International Diabetes Federation: an update of the evidence concerning the prevention of type 2 diabetes

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Summary

There is a need for preventive strategies to help combat the rising prevalence of type 2 diabetes. This article aims to provide an updated summary of diabetes prevention efforts by reviewing relevant literature published between 2007 and 2009. These include results from the long-term follow-up of diabetes prevention trials and the roll-out of community-based interventions in "real world" settings. Some countries have begun to implement population-based strategies for chronic disease prevention, but investment in developing and evaluating population-level interventions remains inadequate. By focussing on the "small change" approach and involving a number of different agencies, it may be possible to shift the population distribution of risk factors for diabetes and cardiovascular disease in a favourable direction. The cost-effectiveness of primary prevention strategies for type 2 diabetes has not been universally demonstrated. Some of the uncertainties relating to screening for diabetes have now been resolved but longer-term data on hard cardiovascular disease (CVD) outcomes are still needed. Recent findings from cardiovascular prevention trials among patients with longstanding diabetes cast doubt on the benefits of very intensive treatment of glycaemia but do highlight the benefits of treatment early in the course of the disease.

In summary, individual countries should aim to develop and evaluate cost-effective, setting-specific diabetes risk identification and prevention strategies based on available resources. These should be linked to initiatives aimed at reducing the burden of cardiovascular disease, and complemented with population-based strategies focusing on the control and reduction of behavioural and cardiovascular risk factors by targeting their key determinants.

Introduction

The International Diabetes Federation (IDF) consensus on type 2 diabetes prevention [1], and an accompanying editorial [2], underlined the need for preventive strategies to help combat the rising prevalence of this serious and costly disease. Since the publication of these articles, there have been a number of significant additions to the diabetes prevention literature. These include results from the long-term follow-up of diabetes prevention trials and the roll-out of community-based interventions in "real world" settings. Some of the uncertainties relating to screening for diabetes have now been resolved. Recent findings from cardiovascular (CVD) prevention trials among patients with longstanding diabetes cast doubt on the benefits of very intensive treatment of glycaemia but do highlight the benefits of treatment early in the course of the disease. In this article we aim to review the relevant literature published between 2007 and 2009 in order to provide an updated summary of diabetes prevention efforts. While it is acknowledged that tackling the burden of type 2 diabetes will involve a number of multi-level strategies, this paper focuses on primary and secondary prevention initiatives i.e. prevention and early detection.

Long-term follow-up of diabetes prevention trials

Intensive lifestyle and pharmacological interventions reduce the rate of progression to type 2 diabetes in people with impaired glucose tolerance (IGT). In a meta-analysis of published diabetes prevention trials, Gillies *et al* [3] reported pooled hazard ratios of 0.51 (95% CI 0.44 to 0.60) for lifestyle interventions vs. standard advice, and 0.70 (0.62 to 0.79) for oral diabetes drugs vs. control. These corresponded to estimated NNTs (number needed to treat) of 6.4 for lifestyle and 10.8 for oral diabetes drugs, during follow-up ranging from 3 to 6 years. Longer-term follow-up for two of the main diabetes prevention trials continue to provide encouraging results. In the Finnish Diabetes Prevention Study (DPS), there was a 43% reduction in the relative risk of developing diabetes between the lifestyle intervention and control group after a median of seven years [4]. Beneficial lifestyle changes and risk reduction were sustained even after discontinuation of active lifestyle counselling. Similar findings were reported in the long-term follow-up of the Da Qing study following six years of active intervention [5], where differences between the combined lifestyle intervention groups and the control group persisted over 20 years of follow-up (HR 0.57; 95%CI 0.41 to 0.81). Despite a slight separation of the Kaplan-Meier curves in the latter part of follow-up, there was no significant difference between the intervention and control groups in the rate of first CVD events (0.98; 95%CI 0.71 to 1.37), CVD mortality (0.83; 95%CI 0.48 to 1.10), and all-cause mortality (0.96; 95% CI 0.65 to 1.41), though for the time being there is limited statistical power to detect differences for these relatively rare outcomes.

Translating findings from diabetes prevention trials into the community

We have proof of concept of the potential to prevent diabetes from trials in people with IGT and long-term results from these studies are encouraging. However, the challenge is now one of translation. Researchers have begun to turn to the design and evaluation of more pragmatic diabetes prevention initiatives that can be implemented in the "real world". These initiatives are less intensive and costly than those evaluated in the diabetes prevention trials, and hence more readily rolled out into the community. We outline a few examples to demonstrate progress in this field.

In Finland, the "Good Ageing in Lahti Region" (GOAL) study [6] recruited 352 middle-aged men and women with elevated type 2 diabetes risk from local primary healthcare centres and implemented lifestyle and risk reduction objectives derived from the Finnish DPS [7]. Physicians and nurses prospectively referred patients with already-identified risk factors (obesity, hypertension, elevated blood glucose or lipids) to the study nurse where

patients were screened using the FINDRISC questionnaire [8]. Following six group counselling sessions delivered by trained public health nurses over one year, 20% of participants achieved at least four of five key lifestyle goals, with significant reductions in important clinical measures and low attrition rates. However, physical activity and weight loss goals were achieved significantly less frequently than in the reference trial, and in order to increase impact, the authors suggested that programme exposure and treatment intensity needed to be increased. Similar initiatives have been implemented in Australia as part of the Greater Green Triangle (GGT) Diabetes Prevention Project [9] and the "Live Life Well" project [10].

Using a comparable approach, the Diabetes Education & Prevention with a Lifestyle intervention Offered at the YMCA (DEPLOY) study aimed to deliver a formal, group-based adaptation of the American Diabetes Prevention Programme (DPP) lifestyle intervention in a small pilot cluster randomized controlled trial (RCT) in community YMCA facilities [11]. 92 overweight adults with abnormal glucose metabolism agreed to take part following a recruitment campaign, which included letters outlining the effectiveness of lifestyle modification to prevent diabetes sent to randomly selected households and invitation to diabetes risk-screening events at participating YMCA centres. Individuals with a BMI ≥ 24 kg/m^2, or ≥ 2 diabetes risk factors, and a random capillary blood glucose of 110-199 mg/dL were invited to take part. Trained lay facilitators delivered 16 classroom-style meetings focused on building knowledge and skills for goal-setting, self-monitoring and problem-solving over 16-20 weeks, followed by monthly larger group meetings (57% overall attendance rate). After 12 months, the intervention group experienced a significantly greater decrease from baseline in body weight (6%; 95%CI 3.8 to 8.3) compared to the controls (1.8%; 95% CI 0.3 to 3.9) (p=0.008) [11] and modelled 10-year CHD risk (p=0.007) [12].

While early results from these and other trials are encouraging, the samples were small and largely self-selected, follow-up was short, the interventions remained relatively intensive and many studies lacked formal comparison (control) groups. Robust measurement of lifestyle behaviours was scarce and there were challenges in recruiting and retaining individuals at high risk. Research into the understanding of diabetes risk suggests that socially and economically disadvantaged groups will be particularly difficult to access and are at high risk. In a survey of clinical records in two American community health centres that served urban African Americans and Hispanics, risk assessment was poor, screening tests were under-utilized, and documentation of counselling and referral interventions for risk factors was low [13]. Providers believed that their lifestyle recommendations were unlikely to be adopted by patients. Very few providers (9%) were appropriately able to identify each of obesity, physical inactivity, glucose abnormalities and hypertension as risk factors for diabetes. Patients reported limited knowledge regarding diabetes risk and prevention, low self efficacy and limited behaviour change skills, in addition to multiple external barriers to lifestyle change.

Aside from the challenges of translating DPS- and DPP-like prevention initiatives into the community, evaluating such interventions will rely in part on a willingness to consider study designs aside from the RCT to examine the feasibility and effectiveness of new prevention initiatives. While RCTs are rightly regarded as the gold standard for evaluating efficacy, their utility for addressing questions in public health intervention research is not universally or uncritically accepted [14]. Indeed, knowing about intervention reach, uptake, acceptability, cost and implementation, as well as how interventions work in different sub-groups of the population and via which mechanisms, is particularly important to public health policy makers and commissioners. The difference in attendance, adherence and drop-out rates between each community-based setting, the higher proportion of women taking part in prevention initiatives [6, 9, 11], and the range of methods used to identify at-risk individuals underlines the importance of *setting-specific* intervention development and evaluation. Ruge *et al* have observed that most eligible individuals choose not to participate in diabetes prevention trials [15].

One size will clearly not fit all. The delivery of the DPP via the YMCA, for example, may be useful in the USA for its accessibility to broad segments of the population and because it sets fees for programme access that are based on cost-recovery alone [11]. However, the low level of participation in community-based diabetes risk screening events in the DEPLOY study suggests that a range of different approaches may be needed to engage people who are at risk for diabetes.

Ackermann *et al* [11] argue that future research should assess and compare the use of multiple recruitment strategies, in both healthcare and non-healthcare settings, to optimize the reach of diabetes prevention translation activities, in conjunction with low-cost intervention delivery by appropriate community partners. There remain multiple and multilevel challenges for the real-world adaptation of DPS- or DPP-like interventions in the community, with a need to balance fidelity of intervention delivery and the optimization of effectiveness, with minimization of costs and improved sustainability [16].

National efforts to prevent diabetes

Finland is one of the first countries to implement a large-scale, multi-level diabetes prevention strategy. The DEHKO project [17] includes a population strategy aimed at improving nutrition and increasing physical activity in the entire nation, an individualized strategy for those at high risk, and a programme of early detection and management for people with type 2 diabetes. In 2010, the population-level effects of the programme will be studied in terms of coverage, effectiveness, rate of adoption, feasibility and permanence. The DE-PLAN study ("Diabetes in Europe – Prevention using Lifestyle, Physical Activity and Nutritional Intervention") [18] is another large-scale diabetes prevention initiative, which aims to develop community-based type 2 diabetes prevention programmes for individuals at high risk across Europe. The implementation of the intervention programme has begun in each local project centre, with the distribution of several thousand FINDRISC questionnaires and the identification of those at high risk. These types of initiatives can also be expected to help reduce risk for other chronic conditions such as obesity, cancer and cardiovascular disease. The recently introduced UK "Change4Life" programme [19] is a society-wide movement that aims to prevent people from becoming overweight by encouraging them to eat better and move about more. The initial stage of the Change4Life campaign is targeting young families by advertising on television, in the press, on billboards and online, and will hopefully help improve risk factors for a range of different conditions.

These types of initiatives advocate a "small-change approach" to chronic disease prevention, an approach which is gathering momentum in the prevention literature [20-22]. Hill writes, for example, that "…a small-changes framework, aimed at helping people make conscious small changes in lifestyle behaviours, in combination with efforts by the private sector to gradually 'ratchet down' some of the environmental factors that have contributed to excessive energy intake and the declining rates of physical activity, can be successful in reducing obesity rates" [21]. Indeed, we can help prevent the increasing prevalence of diabetes and other chronic diseases by shifting the distribution of health behaviours in a positive direction. Such initiatives, supported by educational and social marketing campaigns, and public sector efforts targeting collective determinants, are more likely to have an impact on population health than focussing purely on individual-based prevention strategies. The increase in diabetes prevalence is due to a shift in the whole glucose curve, and not just the movement of a small section of the curve from IGT to type 2 diabetes. In order for these public health endeavours to succeed, more attention needs to be given to understanding the determinants of behaviours linked to chronic disease at the population level and on the evaluation of efforts to shift the entire distribution of behaviour [2].

Cost-effectiveness of diabetes prevention

Three-year results from the Indian-DPP [23] suggest that both metformin and lifestyle are cost-effective for preventing diabetes among those with IGT in India. We have also seen the publication of new modelling studies for diabetes prevention which encompass a screening stage in their calculations of cost-effectiveness. Gillies *et al* [24] modelled four different strategies for the screening and prevention of type 2 diabetes in the UK context: screening for diabetes; screening for diabetes and IGT, followed by either lifestyle intervention or drugs; and no screening. The authors demonstrated that it was likely to be cost-effective to intervene in those found to have impaired glucose regulation rather than wait for individuals to be diagnosed with diabetes [25]. Similarly, Hoerger *et al* [26] showed that screening for IGT and/or impaired fasting glucose (IFG) in the overweight and obese US population followed by a DPP-lifestyle intervention has a relatively attractive cost-effectiveness ratio. While these results are encouraging, modelling studies are only as robust as their underlying assumptions. Uncertainties exist about key model parameters, as well as the real costs and benefits of screening, and practical considerations about the feasibility, acceptability and affordability of interventions [25]. Results from modelling studies of screening and prevention strategies for diabetes are most sensitive to changes in intervention-related parameters [26, 27]. Interventions must therefore be effective for prevention strategies to have attractive cost-effectiveness ratios. However, effective and affordable lifestyle interventions for diabetes prevention in everyday practice are still lacking [25].

There is still a need for data from long-term RCTs with robust outcome data to assess the long-term clinical and economic impact of primary and secondary diabetes prevention programmes. The cost-effectiveness of upstream interventions at the population level will also be hard to establish. As personal behaviours take time to change and the health benefits can take even longer to establish [28], the delayed effects of small lifestyle changes will be difficult to measure and attribute to any population-based prevention measures. However, a narrow focus on diabetes is likely to underestimate the true impact on population health of individual and collective interventions to promote change in key health behaviours such as diet and physical activity.

Screening for diabetes

Since the publication of the IDF consensus, some of the uncertainties relating to screening for diabetes have been resolved. The Anglo-Danish-Dutch Study of Intensive Treatment of people with newly diagnosed diabetes in primary care (ADDITION) consists of a screening phase followed by a pragmatic open-label cluster randomized controlled trial comparing the effect on cardiovascular risk of intensive multi-factorial therapy with standard care in patients with screen-detected diabetes [29]. Data from the ADDITION trial show that people with screen-detected diabetes exhibit an adverse but modifiable cardiovascular risk profile at diagnosis [30, 31]. CVD risk factors improved between diagnosis and one-year follow-up in the Cambridge and Dutch-ADDITION arms and were significantly lower among intensively treated patients [32, 33]. Furthermore, a controlled trial of the psychological impact of stepwise screening for diabetes embedded in the ADDITION-Cambridge trial showed that anxiety, depression, worry about diabetes and self-rated health were not significantly different in participants invited to screening and those not invited (controls), indicating that screening for type 2 diabetes is associated with limited psychological harm [34, 35]. These results suggest that screening for diabetes might be worthwhile. However, the key determinant of the effectiveness and cost-effectiveness of diabetes screening is the magnitude of cardiovascular risk reduction following early detection and intensive treatment, and this remains uncertain.

While evidence is beginning to suggest that earlier, intensive treatment of diabetes is effective, it still remains unclear who to screen, how often, and how to tackle problems of uptake. Evidence from a national pilot screening programme for type 2 diabetes in deprived areas of England demonstrated the difficulty in implementing and evaluating

diabetes screening initiatives in primary care [36]. There was inconsistency in executing the screening protocol, lack of quality control, lack of adequate diagnostic testing after a positive screening test e.g. 31% of individuals with a positive screening test did not have a diagnostic test result recorded on their notes, and a lack of systems for routine data collection on screening. Furthermore, screening for a disease inevitably finds more people at high risk than people with the disease, and as reviewed earlier, it remains unclear what to do with these individuals in a real world setting. Results from the DE-PLAN project, which aims to develop and test models of identification and intervention in individuals at high risk of type 2 diabetes in 17 European countries, will provide further evidence on effective ways of finding and treating those at risk of diabetes [18]. Similarly, the UK Department of Health has just introduced a Vascular Risk Assessment programme [37], which will identify large numbers of people in primary care who might benefit from interventions to reduce their risk of CVD and diabetes, and may provide opportunities to evaluate different risk identification strategies.

Glucose continuum and cardiovascular risk

Observational studies show a consistent and continuous association between glycaemia and CVD risk that extends below the diabetic threshold [38, 39]. However, results from long-term follow-up of diabetes prevention trials show relatively small reductions in glycaemia and have not yet demonstrated reduced CVD morbidity or mortality in intervention groups. Furthermore, recent findings from CVD prevention trials among patients with longstanding diabetes cast doubt on the benefits of very intensive treatment of glycaemia [40]. Conversely, the hypothesis that tight glycaemic control early in the course of type 2 diabetes can reduce CVD risk is supported by subgroup analyses of the recent ACCORD, ADVANCE and VADT trials [40-42]. Similarly, early blood glucose control reduced myocardial infarction and all-cause mortality in patients with diabetes in the UK Prospective Diabetes Study [43], and preliminary findings from the diabetes screening literature support the notion that early detection and treatment might be worthwhile [32, 33]. Skyler *et al* have therefore suggested that glycaemic control may be important before macrovascular disease is well developed but has less impact when vascular disease is advanced [44]. In addition, numerous lifestyle intervention studies (for diabetes prevention [45], weight reduction and/or increasing physical activity) have demonstrated encouraging short-term (6-48 months) benefits in reducing CVD risk factors (blood pressure, cholesterol, insulin resistance etc.) but the effect on CVD mortality and events is unknown. This remains an important gap in the current research base [46], particularly at a time when population-based screening to identify those at high CVD risk is proposed [37, 47].

The continuous association between glycaemia and CVD risk, and perhaps also risk of microvascular complications [48], also challenges the notion of diabetes as a disease defined by a simple threshold. We have previously stated that as "…most of the population burden of cardiovascular disease attributable to hyperglycaemia comes from the large number of people with moderately raised levels of glucose, rather than the smaller number of people with high levels, it follows that the most effective population strategy for preventing this burden is to attempt to shift the mean glucose level in the population by increasing average levels of activity and reducing obesity". This endeavour is similar to the "small change" approach and suggests that if the blood glucose curve can be shifted to the left we may be able to prevent larger numbers of diabetes-related complications than simply focusing efforts just below the current somewhat arbitrary diagnostic threshold.

Discussion

We previously argued for investment in "real world" diabetes prevention initiatives [2]. Encouraging results from community-based prevention efforts have contributed to an emerging evidence base in this field [6, 9, 11, 49, 50]. The translation of evidence from DPS- and DPP-like programmes into larger-scale prevention endeavours has highlighted a number of challenges for the future, including how to identify people at high risk and encourage them to participate; maximizing response and attendance rates; programme intensity, fidelity and sustainability; and the development of effective and cost-effective interventions. It is unclear whether the efficacy of the DPS and DPP interventions in populations with IGT and overweight/obesity would be similar in populations defined as at risk using somewhat different criteria e.g. not dependent on 2-hour blood glucose. We do not know which interventional elements from the prevention trials can be omitted to reduce cost. It is also unclear how much of the programme is required to achieve behaviour change and the nature and frequency of follow-up to achieve maintenance of change. Multiple external barriers to lifestyle change, limited understanding of diabetes risk and prevention by both providers and the public [13], and limited behaviour change skills will also impede the implementation of these types of initiatives on a larger scale. We need further small-scale evaluations using robust measurement of lifestyle behaviours, as well as larger studies evaluating more pragmatic diabetes prevention programmes with longer-term follow-up.

Some countries have begun to implement population-based strategies for chronic disease prevention, but investment in developing and evaluating population-level interventions remains inadequate. By focussing on the "small change" approach and involving a number of different agencies, it may be possible to shift the population distribution of risk factors for diabetes and CVD in a favourable direction. This approach should be combined with more intensive diabetes prevention programmes in those at high risk. The cost-effectiveness of primary prevention strategies for type 2 diabetes has not been universally demonstrated. Feasible, acceptable and affordable diabetes prevention interventions still need developing, and longer term data are needed to assess the clinical and economic impact of diabetes prevention programmes. In relation to screening and earlier detection, while preliminary results from the ADDITION trial suggest that early detection and treatment of diabetes may be beneficial, again, longer-term data on hard CVD outcomes are still needed. Furthermore, the practicalities of implementing and evaluating a diabetes screening programme are unresolved. Goyder *et al* [36] suggest that primary care will have an increasing responsibility for primary prevention and early detection of diabetes and CVD risk and future programmes will be more effective if lessons are learned from the experience of the kinds of initiatives outlined in this article. Finally, while both observational and trial evidence suggests that blood glucose control earlier in the disease trajectory might reduce CVD risk, long-term evidence on the costs and benefits of this approach are unknown.

In conclusion, individual countries should aim to develop and evaluate cost-effective, setting-specific diabetes risk identification and prevention strategies based on available resources. These should be linked to initiatives aimed at reducing the burden of cardiovascular disease, and complemented with population-based strategies focusing on the control and reduction of behavioural and cardiovascular risk factors by targeting their key determinants. The successful evaluation of these types of initiatives will depend in part on a willingness to consider study designs other than the RCT. The answer to some important outstanding questions in the diabetes prevention field rely on waiting for the long-term follow-up of studies that are already in progress, particularly with regards to CVD morbidity and mortality reduction. However, in the meantime there is much that can be done and increasing evidence on which to base decisions about what to do in order to reduce the burden of disease associated with type 2 diabetes.

Acknowledgements

We thank Jonathan Shaw, Paul Zimmet and George Alberti for their helpful comments on the paper.

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