The global agenda for the prevention of type 2 diabetes

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Diabetes represents an enormous and growing clinical and public health problem. Its financial burden is huge and growing and likely to be unsustainable. Lifestyle interventions are safe and effective for preventing diabetes, are associated with improved quality of life, and are cost-effective. Metformin is effective, safe, and cost-effective, if not cost-saving. National and international efforts are needed to identify at-risk individuals and to systematically apply these interventions. Research must focus on how best to implement diabetes prevention in diverse populations and settings.

INTRODUCTION

The global burden of type 2 diabetes is enormous and growing. Between 1997 and 2010, 4 research groups used standardized diagnostic criteria to estimate the number of people around the world with diabetes and to project future numbers (Figure 1).^{1–4} In each instance, the previous estimate was found to have underestimated the number of people with diabetes, and the projections painted an ever more alarming picture of the future burden of type 2 diabetes. The latest study estimated that between 2010 and 2030 the worldwide number of adults with diabetes will increase by 54%, from 285 million to 439 million.⁴ The number of adults with diabetes will increase by 20% in developed countries: 20% in Europe, 42% in North America, and 47% in the Western Pacific.⁴ In contrast, the number of adults with diabetes will increase by 69% in developing countries: 65% in South and Central America, 72% in Asia, 94% in the Middle East, and 98% in Africa.⁴ Much of the growth in the numbers of people with diabetes will occur in middle-aged working adults.⁴ A part of the increase in the number of people with diabetes worldwide is due to increased incidence of type 2 diabetes related to urbanization, greater access to food, and decreased physical activity. A larger part of the increase is due to population growth, aging of the population,

and decreased mortality. Whatever the causes, the estimates are conservative and the future burden of type 2 diabetes is likely to be even greater than projected.

THE COSTS OF DIABETES

The global epidemic of type 2 diabetes has major implications for healthcare spending. In 2010, the global cost of diabetes was estimated to be \$376 billion, which represents 12% of all healthcare costs.⁵ Ninety-five percent of global health expenditures for diabetes was estimated to be from the world's richest countries: 57% from North America, 28% from Europe, and 10% from the Western Pacific.⁵ Indeed, in 2010, the mean annual healthcare expenditure per person with diabetes was estimated to vary by more than 100-fold, from \$5751 per person with diabetes per year in North America to \$458 per person with diabetes per year in South and Central America to \$53 per person with diabetes per year in Southeast Asia.⁵ Not surprisingly, these dramatic differences in mean annual healthcare expenditures for diabetes are associated with differences in the types of expenditures for diabetes. In developed countries, where mean annual expenditures per person with diabetes are high, a large absolute amount, but a small proportion of total healthcare expenditures, is for antihyperglycemic therapy.⁵ The greatest proportion of

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Figure 1 Global estimates and projections of the number of people with diabetes.

healthcare expenditures for diabetes go for the treatment of complications and comorbidities. In contrast, in developing countries, where mean annual expenditures per person with diabetes are low, the greatest proportion of expenditures go to antihyperglycemic therapy.⁵ Although some resources go to the treatment of acute metabolic and infectious complications, little is spent on the treatment of chronic complications and comorbidities such as renal and cardiovascular disease.

THE IMPACT OF ECONOMIC DEVELOPMENT ON COSTS

Because developed countries devote substantial resources to the treatment of chronic diabetic complications and comorbidities but developing countries do not, economic development is likely to be associated with a substantial increase in the costs of diabetes in developing countries. In their analyses, Zhang et al.⁵ assumed constant per-capita healthcare expenditures for diabetes and estimated that by 2030 the global cost of diabetes will increase by 30%, from approximately \$376 billion to \$490 billion. Between 2010 and 2030, developed countries were projected to have a 27% increase and developing countries a 67% increase in expenditures for diabetes. These estimates are likely to substantially underestimate the future costs of type 2 diabetes, especially for developing countries, because they assume constant per-capita healthcare expenditures.

Economic development is associated with increased per-capita healthcare expenditures. This phenomenon is perhaps best illustrated by a study of end-stage renal disease (ESRD) treatment, an expensive but life-saving therapy, by national wealth (Figure 2).⁶ The study found

that in low- and middle-income countries with a per-capita gross domestic product (GDP) of less than approximately \$10 000, rates of ESRD treatment are low but increase with per-capita GDP. The higher the national per-capita GDP in low- and middle-income countries, the greater the rate of ESRD treatment of the population per million. In contrast, in high-income countries with per-capita GDPs above approximately \$10 000, rates of ESRD treatment are consistently higher, reflecting greater access to ESRD treatment. These data suggest that economic development is associated with increased demand for and access to care and will likely be associated with an increase in per-capita healthcare expenditures for the treatment of the chronic complications and comorbidities of diabetes. As low- and middle-income countries with low mean annual per-capita expenditures for diabetes develop economically, the demand for and per-capita cost of diabetes care will increase substantially. This increase in healthcare costs is likely to be many times higher than the costs projected by Zhang et al.⁵ and, if the costs remain unchecked, will have the potential to bankrupt healthcare systems and, indeed, national economies.

LIFESTYLE AND PHARMACOLOGIC INTERVENTIONS FOR DIABETES PREVENTION

What, then, can be done? What is the efficacy of interventions to delay or prevent the development of type 2 diabetes? The evidence for the efficacy of interventions to delay or prevent the development of type 2 diabetes is extensive, robust, and consistent (Table 1).^{7–15} Four trials from China,⁷ Finland,⁸ the United States,⁹ and

Figure 2 End-stage renal disease (ESRD) treatment by national economic wealth. The dashed line represents the boundary between high-income countries and low- and middle-income countries as classified by the World Bank Group.⁶

Table 1 Interventions proven to delay or prevent the development of type 2 diabetes

Intervention	Percentage of risk reduction
Lifestyle (4 trials): Pan et al. (1997), ⁷ Tuomilehto et al. (2001), ⁸ Knowler et al. (2002), ⁹ Ramachandran et al. (2006) ¹⁰	29–58
Metformin (2 trials): Knowler et al. (2002), ⁹ Ramachandran et al. (2006) ¹⁰	26%–31%
Lifestyle and metformin (1 trial): Ramachandran et al. (2006) ¹⁰	28
Acarbose (1 trial): Chiasson et al. (2002) ¹¹	25
Voglibose (1 trial): Kawamori et al. (2009) ¹²	41
Troglitazone (1 trial): Buchanan et al. (2002) ¹³	55
Rosiglitazone (1 trial): DREAM Trial (2006) ¹⁴	60
Pioglitazone (1 trial): DeFronzo et al. (2011) ¹⁵	72

India¹⁰ have demonstrated that lifestyle interventions designed to achieve a 5%–7% reduction in initial body weight and to increase brisk walking to approximately 150 minutes per week can reduce the risk of type 2 diabetes by 29%–58% in at-risk individuals (generally defined as adults with obesity, fasting hyperglycemia, and impaired glucose tolerance based on the 2-hour oral glucose tolerance test). Eight key features characterized the effective, safe, and feasible lifestyle intervention implemented in the Diabetes Prevention Program (DPP). The DPP lifestyle intervention employed (1) individual case managers or “lifestyle coaches,” (2) frequent contact with participants, (3) a structured, state-of-the-art, 16-session core curriculum that taught behavioral

self-management strategies for weight loss and physical activity, (4) supervised physical activity sessions, (5) a more flexible maintenance intervention, combining group and individual approaches, motivational campaigns, and “restarts,” (6) individualization through a “toolbox” of adherence strategies, (7) tailoring of materials and strategies to address ethnic diversity, and (8) an extensive network of training, feedback, and clinical support.¹⁶

Trials have also demonstrated that metformin can reduce the incidence of type 2 diabetes by 26%–31%,^{9,10} α -glucosidase inhibitors by 25%–41%,^{11,12} and thiazolidinediones by 55%–72%.^{13–15} Additional studies have demonstrated the long-term tolerability, safety, and efficacy of metformin for diabetes prevention¹⁷ and have demonstrated that in obese patients with type 2 diabetes metformin reduces the risk of cardiovascular disease¹⁸ and appears to reduce the risk of several cancers.¹⁹

TRANSLATION OF INTERVENTIONS FOR DIABETES PREVENTION INTO PRACTICE

What is the evidence that lifestyle interventions can be translated into clinical and community practice? Long-term follow-ups in the Chinese DaQing Diabetes Prevention Study,²⁰ the Finnish Diabetes Prevention Study,²¹ and the US DPP¹⁷ have demonstrated that the impact of lifestyle interventions may persist for decades and produce a 34%–43% long-term reduction in the risk of type 2 diabetes. A number of research groups

have further demonstrated the feasibility of implementing lifestyle interventions for diabetes prevention in primary care and the effectiveness of incorporating strategies for remote support (phone, email, DVD, and the Web), meal replacements, and weight loss medications into the interventions.^{22–24} Although demonstrating feasibility, most of these studies have assessed effectiveness over a shorter, 1- to 2-year time horizon and used percent weight loss from baseline as an indirect measure of diabetes prevention.

Successes have also been reported with community adaptations of lifestyle interventions for diabetes prevention. Group lifestyle interventions have been shown to be associated with 6% weight loss at 1 year when administered through YMCAs²⁵ or state diabetes prevention and control programs,²⁶ and group maintenance programs offered through YMCAs have been shown to maintain weight loss for up to 2.3 years.²⁷ The US Centers for Disease Control and Prevention has attempted to expand the availability of programs for diabetes prevention in clinical and community settings with its National Diabetes Prevention Program. The program has 4 components: (1) training to increase the workforce providing diabetes prevention services; (2) a recognition program to assure quality of the programs providing diabetes prevention services; (3) the establishment of intervention sites in the community to deliver the program; and (4) health marketing to support program uptake, encourage third-party coverage, and promote sustainability.²⁸ Recently, the American Medical Association has partnered with the Centers for Disease Control and Prevention in a program called Prevent Diabetes STAT (Screen, Text, Act-Today). Its purpose is to promote screening, testing, and treatment of prediabetes in primary care.²⁹

Curiously, despite its proven safety and efficacy,^{9,17} metformin has not been widely implemented for diabetes prevention. Data from the DPP indicate that metformin is as effective as lifestyle intervention among younger and more obese at-risk participants and among women with histories of gestational diabetes.^{9,30} Indeed, a recent post hoc analysis of 10 years of combined DPP/DPP Outcomes Study data that used HbA1c to establish eligibility for diabetes prevention (HbA1c, 5.7%–6.4%) and to define diabetes outcomes (HbA1c, $\geq 6.5\%$) demonstrated that metformin was as effective, if not more effective, than lifestyle intervention for diabetes prevention.³¹ A recent within-trial economic analysis using 10 years of combined DPP/DPP Outcomes Study data further demonstrated that metformin treatment for diabetes prevention was cost-saving over 10 years.³² Despite these data, 2 recent, large, managed-care database studies, the smaller of which included over 17 000 patients with newly diagnosed prediabetes, found that fewer

than 4% of patients with prediabetes receive prescriptions for metformin within 3 years of diagnosis.^{33,34}

BARRIERS TO TRANSLATION

What are the challenges to widespread clinical and community implementation of lifestyle and metformin interventions for diabetes prevention? There are at least 4 challenges: (1) case finding; (2) program uptake and adherence; (3) program funding and sustainability; and (4) offering appropriate pharmacologic therapy.

The failure to identify at-risk individuals is a barrier to the successful translation of interventions for diabetes prevention into clinical and public health practice. In the United States, 86 million individuals have prediabetes, but only approximately 11% are aware of the diagnosis.³⁵ People with prediabetes must be diagnosed before they can be treated. A great deal of attention has focused on screening for abnormal blood glucose and type 2 diabetes. Although screening is important, it has been demonstrated that nearly 70% of nondiabetic US managed-care members age 45 years and older are already being tested at least once every 3 years for prediabetes and diabetes and that almost all of the highest-risk patients are already being tested.³⁶ The shortcoming appears to be in follow-up and definitive diagnostic testing for those who are identified as being at risk. Recent draft recommendations by the US Preventive Services Task Force promoting screening for abnormal glucose and type 2 diabetes mellitus with random glucose and hemoglobin A1c levels in addition to fasting glucose and 2-hour postglucose load glucose levels will likely facilitate case finding.³⁷ In addition, it has been shown that mathematical models can be applied to existing health system data as a practical and inexpensive way to identify patients at increased risk for impaired fasting glucose.³⁸ These models were developed and validated using progressively more complex data, including demographic and claims/diagnosis data with or without pharmacy, laboratory, and clinical data available through electronic medical records. These algorithms can be used to efficiently risk-stratify populations so that additional screening or diagnostic testing may be targeted to the highest-risk subpopulations.

A second barrier to diabetes prevention is the relatively low uptake of and adherence to proven-effective interventions. Can incentives be designed to promote better utilization of interventions for diabetes prevention, and can those interventions be integrated into mainstream medical care? The field of behavioral economics has emerged as an important tool to achieve these ends.³⁹ Effective approaches have included reducing or eliminating out-of-pocket costs, providing financial

incentives for participation, and invoking loss-avoidance. The last of these approaches, which reduces benefits and increases out-of-pocket costs when targeted individuals fail to participate in preventive interventions offered by their health plan, has been shown to be associated with high participation and adherence rates, improved clinical outcomes, and reduced direct medical costs.⁴⁰

A lack of available programs is also a barrier to diabetes prevention. Ideally, it should be as easy to refer to a lifestyle intervention for diabetes prevention as it is to write a prescription for metformin. An important cause of the lack of availability of programs has been a lack of funding for the services provided. With the increasing awareness of the efficacy of behavioral interventions for weight loss⁴¹ and intensive behavioral interventions to promote diet and physical activity for cardiovascular disease prevention in adults who are overweight or obese and have additional cardiovascular risk factors,³⁷ the US Preventive Services Task Force has endorsed lifestyle interventions. Because of this endorsement, the Affordable Care Act mandates their coverage by third-party payers. This should facilitate the implementation and sustainability of lifestyle intervention programs.

The low uptake of metformin for diabetes prevention is perhaps more vexing and problematic than the failure to fully implement lifestyle interventions. As noted above, metformin therapy is effective and safe for diabetes prevention, yet uptake remains exceedingly low. What are the barriers to pharmacologic therapy with metformin? The first barrier is the lack of US Food and Drug Administration approval of metformin for the indication of diabetes prevention. Because metformin was off-patent by the time it was demonstrated by the DPP to be effective for diabetes prevention, there was no financial incentive for the manufacturers to apply for US Food and Drug Administration approval for the indication of diabetes prevention. Although providers can, on an individual basis, prescribe metformin for diabetes prevention, it cannot be promoted for this “off-label” indication. As a result, both provider awareness and patient demand for metformin therapy is low. In addition, the power of pharmaceutical advertising has not been brought to bear on what amounts to a “wonder drug,” an extremely effective and, indeed, cost-saving medication for diabetes prevention.

CONCLUSION

What, then, can one conclude? Diabetes represents an enormous and growing clinical and public health problem. Its financial burden is huge and growing and likely to be unsustainable. Lifestyle interventions for preventing diabetes are effective in the young and elderly, women and men, all racial and ethnic groups, less and

more obese, and less and more hyperglycemic patients. They are associated with improved quality of life and are safe and cost-effective. Similarly, metformin is effective, especially in younger and more obese patients with prediabetes and in women with histories of gestational diabetes. Metformin is also safe and cost-effective, if not cost-saving. Small studies have demonstrated the feasibility and effectiveness of translating lifestyle interventions for diabetes prevention into clinical and community practice. In contrast, the translation of metformin therapy for diabetes prevention into clinical practice has been largely and inexplicably neglected. National and international efforts are needed to identify at-risk individuals and to systematically apply these interventions. Research must focus on how best to implement diabetes prevention in diverse populations and settings. Such a focus should not negate the importance of complimentary approaches to diabetes prevention, including societal interventions to address health education in schools, food policy, and the built environment as well as interventions that promote the early detection and intensive management of type 2 diabetes.

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