes. This has led to the implementation of diabetes prevention initiatives in several countries. However, a number of key areas still need to be addressed. For example, important questions remain regarding how best to identify at-risk individuals and whether the findings from resource intensive research projects can be replicated using pragmatic lifestyle interventions tailored to the resources and infrastructure available to usual health care practice. This article highlights findings from diabetes prevention programmes and discusses key issues involved in translating research into practice.

Type 2 diabetes mellitus is a chronic and debilitating disease characterised by an inability to adequately regulate blood glucose concentrations. In the short term the symptoms of type 2 diabetes are associated with a reduced quality of life, while in the longer term the disease may lead to serious complications such as cardiovascular disease, blindness, renal failure and amputation.[1] The life expectancy of individuals with type 2 diabetes may be shortened by as much as 15 years, with up to 75% dying of cardiovascular disease.[2]

The prevalence of type 2 diabetes mellitus has risen so sharply over the past half century that it is now commonly referred to as an epidemic,[3 4] and it is currently estimated to be the fifth leading cause of mortality globally.[5] In the UK, approximately 5% of the total National Health Service resources and up to 10% of hospital inpatient resources are devoted to the care and treatment of type 2 diabetes[6]; these figures are set to rise in the future and will represent a serious clinical and financial challenge to the UK's health system.[7]

Type 2 diabetes is at one end of a continuous glucose control spectrum with normal glucose control at the other. In between there exists a condition called prediabetes or intermediate hyperglycaemia, defined as impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG),[8 9] where blood glucose concentrations are elevated above the normal range but do not satisfy the criteria for type 2 diabetes (see table 1 for a definition of the current World Health Organization criteria). In most countries around 15% of adults have prediabetes based on WHO criteria,[8 10] of which an estimated 5–12% develop type 2 diabetes per year.[8 10] The risk of cardiovascular disease is also significantly elevated with prediabetes.[11] Given these factors, individuals with prediabetes will form a significant proportion of the health care burden associated with diabetes in the future and therefore have been the target of a number of diabetes prevention initiatives.

The aims of this article are: to give an overview of the evidence from diabetes prevention trials in high risk populations; to review the clinical utility of different strategies for identifying at-risk individuals; and to investigate whether tested diabetes prevention strategies are suitable for implementation in a primary health care setting.

STRATEGIES FOR PREVENTING TYPE 2 DIABETES

Lifestyle

Randomised controlled trials have consistently shown that lifestyle interventions can be successful at reducing the risk of progressing to type 2 diabetes by 40–60% in those with IGT.[12] For example, the Finnish Diabetes Prevention Study (DPS) found that the risk of type 2 diabetes was reduced by 58% in those given lifestyle counselling compared to control conditions over a 3 year period.[13] Identical findings were also seen in the USA in the Diabetes Prevention Program (DPP).[14] These results have also been replicated in India,[15] Japan[16] and China.[17] The aim of these interventions was to promote moderate to vigorous intensity physical activity, generally 150 min per week, and a healthy diet aimed at weight maintenance for normal weight individuals or weight loss for overweight or obese individuals. For example, the Finnish DPS had five intervention goals: a reduction in body weight of 5% or more; <30% of energy intake derived from fat; <10% of energy intake derived from saturated fat; at least 15 g of fibre per 1000 kcal; and at least 30 min of moderate intensity physical activity per day.[13] Of note, there was not a single case of type 2 diabetes over the course of the study in those who achieved at least four of these goals.[13] The same study also reported that, compared to those in lowest tertile of leisure time physical activity change, those in the highest tertile had around a 70% reduction in the relative risk of developing type 2 diabetes[18] Similarly, those in the US DPP who achieved their weight, dietary fat and exercise goals had around a 90% reduction in the relative risk of developing type 2 diabetes compared to those who achieved none of these goals.[19] The large decreases in the risk of type 2 diabetes seen with lifestyle change are unsurprising given that the rising prevalence of type 2 diabetes is

Table 1 World Health Organization criteria for impaired glucose tolerance and impaired fasting glucose

	Fasting glucose range	2 h post challenge glucose range*
Impaired glucose tolerance	<7 mmol/l	≥7.8 mmol/l and <11.1 mmol/l
Impaired fasting glucose	≥6.1 mmol/l and ≤6.9 mmol/l	<7.8 mmol/l

*Venous plasma glucose after ingesting 75 g of glucose solution.

attributable to so called "obesogenic" modern environments where energy dense foods are plentiful and the link between physical activity and food procurement has been broken; the timescale associated with the rising prevalence of type 2 diabetes means genetic change cannot be a causal factor. Therefore, lifestyle change directly targets the root cause of type 2 diabetes.

Importantly, successful lifestyle change programmes have also been shown to have lasting benefits. For example, DPS recently reported that the intervention effect was sustained at 7 years[20] and the China Da Qing prevention study found a sustained reduction in the incidence of type 2 diabetes after 20 years.[21] Both these results were achieved despite the active lifestyle intervention discontinuing after the initial study period. Therefore, it would appear that once individuals are enabled to successfully self regulate their behaviour, change can be sustained long after behavioural counselling has ceased.

Pharmacotherapy

Several oral hypoglycaemic agents have been shown to reduce the risk of developing type 2 diabetes in double blind randomised controlled trials. DPP demonstrated a 31% reduction in the relative risk of developing type 2 diabetes with 850 mg of metformin prescribed twice daily; obese and younger (<60 years) participants received the greatest benefit.[14] The STOP-NIDDM trial found that the glucosidase inhibitor, acarbose, reduced progression to type 2 diabetes by 25% on a dose of 100 mg taken three times a day[22]; however it has been pointed out that serious potential for bias exists at all levels of the trial and as such no valid conclusions can be drawn from the study.[23] The DREAM trial showed that rosiglitazone, a thiazolidinedione, taken daily (8 mg) for a median of 3 years, reduced the risk of type 2 diabetes by 60% in individuals with prediabetes.[24] However, this impressive result is surrounded by controversy because the trial also found that rosiglitazone was associated with a significant increase in congestive heart failure events; this is consistent with several recent meta-analyses which have concluded that rosiglitazone is linked with a significantly increased risk of myocardial infarction and heart failure.[25 26] Results from the ADOPT trial in newly diagnosed individuals with type 2 diabetes also found that substantial weight gain occurred with rosiglitazone; a 7 kg difference was observed between those given rosiglitazone and those given metformin after 4 years.[27]

The anti-obesity drug, orlistat, has also been shown to reduce the progression to type 2 diabetes by 37% over a 4 year period and reduce body weight in those with IGT.[28]

Although no national health regulatory body currently recommends the use of pharmacotherapy to prevent/slow progression to type 2 diabetes in at-risk individuals, a recent consensus statement from the American Diabetes Association recommends for the first time that metformin be considered for treatment as an adjunct to, or instead of, lifestyle modification in those with both IGT and IFG and one other risk factor (table 2).[29] Metformin was chosen because it has a proven preventive efficacy, it is relatively cheap, and is not associated with serious long term side effects. However, this approach remains controversial for several reasons. Firstly, few studies have assessed the impact of metformin and lifestyle modification in combination; the only study to do so, the Indian Diabetes Prevention Program, found that there was no additive benefit of combining metformin with a lifestyle modification programme in those with IGT.[15] Secondly, given the causal factors of type 2 diabetes, lifestyle modification programmes should be the primary focus of diabetes prevention initiatives. Importantly, lifestyle change, such as increased physical activity, is also associated with multiple and wide ranging health benefits that target the known comorbidities that accompany type 2 diabetes.[30] While logistical and feasibility issues remain in implementing lifestyle programmes in a primary health care or community setting, it is the responsibility of funding bodies and research organisations to carry out the necessary research to address this issue. However, we acknowledge that pharmacotherapy may have a role to play when lifestyle modification programmes have been tried and found to fail.

IDENTIFYING THOSE AT RISK

Utility of the oral glucose tolerance test

In order for diabetes prevention strategies to be implemented on a regional or national level it is essential that systematic strategies for identifying those at risk of developing type 2 diabetes are also implemented. Successful diabetes prevention studies have tended to include participants on the basis of IGT, which is diagnosed through the oral glucose tolerance test (OGTT). IGT and IFG represent distinct phenotypes: IFG is predominantly characterised by hepatic insulin resistance, and IGT is characterised by peripheral insulin resistance.[31] Therefore, lifestyle change is likely to be more effective in those with IGT, although this hypothesis has not been tested. IGT is also associated with a higher risk of developing type 2 diabetes and cardiovascular disease compared to IFG, with the highest risk occurring in those with both IGT and IFG.[8 32 33] However, there are important practical limitations and questions regarding the utility and clinical value of carrying out an OGTT to identify those with IGT. Perhaps most importantly OGTTs is not routinely carried out in most health care settings and its inclusion would represent a significant burden on health care resources and patient time. Although studies have shown that screening and treatment programmes for type 2 diabetes and IGT may be cost effective in the longer term,[34] these initiatives

Table 2 American Diabetes Association consensus statement recommendations for individuals with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both

Population	Treatment
IFG or IGT	Lifestyle modification
IGT *and* IGT *and* any of the following: ► <60 years of age ► BMI ≥35 kg/m² ► Family history of diabetes in first degree relatives ► Elevated triglycerides ► Reduced HDL cholesterol ► Hypertension ► HbA1c >6%	Lifestyle modification and/or metformin (850 mg twice daily)

BMI, body mass index; HbA1c, glycosylated haemoglobin; HDL, high density lipoprotein.

are likely to place a significant strain on health care resources in the shorter term. For this reason a recent review of the evidence commissioned by the NHS in the UK concluded that while screening for type 2 diabetes meets most of the National Screening Committee's key criteria, it fails on several, including a lack of adequate staffing and facilities.[35] Therefore, advocating the routine use of OGTTs as a screening tool in primary care is unlikely to be feasible at present in most health care settings.

The categories of IGT and IFG have also been questioned.[36] Prediabetes is associated with a high variation in the risk of both developing type 2 diabetes and cardiovascular disease; importantly, there is also a gradation of risk in those with normal glycaemia. For example, data from DPS found that the risk of type 2 diabetes in those with IGT more than doubled in the presence of other risk factors.[37] It is also known that the risk of cardiovascular disease increases linearly with increasing levels of 2 h glucose and fasting glucose[38]; moreover, there does not appear to be a distinct threshold which justifies the use of distinct categories.[8] Given these concerns there is a need for a global tool for risk assessment that is simple and applicable for use in a primary health setting and quantifies risk based on multiple risk factors.

Risk scores

Several risk assessment tools have been developed, the most widely validated and used of which is FINDRISC. FINDRISC was developed in Finland and uses weighted scores from eight risk characteristics to calculate an overall risk score (table 3).[39] It can be used as a method of identifying those with undiagnosed type 2 diabetes or those at risk of developing type 2 diabetes. FINDRISC has been shown to have good sensitivity (~0.8) and specificity (~0.8) at predicting the 10 year absolute risk of type 2 diabetes in a white European population.[39] Similar results were seen for a risk score developed in Germany.[40] Other risk scores have been developed and validated cross-sectionally in diverse populations,[41 42] although in contrast to the Finnish and German risk scores, few have been validated prospectively. Others have shown that a combination of body mass index (BMI), fasting glucose and glycosylated haemoglobin (HbA1c) are highly sensitive at predicting future incidence of type 2 diabetes and that there was little additional value of adding 2 h glucose to the model.[43] This contrasts with a recent review of the evidence which concluded that neither HbA1c or fasting glucose was effective at detecting IGT,[44] which is the position currently taken by WHO.[8] Therefore, caution should be applied when using fasting glucose or HbA1c to identify those at risk of type 2 diabetes. Given these considerations it is important that risk scores which take account of data routinely collected in primary care are developed and tested in ethnically diverse settings. It is also important that, given the elevated risk of cardiovascular disease in prediabetes, risk scores are multifactorial and designed to include a quantification of cardiovascular disease risk.

Despite the potential clinical utility of diabetes risk scores there is a lack of data from randomised controlled trials investigating whether intervening in high risk individuals, as identified through a risk score, is effective at initiating behaviour change and reducing the risk of developing type 2 diabetes. This is an important limitation because at-risk individuals identified through a risk score may only contain a relatively small proportion of individuals with impaired glucose tolerance, the traditional target of intervention studies.

Table 3 FINDRISC score

Risk factor	Score
Age (years)	
<45	0
45–54	2
55–64	3
>64	4
Body mass index (kg/m²)	
<25	0
>25–30	1
>30	3
Waist circumference (cm)	
Men, <94; women, <80	0
Men, 94 to <102; women, 80 to <88	3
Men, ⩾102; women, ⩾88	4
History of hypertension medication	
Yes	0
No	2
Previously measures high blood glucose	
No	0
Yes	5
Consumption of vegetables, fruits or berries	
Everyday	0
Less often than once a day	1
Physical activity (min/day)	
⩾30	0
<30	2
Family history of diabetes	
No	0
Yes, secondary degree	3
Yes, first degree	5

Total risk score: <7 = low risk; 7–11 = slightly elevated risk; 12–14 = moderate risk; 15–20 = high risk; >20 = very high risk.

TRANSLATING RESEARCH INTO PRACTICE

There is now growing recognition by many governments and international organisations that a systematic approach to identifying and treating diabetes risk is needed. Finland has led the way in developing, evaluating and implementing diabetes prevention programmes. To date, it is one of the few countries that has piloted and implemented a systematic framework for preventing type 2 diabetes on a national level; this includes routinely classifying risk status using FINDRISC and enrolling identified at-risk individuals into a lifestyle modification programme based on DPS.[45] Germany has also developed a systematic strategy for identifying and treating diabetes risk, called TUMAINI, which is aimed at effectively translating evidence based practice into a routine health care setting.[46] In the UK, the Department of Health has recently announced plans to introduce a systematic vascular risk assessment and management programme for all individuals between 40–74 years of age.[47] A comprehensive handbook is also available that provides evidence for the programme along with delivery strategies, resources, and tools for health care professionals implementing the programme.[48] It is estimated that the programme will prevent around 4000 cases of type 2 diabetes per year,[49] although the design and efficacy of any lifestyle modification programme imbedded within this scheme have yet to be established and tested. In addition to such national level initiatives, the European Union has announced plans to develop practice orientated guidelines for the prevention of type 2 diabetes which include a standardised approach to training health care professionals, an e-health training portal, and standards for accessing efficacy.[50] The European Union is also

Key learning points

- The prevalence of type 2 diabetes mellitus is increasing globally and represents a serious burden to national health care resources.
- Type 2 diabetes is preceded by impaired glucose tolerance and/or impaired fasting glucose, collectively called prediabetes.
- Type 2 diabetes and prediabetes are attributable to lifestyle factors.
- Diabetes prevention programmes have consistently shown that lifestyle modification programmes can reduce the risk of developing type 2 diabetes by over 50% in individuals with impaired glucose tolerance.
- Risk scores, rather prediabetes screening strategies based around 2 h post-challenge glucose and/or fasting glucose, may have greater clinical utility for classifying type 2 diabetes risk status in the general population.
- Prevention strategies based around group based education may be suitable for implementation in a primary health care setting.

providing funding to 25 institutions in 17 countries to develop efficient screening strategies for identifying type 2 diabetes risk and to develop core intervention programmes for the primary prevention of type 2 diabetes.[51]

Despite these encouraging developments there are important gaps in the evidence when it comes to translating diabetes prevention research into practice.[52 53] This is because the majority of tested lifestyle intervention studies have used intensive behaviour change strategies. For example, DPS had a median of 20 one-to-one counselling sessions over a 4 year period.[20] Therefore, even if such interventions are proven to be cost effective in the long term, implementing them would have a crippling effect in all but the wealthiest national health care services in the short term. Indeed, even national diabetes prevention initiatives in Finland and Germany have not been able to replicate fully the resource intensive nature of the DPS or DPP studies. Pragmatic diabetes prevention interventions, that are tailored to the resources and infrastructure available to national health care services, need to be developed and rigorously evaluated. Several research groups have responded to this need by developing and evaluating theory driven, group based educational programmes. For example the Good Ageing in Lahti Region (GOAL) lifestyle implementation trial in Finland used a health action process approach to design a six-session group educational programme aimed at promoting lifestyle change in those identified with an increased risk of developing type 2 diabetes, which was piloted in a real world health care setting.[54] The same intervention has also been adopted and piloted in Australia.[55] However, while encouraging, this approach remains untested in a randomised controlled trial.

A recent study in the UK developed a pragmatic 3 h structured education programme, based on the DESMOND model,[56] aimed at promoting physical activity by targeting illness perceptions and efficacy beliefs, and promoting self regulatory strategies surrounding pedometer use in those with IGT.[57] The programme is being tested in a randomised controlled trial; initial follow-up at 3 months indicates that the programme is successful at increasing physical activity and reducing 2 h post-challenge glucose concentrations.[58] This study therefore suggests that group based education can be effective at promoting lifestyle change and achieving clinical results; however, before recommendations can be made to policy-makers, this result needs to be confirmed in community based randomised controlled trials with individuals included on the basis of a risk score and incidence of type 2 diabetes as the primary outcome. Several such trials are currently underway, therefore the efficacy of this approach should be known in the next 4–5 years. If implemented, this approach to preventing type 2 diabetes could utilise existing educator training and quality assurance protocols and infrastructure that have been developed for the DESMOND programme, a nationally available structured education programme for those with type 2 diabetes.[56]

Research questions

- Can combining lifestyle modification with metformin have an additive effect in the prevention of type 2 diabetes?
- Can individuals who have been identified as at-risk using a risk score be successfully targeted by lifestyle modification programmes aimed at preventing type 2 diabetes?
- Can group based structured education aimed at promoting physical activity and a healthy diet reduce the risk of type 2 diabetes in a primary health care setting?

POPULATION VERSUS INDIVIDUAL INTERVENTIONS

Finally, it is also necessary to draw a distinction between screening and treatment interventions aimed at targeting those with a high risk of developing type 2 diabetes, and interventions aimed at shifting the degree of risk in the entire population. For example, shifting the distribution of body weight in the general population towards lower levels is likely to have a dramatic public health benefit. This is particularly important because single factors such as obesity and physical inactivity are known risk factors for type 2 diabetes, but the size of the groups identified by such factors are so large that only population based interventions are appropriate.[59] Therefore, planning and policy-makers need to weigh up the costs and benefits of investing in individually focused intervention programmes, which are likely

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to have a large impact on relatively few, and population based approaches which are likely to have a small impact on many.

CONCLUSION

The prevention of type 2 diabetes is a public health priority. While several lifestyle intervention programmes have proven highly effective at reducing the progression to type 2 diabetes in individuals with prediabetes, important issues remain surrounding the applicability of such interventions to a primary health care setting. Effective and feasible methods of identifying and targeting individuals with a high risk of developing type 2 diabetes are therefore needed. Future results from several community based randomised controlled trials should help answer these questions in due course.

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AFTER THE REFERENCES)

1. The following blood tests are needed to identify impaired glucose tolerance:

A. HbA1c
B. Fasting glucose
C. Fasting glucose and 2 h post-challenge glucose

2. The following is a validated risk assessment tool for identifying risk of type 2 diabetes:

A. FINDRISC
B. STOP-NIDDM
C. DREAM

3. The highest risk of developing type 2 diabetes is in those people diagnosed with:

A. Impaired fasting glucose (IFG)
B. impaired glucose tolerance (IGT)
C. IFG and IGT

4. The USA Diabetes Prevention Program (DPP) found that those who achieved their weight, dietary fat and exercise goals, compared to those who achieved none, reduced their risk of developing type 2 diabetes by:

A. 20%
B. 50%
C. 90%

5. The Finnish Diabetes Prevention Study (DPS) found that those who received lifestyle counselling over a 3 year period, compared to those who did not, reduced their risk of developing type 2 diabetes by:

A. 33%
B. 46%
C. 58%

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Answers

1. A (F); B (F); C (T)
2. A (T); B (F); C (F)
3. A (F); B (F); C (T)
4. A (F); B (F); C (T)
5. A (F); B (F); C (T)