Naik et al. Int J Diabetes Clin Res 2015, 2:6
ISSN: 2377-3634

International Journal of
Diabetes and Clinical Research

Review Article: Open Access

Evidence Based Prevention of Type 2 Diabetes: Role of Lifestyle Intervention as Compared to Pharmacological Agents

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Abstract

Background: The global epidemic of type 2 Diabetes Mellitus (T2DM) presents significant challenges to world health both in terms of financial costs as well as morbidity. Thus, considerable research has been focussed on the prevention or delay of the onset of T2DM.

Aim: The aim of this article is to review published studies that evaluate lifestyle and pharmacological interventions aimed at preventing T2DM and to compare both these interventions.

Methods: We undertook an electronic search of MEDLINE, PubMed, EMBASE and Cochrane Register of Controlled Trials, with the English language restriction and published until May 2015. Five major diabetes prevention trials using lifestyle intervention (LSI) and five using pharmacological intervention were identified.

We reviewed the study design, key components, and outcomes for each study aimed to delay T2DM.

Results: Both LSI and pharmacological intervention were found to be effective to reduce the risk of developing T2DM in at risk population. LSI with modest goals of weight loss and physical activity is safe, cost saving and prevents or delays the onset of diabetes, even after discontinuation of the treatment providing long term benefits. A Considerable effort from well-trained, multidisciplinary staff is needed to achieve these modest goals. For patients who are unable to achieve the lifestyle goals or those who progress to T2DM despite being on LSI, pharmacological intervention has shown to be effective, especially in younger obese patients. Adverse effects with pharmacological intervention were common.

Conclusion: Strong evidence exists for the prevention or delay of type 2 diabetes through lifestyle and pharmacological intervention. LSI with weight loss and increased physical activity are safe, cost-effective and are currently recommended for the prevention of diabetes.

Keywords

Type 2 Diabetes Mellitus, Prevention, Lifestyle management, Pharmacotherapy, Cost effectiveness.

Introduction

Type 2 Diabetes Mellitus (T2DM) is one of the most costly and burdensome of chronic diseases and is a global epidemic. Estimates by the International Diabetes Federation indicate that 387 million people have diabetes, and that this figure is expected to rise to 592 million by 2035 with an additional 175 million cases currently undiagnosed [1].

Individuals with T2DM are at a significantly higher risk of co-morbidities particularly cardiovascular disease (CVD) [2,3]. Additionally, pre-diabetes independently increases the risk of CVD and death [4]. Furthermore, micro vascular disease is already present in many individuals with undiagnosed or newly diagnosed T2DM. The onset of retinopathy has been observed to occur around 4-7 years before a clinical diagnosis of diabetes [5].

The considerable economic burden of diabetes is shared by patients and countries (developed and developing). It is estimated that subjects with diabetes account for an average of nearly $85,500 in treatment costs over their lifetime [6]. Thus, the focus of recent research is toward prevention or delaying the onset of T2DM.

Candidates for prevention of T2dm

The focus of diabetes prevention is mainly recommended for individuals at high-risk of developing diabetes, particularly those with Impaired Glucose Tolerance (IGT) or Impaired Fasting Glucose (IFG). In fact, the National Institute for Health and Care Excellence guidelines [7] recommends risk assessment to be done using validated tools for all eligible adults aged 40 and above, except pregnant women; people aged 25-39 years of South Asian, Chinese, African-Caribbean, black African and other high-risk black and minority ethnic groups, except pregnant women; and adults with conditions that increase the risk of type 2 diabetes.

Those at high-risk on risk scoring should undergo venous blood tests (fasting plasma glucose (FPG) or HbA1c). A FPG of 5.5-6.9 mmol/L or HbA1c level of 42-47 mmol/mol (6.0-6.4%) indicates high risk [7].

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Citation: Naik V, Dave R, Stephens JW, Davies JS (2015) Evidence Based Prevention of Type 2 Diabetes: Role of Lifestyle Intervention as Compared to Pharmacological Agents. Int J Diabetes Clin Res 2:049

Received: November 03, 2015: **Accepted:** December 04, 2015: **Published:** December 08, 2015

Table 1: Lifestyle Intervention Studies

Study	Features and duration	Intervention	Objective	Primary Outcome	Reduction in Incidence of diabetes
Da Qing [8,9]	577 Subjects identified to have IGT using the WHO Criteria 20 yrs with first analysis at 6 years	The subjects were **randomised into 4 groups** • Control • Diet only • Exercise only • Diet and exercise Those with BMI > 25 Kg/m^2 to reduce calorie intake to lose weight to goal of BMI < 23 Kg/m^2. Those with BMI < 25 Kg/m^2, to eat more vegetables, limit sugar and alcohol.	To study whether diet and exercise interventions delayed the onset of NIDDM in an IGT population	Group-based lifestyle interventions over 6 years can prevent or delay diabetes for up to 14 years after the active intervention	Diet only group:33% (P < 0.03) exercise-only group 47% (P < 0.0005) 38% in the diet-plus-exercise group
IDDP [12]	531 subjects identified to have IGT using the WHO Criteria 3 years	The subjects were **randomised into 4 groups** • Control • Life Style Modifications • Metformin only • Life Style Modifications and Metformin	To study whether the progression of IGT to diabetes could be delayed in Indian population. The study population was younger leaner and more insulin resistant than the population studied in the Chinese, Finnish and the American population in whom the interventions were a success.	It is possible to prevent diabetes in native Asian Indian subjects with IGT using lifestyle modification, despite their relatively low BMI and highly insulin-resistant characteristics	Relative Risk Reduction in incidence of diabetes as compared to control: LSM: 28.5% Metformin: 26.4% LSM + Metformin: 28.2%
FDPS [10]	522 overweight subjects with IGT using the WHO criteria 3.2 years	The subjects were **randomised into 2 groups** Control Lifestyle Goal was of weight loss > 5%, decreased SFA intake, fibre intake of > 15 g/1000 kcal and > 30 min/day of moderate PA.	Whether type 2 diabetes can be prevented by interventions that affect the lifestyles of subjects at high risk for the disease	Primary prevention of type 2 diabetes by a non-pharmacologic intervention which can be implemented in a primary health care setting.	The overall incidence of diabetes was reduced by 58%
Swedish Malmo feasibility Study [13]	41 subjects with early type 2 diabetes and 181 subjects with IGT 6 years	The subjects were **randomised into 2 groups** Control Life Style Modification	To test the feasibility aspect of long-term intervention with an emphasis on life-style changes.	Improvement in glucose tolerance was correlated to weight reduction and increased fitness	Incidence of diabetes: Reference group: 29% Intervention group: 11% The incidence in the intervention group was less than half that of the other group.

Abbreviations: BMI: Body Mass Index, PA: Physical Activity, SFA: Saturated Fatty Acids

Methods

Source articles were identified in PubMed Central (including MEDLINE); EMBASE; Cochrane Central Register of Controlled Trials (CENTRAL), up to May 2015. We searched the English language literature using the keywords: impaired glucose tolerance, type 2 diabetes prevention, lifestyle intervention, pharmacological intervention. Primary focus was on large scale outcome trials, which are generally considered the best to guide evidence-based decisions; in addition, specific emphasis was placed on studies having a follow-up time period of at least 2 years, allowing assessment of the durability of any treatment effect and more complete safety evaluation. Five prevention studies utilizing lifestyle changes (Da Qing [8,9], FDPS: Finnish Diabetes Prevention Study [10] , USDPP: United States Diabetes Prevention Program [11], IDPP: Indian Diabetes Prevention Program [12] and Swedish Malmo Study [13]), and five utilizing pharmacological agents to prevent diabetes (USDPP: Unites States Diabetes Prevention Program [11]; DREAM: Diabetes Reduction Assessment with ramipril and rosiglitazone medication [14]; NAVIGATOR: Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research trial [15]; ORIGIN: Outcome Reduction with Initial Glargine Intervention [16] and, STOP-NIDDM: Study to Prevent Non-insulin-dependent Diabetes Mellitus) [17,18] were identified.

Approach to prevention of T2dm

Two major approaches are adopted for prevention of T2DM:

1. Lifestyle Intervention (LSI)

2. Pharmacological Interventions

Evidence of lifestyle interventions: LSI is a comprehensive approach to correct several risk factors for T2DM in those at risk.

The targets for LSI in the FDPS study were: (i) Weight loss more than 5% (ii) To reduce the intake of fat to less than 30% of total energy intake, and that of saturated fats to less than 10% of total energy (iii) To increase of dietary fibres to more or equal 15 gram per 1000 kilocalorie, and (iv) To increase the level of physical activity to at least 150 minutes per week [10].

Table 1 illustrates the major studies conducted comparing LSI and pharmacotherapy. Relevant and significant findings have been listed in table 2.

The LSI interventions have been observed to be successful in preventing or delaying the onset of T2DM in high risk individuals. Findings of the Da Qing study suggest that LSI interventions continue to prove beneficial for a long time [8,9]. A reduction in the incidence of diabetes observed during the active phase continued for 14 years post active intervention. The authors conclude that in absence of active intervention the risk of developing diabetes remains high in this population. This reflects the challenges of maintaining patients on LSI over prolonged periods of time [8,9].

Interestingly the Indian Diabetes Prevention Program (IDDP) study [12] found that the rate of progression of diabetes in high-risk individuals of Indian origin was much faster compared to other populations. It was suggested that small doses of metformin be used prophylactically in order to slow the progression of IGT to T2DM

as the effects of LSI and metformin intervention were the same [12]. This finding is applicable only to the Indian population which may be important in the overall approach of care in real settings.

The United States Diabetes Prevention Program (USDPP) study describes use of LSI mediated weight reduction to be effective across age, gender, racial and ethnic groups [11,19] while the Finnish Diabetes Prevention Study (FDPS) documented an overall reduction in the incidence of diabetes by 58% suggesting that primary prevention of T2DM is possible in the primary care setting using non pharmacologic interventions [10,20]. The Swedish Malmo study not only documented normalised glucose tolerance in the intervention group but also documented a reduction in blood pressure, lipids and hyperinsulinemia. These metabolic benefits were correlated with weight reduction and increased fitness. The Swedish Malmo study included subjects with early diabetes. More than 50% subjects with diabetes were in remission at the 6 year follow-up, showing the LSI benefits carry on for a significant duration in patients with existing diabetes as well and may be used to reverse diabetes in early diagnosis [13,21].

The LSI benefits seem to long lasting across varied populations, gender and age. They not only reduce the incidence of diabetes but also seem to delay and prevent in onset of diabetes while being cost effective and can be used easily in primary health care setting. The real challenge is however to achieve compliance and keep the subjects motivated enough to continue following the rigorous regime.

Evidence for pharmacological interventions in prevention of T2DM: Pharmacological therapies have also been proven to be effective in preventing or delaying the onset of T2DM (Table 3). The risk reduction in diabetes is the most evident with rosiglitazone (62% risk reduction), followed by metformin (31%), insulin glargine (30%), acarbose (25%) valsartan (14%), Nateglinide (0%) [22]. Reduction in CVD outcomes were studied in Study to Prevent NIDDM (STOP-NIDDM) study and was reported to be lowered by 49% [17,18]. One should be cautious given the differing glucose and cardiovascular end-point criteria, as well as adverse effect profile (Table 4) [22]. It is important that the risk benefit ratio of every treatment option and modality is weighed before initiation.

Other notable studies

The Troglitazone in Prevention of Diabetes (TRIPOD) study randomised 266 Hispanic women with prior gestational diabetes to troglitazone or placebo [23]. The study showed a reduction in T2DM incidence of > 50% after 1.5 years in the troglitazone group. However, troglitazone was withdrawn in 2000 due to reports of fatal liver toxicity.

The XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study compared orlistat to LSI [24]. It was a multicentre, randomized, double blind, placebo-controlled parallel group prospective study performed in Sweden over a period of 4 years, and showed that patients with IGT showed a significant reduction of progression to diabetes of 18.8% in the orlistat group, compared to 28.8% in the placebo group ($p < 0.005$), along with a favourable and sustainable cardio-metabolic risk profile. Gastrointestinal adverse effects, such as steatorrhoea, faecal incontinence and frequent bowel movements were commonly reported.

Comparison: lifestyle or medication?

Table 5 compares the diabetes and CVD risk reduction observed in studies of lifestyle and pharmacological intervention. As shown, both LSI and pharmacological agents show short-term risk reduction in incidence of diabetes. However, none of the studies using pharmacological agents have been able to demonstrate a continued reduction in diabetes risk after drug discontinuation. On the other hand, results from the follow-up of LSI studies reveal that LSI was successful in reducing diabetes incidence even after several years of follow up without any active intervention [8,25] LSI was also associated with reduction in the CVD mortality [8,20] not seen with pharmacological agents.

Table 2: Conclusions of lifestyle intervention studies

Name of study	Other Relevant Findings
Da Qing [8] (20 yrs follow up)	• The reduction in diabetes incidence seen during the 6-year period of active intervention persisted for two decades. • Participants with impaired glucose tolerance randomised to lifestyle intervention groups had a 43% lower diabetes incidence for up to 14 years after the active intervention ceased, and diabetes onset was delayed an average of 3.6 years. • The risk of eventually developing diabetes in people with impaired glucose tolerance in the absence of intervention remains high for many years, since 93% of the controls developed diabetes over 20 years
IDDP [12]	• The rate of progression in the Indian subjects was much higher that other populations in whom similar studies have been conducted. The rates in the Indian population were found to be 18.3%/year as opposed to 6%/year in the Finnish study. • Metformin in doses as low as 500mg/day effectively reduced the progression of IGT to Diabetes in Indian populations • In Indian Populations effectiveness of LSM and metformin were found to be similar whereas in all other populations LSM was found to be a superior intervention
US DPP [11,19]	• 50% of the participants in the lifestyle intervention group achieved the goal of weight loss of 7% or more by the end of the 24 weeks,and 74% met the goal of at least 150 minutes of physical activity per week. The daily energy intake decreased by a mean of 249 ± 27 kcal in the placebo group, 296 ± 23 kcal in the metformin group, and 450 ± 26 kcal in the lifestyle-intervention group ($P < 0.001$). • The participants assigned to the lifestyle intervention had much greater weight loss and a greater increase in leisure physical activity than did participants assigned to receive metformin or placebo. The average weight loss was 0.1, 2.1, and 5.6 kg in the placebo, metformin, and lifestyle-intervention groups, respectively ($P < 0.001$). • The effects of reduction in the incidence of diabetes were similar in men and women and in all racial and ethnic groups. The intensive lifestyle intervention was at least as effective in older participants as it was in younger participants. • These findings suggest that dietary composition and physical activity are important in diabetes prevention, but their effect on diabetes risk is primarily mediated through resulting weight reduction [23].
FDPS [10,20]	• The mean (± SD) amount of weight lost between base line and the end of year 1 was 4.2 ± 5.1 kg in the intervention group and 0.8 ± 3.7 kg in the control group; the net loss by the end of year 2 was 3.5 ± 5.5 kg in the intervention group and 0.8 ± 4.4 kg in the control group. • Weight change was significantly associated with the achievement of each of the four lifestyle goals, consequently, success score was strongly and inversely correlated with weight reduction [24].
Swedish Malmo Feasibility Study [13,21]	• There was significant weight loss in the intervention group: body weight was reduced by 2.3-3.7%. Weight increased in the reference group by 0.5-1.7% ($p < 0.0001$). • In > 50% of the participants' glucose tolerance was normalized. • At the end of the study, (95% CI 0.3-1.0). • In the intervention group, after completing the trial, blood pressure, lipids, and hyperinsulinaemia were reduced. • More than 50% of the diabetic patients were in remission at 6-year follow-up.

Table 3: Pharmacologic interventions for the prevention of diabetes [22]

Studies/ Pharmacologic Intervention(s)	DPP [11] (n = 3234)	STOP-NIDDM5, [17,18] (n = 1429) Acarbose	DREAM [14] (n = 5269) Rosiglitazone, Ramipril	NAVIGATOR [15] (n = 9306) Nateglinide, Valsartan	ORIGIN [16] (n = 12537) Insulin Glargine
Eligible participants	IGT (a plasma glucose concentration of 95-125 mg/dl (5.3-6.9 mmol/l) in the fasting state and 140-200 mg/dl (7.8-11.1 mmol/l) 2 h after a 75 g oral glucose load)	IGT (2-h plasma glucose concentration between 140 and 200 mg/dl (7.8-11.1 mmol/l) after a 75 g glucose load and a fasting plasma glucose concentration between 101 and 140 mg/dl; 5.65-7.8mmol/l)	IGT (fasting plasma glucose concentration < 126 mg/dl (7.0 mmol/l) and 2-h plasma glucose concentration between 140 mg/dl (7.8 mmol/l) and 200 mg/dl; 11.1 mmol/l) and/or IFG (fasting) plasma glucose concentration between 110 (6.1 mmol/l) and 126 mg/dl (7.0 mmol/l) and 2-h plasma glucose concentration < 200 mg/dl (11.1 mmol/l) during OGTT) without known CVD or renal insufficiency	IGT (defined as 2-h plasma glucose concentration between 140 and 200 mg/dl (7.8 and 11.1 mmol/l) after a 75 g glucose load and a fasting plasma glucose concentration between 95 and 126 mg/dl; 5.3 and 7.0 mmol/l) and established cardiovascular disease or cardiovascular risk factors	Subjects with a prior CV event; angina+documented ischaemia; albuminuria; left ventricular hypertrophy; angiographic evidence of > 50% stenosis of a coronary, carotid or lower extremity artery; or an ankle/brachial index < 0.9 were recruited if they also had a history of type 2 diabetes that was stable on 0 or 1 oral glucose lowering agents; or IFG, IGT or newly detected diabetes based on either a FPG ≥ 6.1 mmol/l [110 mg/dl] or a 2h plasma glucose ≥ 7.8 mmol/l [140 mg/dl] after a 75 g oral glucose load
Mean age(yrs)	51	54	55	64	63.5
BMI (kg/m²)	34	31	31	Nateglinide:31 Valsartan: 30	Insulin glargine: 29.8 Placebo: 29.9
Primary outcome	Incident diabetes diagnosed with annual OGTT or semiannual fasting plasma glucose test	Incident diabetes diagnosed on an annual OGTT	Incident diabetes (OGTT performed at year 2 and study end, FPG collected annually) or all-cause mortality	Incident diabetes (FPG semi-annually for 3 year, then annually; annual OGTTs), extended and core CV outcomes	CV end-points
Median follow-up for incident of diabetes (years)	2.8	3.3	3.0	5.0	6.2
Risk reduction of diabetes progression (%)	31%	25%	Rosiglitazone:62% Ramipril: no effect	Nateglinide: no effect Valsartan: 14%	30%
Risk reduction of CVD	Not measured	49% reduction in CV events	No	No	No
Definition of diabetes	FPG ≥ 126 mg/ dl (7.0 mmol/l) or 2 hr ≥ 200 mg/dl (11.1 mmol/l)	2h ≥ 200 mg/dl (11.1 mmol/l)	FPG ≥ 126 mg/dl (7.0 mmol/l) or 2 h ≥ 200 mg/dl (11.1 mmol/l), confirmed by a second test or physician diagnosed diabetes supported by prescription of an antidiabetic agent and confirmatory testing	FPG ≥ 126 mg/dl (7.0 mmol/l) or 2 h ≥ 200 mg/dl (11.1 mmol/l), confirmed by a second test	Either 1. Two consecutive FPG levels within a 4-month period > 126 mg/dl (7.0 mmol/l); 2. a diagnosis of diabetes made by a physician (a), plus use of a pharmacologic antidiabetic agent (b), plus evidence of a FPG of ≥ 126 mg/ dl (7.0 mmol/l), or any blood glucose ≥ 200 mg/dl (11.1 mmol/l) OR 3. evidence (a) of at least one capillary glucose ≥ 200 mg/dl (11.1 mmol/l) confirmed by FPG ≥ 126 mg/dl (7.0 mmol/l) or (b) of a random glucose ≥ 200 mg/dl (11.1 mmol/l) FPG ≥ 126 mg/dl (7.0 mmol/l) OR 2 h plasma glucose > 200 mg/dl; 11.1 mmol/l) during either the 1st or 2nd OGTT after the end of usual follow-up
Most common or important adverse event	Gastrointestinal symptoms	Gastrointestinal symptoms	Rosiglitazone: edema, weight gain and non-fatal congestive heart failure Ramipril: cough	Nateglinide: hypoglycaemia Valsartan: hypotension-related adverse events	Hypoglycaemia, weight gain

Abbreviations: BMI: Body mass index, DREAM: Diabetes REduction Assessment with ramipril and rosiglitazone Medication, DPP: Diabetes Prevention Program, FPG: Fasting plasma glucose, IGT: Impaired glucose tolerance, IFG: Impaired fasting glucose, NAVIGATOR: Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research trial, ORIGIN: Outcome Reduction with Initial Glargine Intervention, OGTT: Oral glucose tolerance test, OR: Odds ratio, STOP-NIDDM: Study to Prevent Non-insulin-dependent Diabetes Mellitus.

Table 4: Qualitative summary of effect of pharmacologic agents studied for diabetes prevention [22]

Pharmacologic agent	Diabetes incidence	Cardiovascular disease	Cancer	Fracture	Other
Metformin	↓	↓	↓	-	GI Events
Acarbose	↓	↓	-	-	GI Events
Rosiglitazone	↓	↑	-	↑	↑Non-fatal congestive heart failure, weight gain and edema
Nateglinide	No effect	No effect	-	-	
Ramipril	No effect	↓	No effect	-	
Valsartan	↓	↓	No effect	-	
Insulin	↓	No effect	No effect	No effect	↑Hypoglycaemia ↑ Body weight

Table 5: Comparison of Studies of Lifestyle Intervention vs Pharmacological Agents

Study	Intervention	N	Duration (yrs)	Risk Reduction (%)	Follow up time(yrs)	Follow up risk reduction(%)	CVD events/Total mortality reduction (%)
Lifestyle Intervention studies							
Da Qing [8,9]	Diet	130	6	**31**	20	43	2/4
	Exercise	141		**46**			
	Diet and Exercise	126		**42**			
	Control	133					
DPS Finland [10,20]	Diet and Physical Activity	265	3.2	**58**	7	43	4/43
	Control	257					
DPP US [11]	Diet and Physical activity	1079	2.8	**58**	10	34	No Data
	Metformin	1073		**31**			
	Placebo	1082					
Pharmacological Intervention studies							
DPP US [11]	Metformin	1073	2.8	**31**	10	18	No Data
TRIPOD [23]	Troglitazone	236	2.5	**55**			
STOP-NIDDM [17,18]	Acarbose	1368	3.2	**36**	NA	NA	49
DREAM [14]	Rosiglitazone	5269	3.0	**60**	NA	NA	No Data
XENDOS [24]	Orlistat	3305	4.0	**37**	NA	NA	No Data

Cost effectiveness

The DPP investigators analyzed the cost per quality-adjusted life year (QALY), comparing the lifestyle and metformin interventions to placebo. The cost per QALY for the LSI was approximately $1,100 compared to $31,300 for the metformin intervention [26]. Hence LSI was not only the most effective treatment for diabetes prevention, but also the most cost-efficient. They also concluded that both DPP interventions would be cost-effective from societal and health system perspectives.

The follow-up data from the Finnish DPS shows that after the intensive lifestyle intervention that was provided to the intensive intervention group for 4 years, additional benefits in terms of a lower risk of T2DM were still obtained during at least 3 years without any effort from health personnel [27]. This will improve the long-term cost-effectiveness estimates markedly. With pharmacologic intervention, such long-term effects after stopping the treatment are unlikely, and if treatment is continued for the long term, it will require efforts from health care providers in addition to the cost of the drug itself. Table 6 illustrates the various studies that analysed the cost-effectiveness of T2DM prevention [28].

Discussion

The available reported evidence suggests that there is much greater benefit for LSI as compared to pharmacological agents. LSI is cost saving and appears to be very safe as no untoward effects of LSI were noted in either the Finnish [10] or DPP study [11]. Both the Finnish study and the DPP reduced the magnitude of some CVD risk factors, suggesting that LSI may have additional health benefits.

Drug therapy to prevent or delay diabetes appears to be much less beneficial for a variety of reasons [29]. (i) As shown in the DPP, metformin was half as effective as lifestyle modifications (31% vs 58%) in prevention of diabetes. The advantage of lifestyle modification was even greater in older or less overweight patients. The relative risk reduction using acarbose (36%) appears similar to that of metformin. (ii) All glucose-lowering drugs require monitoring, have been associated with significant adverse side effects, and are contraindicated in some individuals. (iii) Most of the hypoglycemic agents available have not been studied with regard to protection against CVD or have any other clinical benefit to non diabetic individuals. (iv) Medications used for delaying the onset of diabetes are already used for treatment of diabetes. Prescribing such medications will increase a patient's total years of drug exposure and may increase the likelihood of untoward drug effects.

None of the pharmacological agent has been able to show a durable effect after discontinuation. This highlights that these medications simply delays the diagnosis of diabetes rather than alter the underlying pathophysiology and begs the question: Are we treating early T2DM or are we preventing it?

In contrast, the lifestyle interventions appeared to prevent or delay the onset of diabetes, even after discontinuation of therapy, as shown in the follow-up studies (34% Risk Reduction (RR) in DPP and 43% RR in Da Quing study).

It is also necessary to bear in mind the limitations associated with the studies included in the review. One of the main limitations of the studies was a high or unclear risk of bias largely due to inability to blind patients in the treatment group and lack of consistency and precision among studies. This led to low or insufficient strength evidence for most outcomes.

Another limitation includes the group of patients that were identified as being at increased risk for diabetes. This is a controversial area, with various definitions and diagnostic cut points having been proposed over the past few years [30]. Furthermore, there is no evidence of benefit in all-cause mortality and insufficient evidence to suggest benefit on cardiovascular and microvascular outcomes (a non-significant 17% reduction in CVD mortality, in the Finnish study) [10]. Improvement was seen for some secondary outcomes, but it generally did not persist beyond the intervention phase, and the clinical significance is unclear.

Even though the lifestyle goals set were modest, and the participants were already motivated, there was only partial success in achieving the desired objectives. In the Finnish study, only 43% achieved the weight reduction goal, and 36% of subjects increased their physical activity [10]. In the DPP, only 50% reached the weight-loss goal, and 74% reached the exercise goal [11]. In both studies, some weight was regained despite the continuation of intensive strategies.

Another potential limitation is the interpretation of the LSI achievements beyond the confines of a trial. Although in the LSI studies, diabetes could be delayed or prevented with only modest changes in weight and activity, considerable effort from well-trained staff was needed to achieve these behavioural changes. A multidisciplinary care team consisting of nurses, clinicians, dietitians, psychologist, physiotherapists and health educators is needed. The prevention programs have to be culturally adaptive for office-based counselling which may be challenging in diverse communities.

Table 6: Summary of Published Cost-Effectiveness Analyses [28]

Study and setting(s)	Year of Costs	Methods	Findings
Sweden [32]	2003 (SEK)	Within trial cost-effectiveness analysis of acarbose, based on STOP-NIDDM, 40 month time horizon, projected total direct costs based on progression to T2DM or cardiovascular disease.	Acarbose dominant to placebo for high risk groups.
Canada [33]	2000 ($CD)	Markov model based on DPP, DPS and STOP-NIDDM, projected LE, diabetes-free years, and total direct lifetime costs, 10 year time horizon.	Acarbose and metformin dominant versus control, ILC cost-effective to control (ICER $749 per life year gained)
USA [11]	2000 ($US)	Within trial cost-effectiveness of DPP interventions (3 years), direct and indirect costs, extensive sensitivity analyses.	ILC cost-effective versus placebo. Significant improvements in economic benefits if implementation costs reduced.
USA [26]	2000 ($US)	Markov model, DPP and UKPDS data adapted to US setting, projected LE, QALE and total direct medical costs, lifetime time horizon, healthcare payer and societal perspectives taken.	ILC dominant versus metformin, metformin not cost-effective for over 65 years of age, outcomes sensitive to the pricing of treatments.
Australia, [34] France, Germany, Switzerland, UK	2002 (€)	Markov model, based on DPP, projected LE, years free of diabetes and total direct costs, lifetime time horizon, extensive sensitivity analyses and sub-group analyses on age and BMI.	ILC and metformin dominant versus control except UK (ICER €6,381 and 5,400 per life year gained, respectively)
Italy[35]	2004 (€)	Markov model, based on DPP, adapted to italian setting, projected LE,years free of diabetes and total direct costs,lifetime time horizon.	ILC and metformin cost effective vs control (ICER € 11,234 and 11,556 per life year gained,respectively)
Spain [36]	2004 (€)	Markov model, based on DPP, adapted to Spanish setting, projected LE, years free of diabetes and total direct costs, lifetime time horizon.	Metformin cost-effective versus control (ICER €5,080 per life year gained), IILC costs prohibitive due to personnel costs.
USA [37]	2005 ($US)	Archimedes model, based on ILC intervention from DPP, projected LE, total direct costs, 30 year time horizon.	ICER $62,602 and $35,523 for ILC and metformin versus control, respectively.

Abbreviations: ILC: Intensive Lifestyle Change, LE: life expectancy, QALE: Quality-Adjusted Life Expectancy, ICER: Incremental Cost-Effectiveness Ratio

Conclusion

Recent studies have convincingly shown that lifestyle modification is the most effective tool in the prevention or delay of T2DM. A modest weight-loss goal of 5-10% and moderate-intensity physical activity such as brisk walking for at least 150 minutes per week plays an important role in reducing diabetes risk [31].

For patients who are unable to achieve the lifestyle goals or those who progress to T2DM despite being on LSI, metformin has also been proven effective, especially in younger obese patients. Acarbose may also confer a moderate risk reduction. The reports of cardiovascular and fracture risk make thiazolidinediones less attractive as a prevention strategy. However, none of these medications are as effective in diabetes prevention as the lifestyle intervention strategies, and cost-effectiveness analyses suggest that pharmacotherapy may have greater financial costs.

Acknowledgements

- University of South Wales
- Caroline McPhillips
- Dudu Ndebele
- Gaafar Abdalla
- Hisham Seid Ahmed
- Julien Charles
- Mohamed Alsohli
- Obaid Reedy

Sairabanu Sokwalla

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