Primary prevention of diabetes mellitus: current strategies and future trends

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ABSTRACT

Aim of this paper is to find evidence for primary prevention of type-2 diabetes mellitus (T2DM) from epidemiological studies and clinical trials, and the feasibility of applying these interventions in resource limited countries. T2DM, which accounts for more than nine-tenths of all diabetics, results from inadequate insulin secretion or underlying insulin resistance. The prevalence of diabetes, mainly T2DM, has increased rapidly during the last few decades worldwide. Since the genetic background is unlikely to change during this short time period, the growing epidemic of T2DM is more likely due to changes in environmental or lifestyle risk factors including obesity, physical inactivity, smoking, alcohol and stress. The scope and feasibility for primary prevention of T2DM is based on elimination of these risk factors. This evidence that T2DM is preventable comes from epidemiologic studies and clinical trials of effect of lifestyle changes and drugs in development of T2DM. The positive effects are more profound and safer with lifestyle modifications (LSM) compared to medications. This is shown to be effective globally, across various ethnicities and races and sustainable on long-term follow-up. However, there is a major challenge in translating this evidence into economically viable and sustained community programs, as these LSM interventions are expensive, even from western standards point of view. Future plan should focus on health education of the public, improving the national capacity to detect and manage the environmental risks including strategies to reduce stress, and development of innovative, cost effective, and scalable methodologies.

Introduction

Diabetes mellitus is a group of metabolic diseases whose common feature is an elevated blood glucose level resulting from defects in insulin secretion, insulin action, or both. Both forms are due to complex interplay between genetic susceptibility and environmental factors. Type-2 diabetes mellitus (T2DM), which accounts for 90%-95% cases, develops when insulin production is insufficient to overcome underlying insulin resistance. The prevalence of diabetes has increased rapidly during the past few decades, from 35 million in 1985 to nearly 387 million in 2014 and is projected to rise to 592 million in 2035.1,2 This increase has occurred mainly in T2DM as compared to type-1 diabetes mellitus (T1DM). T1DM has few known modifiable environmental risk factors. In case of T2DM, since genetic background is unlikely to change during this short time period of few decades, the growing epidemic of T2DM is more likely due to changes in environmental factors. This increase in the prevalence of T2DM also closely parallels the global increase of obesity.3 The scope for primary prevention of T2DM is limited on the basis of current knowledge and is probably not appropriate. However, the development of prevention programs for T2DM based on elimination of environmental risk factors is possible.

The aim of this paper is to find evidence for primary prevention of T2DM based on epidemiological studies and clinical trials on the effects of lifestyle modification and drugs and the feasibility of applying these interventions in the prevention of T2DM in resource limited countries like India.
Data source and search strategy

The literature search was aimed at identifying all epidemiological studies and randomized control trials pertaining to primary prevention of T2DM. We searched online through the PubMed, Medline, EMBASE, Cochrane databases and Google Scholar search engine, using the keywords diabetes mellitus, type 2 diabetes mellitus, risk factors, primary prevention, and lifestyle modifications. We considered studies in English language only found by these search engines. Electronic searches were supplemented by hand searching of reference lists, reviews, relevant book chapters, conference abstracts, reports, organizational guidelines and specialist journals. We evaluated each paper for inclusion in this current study on the basis of the following criteria: i) study design: epidemiological studies and randomized controlled trial; ii) objective: Evidence of efficacy of preventive measures in primary prevention of T2DM. The scheme of literature search is shown in Figure 1.

Prevention of diabetes mellitus

Prevention strategies for diabetes or for any chronic disease can be broadly categorized into four stages: i) primordial prevention; ii) primary prevention; iii) secondary prevention; and iv) tertiary prevention (Figure 2).

Primordial prevention is the adaptation of strategies during the phase of normal glucose tolerance to stop the emergence of the risk factors before they have appeared. The preventive measures comprise the maintenance of normal body weight through the adoption of healthy nutritional habits and physical exercise.

Primary prevention is possible during the stage of pre-diabetes [impaired fasting glucose (IFG)/impaired glucose tolerance (IGT)], before the development of diabetes mellitus.

Secondary prevention: preventive strategies that are carried out after diabetes have been detected to prevent or delay the development of long-term complications of the disease.

Tertiary prevention: it is carried out at the stage when complications have already set in, with the aim of preventing the progression of these complications.

Rationale for preventive measures

T2DM is associated with serious health problems. It is a major risk factor for cardiovascular diseases like coronary artery disease and stroke and is also a leading
cause of blindness, kidney failure, and non-traumatic amputations. The economic burden is enormous and will continue to rise with the rising prevalence of the disease. Since there is no cure for diabetes, primary prevention, by diet and lifestyle modifications (LSM) is of paramount importance. This would result in significant reduction in social burden and economic costs.4

Feasibility of prevention

T2DM has a long asymptomatic period in natural history. There are several risk factors for the development of the disease and people with one or more of these risk factors are more prone to develop the disease than the general population. There are safe and relatively simple screening tests, which can reliably identify the high-risk groups. Moreover, there are safe and potentially effective interventions, which are shown to reduce the development of the disease.5,6

Major lifestyle risk factors for type-2 diabetes mellitus

The major risk factors responsible for T2DM are obesity, physical activity, tobacco smoking, alcohol consumption and mental stress.

Obesity is the single most important risk factor for T2DM. In a large prospective cohort study7 (Nurses’ Health study) it was shown that the most important risk factors for T2DM were overweight and obesity. The relative risks (RR) were 38.9 for a body mass index (BMI) ≥35 kg/m² and 20.1 for a BMI of 30.0 to 34.9 kg/m², as compared with a BMI <23 kg/m².

Physical activity: convincing epidemiologic data support the role of physical activity in preventing diabetes. Aerobic exercise by overweight and obese adults, results in modest weight loss, which is independent of the effect of caloric reduction through dieting.8 However, only part of the beneficial effect of physical activity on diabetes is mediated through body weight. Physical activity is clearly associated with increased insulin sensitivity.9 Further, it has been shown that sedentary behaviors such as prolonged television watching are strongly associated with obesity, weight gain, and risk of diabetes. However, this increased risk cannot entirely be explained by the decreased physical activity and unhealthy eating patterns associated with television watching.10

Smoking: several prospective studies showed that smoking modestly increases the risk of T2DM.11,12 Although smoking cessation is associated with a modest increase in weight, it increases insulin sensitivity and improves the lipoprotein profile.13 Prospective studies clearly demonstrated that the beneficial effects of smoking cessation on diabetes risk outweigh the adverse effects on weight gain.14

Alcohol: effects of alcohol consumption on the risk of development of T2DM follow a U-shaped curve. While moderate consumption is shown to be associated with lower incidence, this beneficial effect is reversed with heavy consumption.15

![Figure 2](image-url)  
Figure 2. Showing the different stages in the development and progression of type-2 diabetes mellitus and the steps for various types of preventions. Red arrow shows steady progression from euglycemic stage through pre-diabetes into clinical diabetes and subsequent complications in the natural history of type-2 diabetes mellitus. Dotted green arrows show the possible effects of interventions in the prevention or reversion of progression of this process. IFG, impaired fasting glucose; IGT, impaired glucose tolerance.
Evidence for preventability of type-2 diabetes mellitus

The evidence that T2DM is preventable comes from three major areas of research, namely from i) epidemiological, clinical trials on effect of ii) LSM and iii) drugs in development of T2DM.

Epidemiologic evidence for prevention of type-2 diabetes mellitus

Strong epidemiologic evidence indicates that diabetes is associated with lifestyle patterns of populations. People who migrate to westernized countries, with their more sedentary lifestyles and westernized diets, were shown to have greater risk of developing T2DM than do their counterparts, who remain in the native countries. Populations which have been undergoing westernization even in the absence of migration to the West, such as North American Indians and Western Samoans, also have experienced dramatic rises in obesity and T2DM. Further, population studies, which have examined multiple risk factors simultaneously, e.g., the Nurses’ Health Study have clearly defined a low-risk group for development of T2DM which are attributable to five variables: i) BMI <25 kg/m²; ii) diet high in cereal fiber and polyunsaturated fat and low in trans-fat and glycemic load; iii) engagement in moderate-to-vigorous physical activity for at least half an hour per day; iv) no current smoking; v) alcohol in moderation.

Women in low-risk group (3.4%) had a RR of diabetes of 0.09 compared to rest of cohort and 91% of the diabetics were attributed to those five factors. These data provide strong epidemiologic evidence that the majority of T2DM cases could be prevented by the adoption of a healthier lifestyle.

Clinical trials on lifestyle changes for prevention of type-2 diabetes mellitus

Clinical trials on lifestyle changes for prevention of T2DM are presented in Table 1:

Table 1. Randomized trials on diet and lifestyle in prevention of type-2 diabetes mellitus in subjects with impaired glucose tolerance.

<table>
<thead>
<tr>
<th>Study population</th>
<th>Da-Qing study (China)</th>
<th>Finnish diabetes prevention study (Finland)</th>
<th>Diabetes prevention program (USA)</th>
<th>Indian diabetes prevention program (India)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean age)</td>
<td>&gt;25 (45.0)</td>
<td>40-65 (55)</td>
<td>&gt;25 (50.6)</td>
<td>35-55 (45.9)</td>
</tr>
<tr>
<td>Interventions arms</td>
<td>Diet alone, Exercise alone, Diet + Exercise Control</td>
<td>LSM Control</td>
<td>LSM Metformin Control</td>
<td>LSM Metformin LSM+Metformin Control</td>
</tr>
<tr>
<td>Follow-up (in years)</td>
<td>6</td>
<td>3.2</td>
<td>2.8</td>
<td>3.5</td>
</tr>
</tbody>
</table>
| Outcomes

**Weight change**

- Weight loss in all groups in subjects developing diabetes; weight gain in nondiabetics in control, diet, and activity groups; weight loss in non-diabetics in diet + exercise group

- Intervention group: −4.2 kg (−4.7%) Control group: −0.8 kg (−0.9%)

- Lifestyle intervention group: −5.6 kg Metformin group: −2.1 kg Control group: −0.1 kg

**Diabetes risk reduction with intervention**

- Diet only: 31% Exercise only: 46% Diet + exercise: 42%

- Lifestyle intervention group: 58% Metformin group: 31% LSM−28.5% Metformin−26.4% LSM+ Metformin−28.2%

LSM, lifestyle modifications.
or diet plus exercise). Participants in the diet-intervention group were prescribed a diet with a specific fat content and with individual goals for cereal, vegetables, meat, milk, and oil intake. The intervention groups fared better than the controls in reducing risk of developing diabetes.

- **Diabetes Prevention Program**: 3234 persons with IGT were randomly assigned to placebo, metformin (850 mg twice daily), or a LSM program targeting ≥7% weight loss and physical activity ≥150 min/week. During the 2.8 years of follow-up, LSM reduced diabetes incidence by 58% compared to control group. LSM was equally effective in both men and women and in different ethnic groups.

- **Finnish Diabetes Prevention Study**: 522 persons with IGT were randomly assigned to either a control group or an intervention group, where subjects received counselling aimed at reducing weight, total fat intake, and saturated fat intake and increasing both intake of fiber and physical activity. The intervention resulted in an overall risk reduction of 58%.

- **Indian Diabetes Prevention Program**: 531 native Asian Indians with IGT were randomized to either: i) LSM; ii) metformin; iii) LSM plus metformin; and iv) controls. While the progression of IGT to diabetes was high, both LSM and metformin significantly reduced the incidence of diabetes in these Asian Indians with IGT but there was no added benefit from combining both.

**Drug trials for prevention of type-2 diabetes mellitus**

- **Diabetes Prevention Program**: The metformin group experienced a 31% diabetes risk reduction over a 3-year intervention period compared with the controls, although this effect was considerably smaller than that observed for the LSM group (58%).

- **Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOPNIDDM)**: In this multicenter trial in Austria, Canada, Germany, Denmark, Finland, Israel, Norway, Spain, and Sweden, 1429 subjects with IGT were randomly assigned to either an acarbose intervention or a placebo group. The intervention group had a 25% diabetes risk reduction compared with placebo.

- **Troglitazone in Prevention of Diabetes study (TRIPOD)**: 266 women with a history of gestational diabetes and at high risk of developing T2DM were randomly assigned to troglitazone treatment (400 mg/d) or placebo. During 3.5 years, treatment group resulted in a 55% lower diabetes risk compared with placebo. However, troglitazone was eventually retired on account of its associated hepato-toxicity.

- **Post-hoc analyses of drug intervention trials in cardiovascular disease**: post-hoc analyses of several drug intervention trials with cardiovascular diseases as primary outcomes suggest that antihypertensive and cholesterol-lowering medications can prevent T2DM: i) **Heart Outcomes Prevention Evaluation (HOPE) trial**: Among 5720 patients without known diabetes but with vascular disease at baseline, patients randomized to receive treatment with ramipril had a RR of 0.66 [95% confidence interval (CI): 0.51-0.85] to develop T2DM over a 4.5-year period compared with those who received placebo; ii) **West of Scotland Coronary Prevention Study (WESCOPS)**: The WESCOPS study concluded that the assignment to Pravastatin therapy resulted in a 30% reduction (P=0.042) in the hazard of becoming diabetic. However, on the contrary, other studies have concluded that pravastatin did not reduce the incidence of diabetes. Furthermore a recent meta-analysis has suggested that statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio 1.09; 95% CI: 1.02-1.17). iii) **Losartan Intervention For Endpoint reduction in hypertension study (LIFE)**: fewer hypertensive patients with left ventricular hypertrophy developed T2DM if they were treated with losartan (angiotensin II antagonist) than if they were treated with atenolol (β-blocker), (RR: 0.75, 95% CI: 0.63 to 0.88). In the post hoc analysis of the HOPE trial, ramipril was associated with a 34% reduction in the risk of new-onset diabetes (RR: 0.66; 95% CI: 0.51-0.85; P<0.001) when compared with placebo.

Analysis of the major trials has uniformly shown that drug treatments were less effective than LSM and could cause side effects. In contrast, healthy diet and LSM were effective not only in preventing diabetes but also in reducing risk of other chronic diseases such as coronary artery disease and colon cancer. Majority of the LSM intervention studies followed subjects with IGT/IGF between 3-20 years. While the western studies targeted weight reduction in obese subjects by LSM, the Asian studies had relatively leaner subjects and weight loss was not a major contributor to improved outcome of LSM.

**Dietary patterns and risk for diabetes**

High consumption of vegetables, fruits, fish, poultry, and whole grains was associated with a modest risk reduction for T2DM, whereas a Western pattern, characterized by high consumption of red meat, processed meat, French fries, high-fat dairy products, refined grains, sweets and desserts, was associated with an increased risk. In the Nurses’ Health Study, Hu et al. found that an a priori-defined pattern score based on the intake of cereal fiber, polyunsaturated fatty acids, trans-fatty acids, and glycemic load had a tremendous effect on diabetes incidence. Women within the highest quintile of the pattern score
had a RR of 0.49 (95% CI: 0.42-0.56) compared with women in the lowest quintile.

**Translation of diabetes prevention into community practice**

Wide gap exists between scientific knowledge derived from research and its practical application. A broad-based public health perspective is needed to control the diabetes epidemic. The Centers for Disease Control and Prevention (CDC)-led National Diabetes Prevention Program (NDPP) is an evidence-based lifestyle change program for preventing T2DM,\(^ {41}\) based on the results of the DPP.\(^ {26}\) This year-long program helps participants make real lifestyle changes such as eating healthier, incorporating physical activity into their daily lives, and improving problem-solving and coping skills.

**Feasibility of prevention programs**

Follow up of the patients of the DPP program\(^ {26}\) showed that the incidence of T2DM was reduced by 58% with LSM and 31% with metformin in 2.8-year follow up. On 10-year follow-up\(^ {42}\) the original LSM group maintained a reduced risk for diabetes by 34%.\(^ {42}\) Individuals >60 years were more successful, showing a decreased risk of progression to diabetes by 49%.\(^ {42}\) Although results were groundbreaking, cost of intensive individual counseling model in LSM group was high ($1400/participant).\(^ {43}\) However, these results could be replicated at a much lower cost in a community-based group setting in the YMCA-DEPLOY study (Y-DPP), thereby reducing costs to $275-325 per participant.\(^ {44}\) Although it was subsequently taken up by CDC as the NDPP, it could cover only a fraction of the 85-90 million pre-diabetics of USA.

In contrast to western population, in Asian Indians progression rate of IGT to diabetes was very high: 18.3% per year with a cumulative incidence of 55.0% in 3 years, as compared to Europeans (Finnish - 6%; US - 11/person-years) and Chinese (11.3%).\(^ {29}\) Weight reduction was not a major determinant of benefit and the subjects were mostly lean with high insulin resistance (IR).\(^ {45}\) Nevertheless, subjects with high IR and low BMI also benefited from LSM.\(^ {36,47}\)

In India, the estimated treatment cost of diabetes is $ 140-150/person/year.\(^ {39}\) Prevention or delay in diabetes by LSM would result in a net gain in healthcare investments.\(^ {48}\) It is necessary to develop pragmatic, cost effective strategies for primary prevention to extend the benefits in community. Recent studies using information technology such as mobile phone-based SMS were tested for this purpose.\(^ {49}\) In a recent 2-year program in India, effectiveness of SMS in educating and motivating men with IGT to follow LSM was demonstrated and was found to be highly effective with a relative risk reduction of 36% compared to the participants who had only standard care.\(^ {30}\) Future plan should focus on health education of the public, improving the national capacity to detect and manage non-communicable diseases and development of innovative, cost effective, and scalable methodologies.\(^ {38}\) Examples of national programs like the Finnish DEKHO\(^ {50}\) and in Singapore\(^ {51}\) should be taken as model endeavors to formulate strategies to promote and implement community health programs.

**Conclusions**

Prevalence of diabetes has increased manifold worldwide during past few decades; the increase occurring mainly in T2DM compared to T1DM, is more likely due to changes in environmental risk factors. Epidemiologic studies, LSM and medications have conclusively proved that primary prevention, targeted during the stage of pre-diabetes prevents and/or delays the onset of diabetes. The positive effects are more profound and safer with LSM as compared to medications. This is shown to be effective globally, across various ethnicities and races, and sustainable on long-term follow-up. However, these interventions are expensive, even according to the western standards. Similar results have been shown to be replicated at much lower cost in community-based settings in USA but it could cover only a fraction of pre-diabetics of the country. Similar low-cost community based programs of primary prevention are essential for developing countries like India where the burden of diabetes is much higher.

**References**


41. Centers for Disease Control and Prevention (CDC). Na-