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PREVENTION OR DELAY OF TYPE 2 DIABETES BY PHARMACOLOGICAL OR LIFESTYLE INTERVENTIONS

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SUMMARY

The purpose of this essay is to review available evidence on lifestyle, pharmacological and herbal remedies influence on the prevention or delay of the onset of type 2 diabetes and adapting these lessons from clinical trials to clinical practice. A Medline literature search from 1997-2006 was performed to identify articles on the prevention or delay of type 2 diabetes in adults. The limits were practical guidelines, systematic reviews, randomized controlled trials (meta-analyses), as full text articles or abstracts, and with no limits for the period searched. Different trials and systematic reviews have revealed that pharmacological and lifestyle interventions can reduce the rate of progression to type 2 diabetes in people with impaired glucose tolerance. The overall goal for diabetes prevention is to reach and maintain an active, healthy weight with a tendency toward a hypo-caloric diet. Pharmacological interventions also reduced diabetes risk. However, lifestyle changes were

more effective and are recommended as first-line strategy. For pharmacological interventions adverse effects need to be fully understood to enable the potential harms and benefits to be assessed. Therefore, better approach to patients for lifestyle changes should be achieved through a structured program in order to delay or prevent type 2 diabetes. Multidisciplinary healthcare teams may provide more intensive counseling and increase the contact the patient has with the overall healthcare system.

INTRODUCTION

The incidence of type 2 diabetes mellitus is increasing worldwide. Type 2 diabetes results from the interaction between genetic predisposition, and behavioral and environmental risk factors (1). While the genetic basis of type 2 diabetes has yet to be identified, there is strong evidence that modifiable risk factors such as obesity and physical inactivity are the main non-genetic determinants of the disease (2-4). The prevalence of diabetes for all age groups worldwide was 2.8% in 2000 and has been estimated to be 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 (5). Individuals with diabetes

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have a life expectancy that can be shortened by as much as 15 years, with up to 75% of deaths from macrovascular complications (6).

Impaired glucose tolerance (IGT) is an intermediate category between normal glucose tolerance and overt diabetes (7,8), and it can be identified by glucose tolerance test. Subjects with IGT have an increased risk of type 2 diabetes (9), and consequently many trials of interventions for the prevention of type 2 diabetes have focused on such individuals. By 2025, the number of people with IGT is projected to increase to 418 million, or 8.1% of the adult population (10).

Interventions to delay or even to prevent type 2 diabetes have a potential to improve the health of the population and reduce the burden of healthcare costs. The interventions assessed have been diverse and include pharmacological, lifestyle, and herbal remedies. Several current reviews have been carried out on the prevention of type 2 diabetes (4,11-13), covering different aspects such as pharmacological interventions or the effects of weight loss.

The purpose of this paper is to review available evidence on lifestyle, pharmacological and herbal remedies on the prevention or delay of the onset of type 2 diabetes and adapting these lessons from clinical trials to clinical practice.

METHODS

A Medline literature search for the 1997-2006 period was performed to identify articles about the prevention or delay of type 2 diabetes in adults. The key phrases included were: impaired glucose tolerance, type 2 diabetes prevention, lifestyle intervention, pharmacological prevention, nutrition and exercise, and combinations thereof. References of relevant articles were searched as well. The limits were practice guidelines, systematic reviews, randomized controlled trials, meta-analyses, as full text articles or abstracts, with no limits for the period searched.

RESULTS AND DISCUSSION

Impaired insulin secretion with relative and subsequently absolute insulin deficiency with or without insulin resistance is the pathophysiological basis for the development of type 2 diabetes. The best-known predictor of incident diabetes is the presence of insulin resistance. Direct measures of insulin sensitivity can be laborious, complicated, and expensive to be applicable for routine use in the general population as a screening tool. Markers like HOMA-IR index or 2-hour post-challenge glucose levels are being used. Abnormal glucose tolerance is also a well-known risk factor of incident diabetes (14).

Impaired glucose tolerance and risk of diabetes

IGT when compared to impaired fasting glucose (IFG) is a stronger risk factor in predicting the onset of diabetes. Diagnosing of IGT requires oral glucose tolerance test (OGTT), a test of high specificity (92%) but low sensitivity (52%) in the prediction of diabetes (15). The prediction of diabetes using OGTT has been used in multiple intervention studies like the Da Qing, Swedish diabetes prevention, Diabetes Prevention Study (DPP), Stop Non-Insulin Dependent Diabetes (STOP-NIDDM), XEnical in the Prevention of Diabetes in Obese Subjects (XENDOS), and the TRglitazone In the Prevention of Diabetes (TRIPOD) (16-19), etc.

The World Health Organization (WHO) criteria including either IFG (fasting plasma glucose concentration ≥ 6.1 mmol/L and < 7.0 mmol/L and 2-h plasma glucose concentration < 11.1 mmol/L during the oral glucose tolerance test) or IGT test (fasting plasma glucose concentration < 7.0 mmol/L and 2-h plasma glucose concentration ≥ 7.8 mmol/L and < 11.1 mmol/L) are used to diagnose people with IGT. In 2003, the Steering Committee expanded the original eligibility criteria from IGT to also include individuals with isolated IFG (fasting plasma glucose concentration ≥ 6.1 mmol/L and < 7.0 mmol/L and 2-h plasma glucose concentration < 7.8 mmol/L) to broaden the generalizability of study results (20).

Patients at risk of diabetes are asymptomatic; reliable methods are needed to identify those at a high risk. The American Diabetes Association (ADA) Expert Committee has recommended decreasing the lower limit for IFG from 110 to 100 mg/dL to optimize the sensitivity of predicting future diabetes (21). Clinical characteristics also predict the risk of diabetes (22). The clinical characteristics associated with type 2 diabetes risk include obesity and overweight, age (the risk rises steadily from puberty into geriatric years), a history of gestational diabetes, polycystic ovary syndrome, a family history of type 2 diabetes, and membership in certain high-risk minority groups: African American, Hispanic, Native American, and Asian-Pacific Islanders (14). The ADA recommends screening youth and adults with multiple risk factors for type 2 diabetes; fasting plasma glucose is the preferred first-line test (23,24).

A subject with metabolic syndrome is more likely to develop new-onset diabetes. People with metabolic syndrome are at a high risk of ischemic atherosclerotic diseases. Several studies have shown that metabolic syndrome is a strong predictor of incident diabetes (25-27).

The Insulin Resistance Atherosclerosis Study (IRAS) assessed a series of risk factors and identified five significant risk factors for the development of type 2 diabetes including high plasminogen activator inhibitor 1 (PAI-1), hypertension (HTN), high triglycerides (TG), low high-density lipoprotein (HDL), and IGT. The incidence of type 2 diabetes increases with the increasing number of risk factors, 5% with 0 risk factors to 50% when all 5 risk factors are present ($p < 0.001$) (13).

Every year about 5%-10% of people with IGT will develop diabetes and acquire the disease burden related to its diagnosis symptoms, need for surveillance for chronic consequences, and associated costs, and they will also be at a high risk of several chronic diseases (28). Below are described several studies found in the literature searched, including people with IGT with the aim to prevent or delay type 2 diabetes by different types of intervention.

Lifestyle trials – diet and physical activity

In the DaQing study, 577 subjects with IGT as defined by the WHO criteria were followed over 6 years. They were randomized into diet-only, exercise-only, diet plus exercise groups, and a control group, which were associated with a 31% ($p \leq 0.03$), 46% ($p \leq 0.0005$) and 42% ($p \leq 0.005$) reduction in the risk of developing diabetes, respectively, when compared to the control group. Factor analysis showed that both insulin resistance and insulin secretion had a significant association with the development of diabetes, and lifestyle intervention was more effective in subjects with lower insulin resistance and higher insulin secretion (13,16,29).

The Swedish Diabetes Prevention Study was the first individually randomized clinical trial, where 522 middle-aged overweight subjects (body mass index/BMI > 25) with IGT were randomized to the control group or intervention group and followed over a mean of 3.2 years. The intervention group received individual counseling regarding diet and exercise and lost 4.2 ± 5.1 kg *versus* 0.8 ± 3.7 kg in the control group, which translated to a 58% ($p \leq 0.001$) reduction in the risk of developing diabetes and was directly associated with changes in lifestyle (17,30).

The Diabetes Prevention Program (DPP) study was a double-blind randomized controlled trial (RCT) involving a larger number of subjects, 3234 with IGT or IFG with BMI > 24 kg/m² (> 22 in Asian population) followed over 2.8 years. They were randomized to standard lifestyle recommendations with placebo or with metformin or to an intensive program of lifestyle modifications. The incidence of developing diabetes was 4.8 cases *versus* 11 cases *per* 100 person years for 3 years in the intensive lifestyle and placebo groups, respectively, which was a 58% lower incidence of developing diabetes in the intensive lifestyle group. Just like in the Da Qing study, the effects were significantly greater among subjects with lower baseline 2-hour postglucose load, in older subjects, and in those with a lower BMI. Lifestyle intervention was effective in normalizing both fasting glucose values and postload glucose values (14,16).

Pharmacological trials

As shown above, lifestyle modification is the best strategy to prevent the progression of metabolic risk factors and to prevent cardiovascular events and the onset of diabetes. However, pharmacological trials showed important results.

Metformin

Metformin (MF) 850 mg was used in one arm of the DPP study along with standard lifestyle recommendations. Subjects in this study had a decrease in their calorie intake by a mean of 296 ± 23 kcal compared to 249 ± 27 kcal in the placebo group; their average fat intake decreased by $0.8 \pm 0.2\%$ in both the MF and the placebo group ($p=NS$). The numbers needed to be treated (NNTB) imply benefit, i.e. the number needed to be treated with the intervention compared with the control treatment to prevent or delay one case of diabetes (31). NTB to prevent one case of diabetes during 2.8 years was 13.9 (95% CI 8.7 to 33.9) for the MF group and the effects of MF were less in subjects with lower BMI and lower fasting glucose levels. MF was effective in normalizing fasting glucose values only (13,14).

Acarbose

Acarbose acts mainly in the intestine through inhibition of intestinal glucosidases. It thus slows the digestion and absorption of complex carbohydrates in the gut and is useful in diabetes for the treatment of postprandial hyperglycemia (13). Acarbose was tested in the STOP-NIDDM study as an agent to prevent diabetes. The STOP-NIDDM study was a double-blind, placebo-controlled RCT that enrolled subjects with IGT with fasting plasma glucose between 110 and 140 mg/dL followed over a period of 3.3 years. The subjects were randomized to either the placebo group or the acarbose 100 mg along with routine advice regarding weight loss and regular exercise. Subjects on acarbose were by 25% less likely to develop diabetes compared to placebo at the end of 1 year, and this continued to the end of the study. The reduced risk was present even after adjusting for change in weight, age, sex, or BMI ($p=0.0063$) (32).

Thiazolidinediones

Thiazolidinediones (TZD) are insulin sensitizers that act by facilitating glucose transport into the muscle and by acting on Peroxisome Proliferator Activated Receptor (PPAR)- γ receptors in the adipose cells to shift fat from visceral to less active subcutaneous fat compartment thus reducing insulin resistance. The TRIPOD was a single-center, placebo-controlled RCT, which enrolled Mexican-American women with prior gestational diabetes mellitus (GDM) randomized to either placebo or troglitazone 400 mg/day. The mean annual incidence of diabetes was 5.4% in the troglitazone group *versus* 12.1% in the placebo group ($p=0.009$), which was a $>50\%$ reduction with troglitazone use (18). Analysis done 8 months after troglitazone had been stopped showed that the mean annual incidence of diabetes was 21.2% and 3.1% in the placebo and troglitazone group, respectively. This indicated that the protection by the drug persisted even after it had been stopped. The study was continued in the same group of women using pioglitazone called the Pioglitazone In the Prevention Of Diabetes (PIPOD) study and the results published indicated that the benefit in terms of β -cell function achieved with troglitazone was maintained with the use of pioglitazone, indicating that it could be a class effect (33).

Recently, a report appeared on diabetes reduction assessment in the Ramipril and Rosiglitazone medication (DREAM) trial (28). This trial reported only combined results for individuals with either IGT or IFG. Briefly, it was found that the ACE inhibitor ramipril did not significantly reduce the incidence of diabetes (hazard ratio 0.91, 0.80 to 1.03) but rosiglitazone, an oral diabetes drug, did (0.38, 0.33 to 0.44).

Orlistat

Orlistat is another pharmacological agent used in the prevention of diabetes. Orlistat is a weight-reduction agent that inhibits the activity of intestinal lipase and thus decreases the amount of fat (triglycerides) absorbed. The XENDOS study was a 4-year double-blind prospective study in which 3305 subjects with

NGT and IGT were randomized to orlistat or placebo (16). This study showed that in the very obese population on intensive lifestyle modification program, Xenical treatment was associated with a 37.3% reduced incidence of diabetes compared to placebo ($p=0.003$), thus indicating that weight loss is an important factor in the prevention of diabetes and its comorbidities (13).

Angiotensin converting enzyme inhibitor (ACEI)/angiotensinogen receptor blocker (ARB)

In addition to the beneficial effects on hypertension, the kidneys and the heart, both ACEI and ARBs have been shown to improve insulin sensitivity and glycemic control. Therapy with ACEI, like captopril and ramipril, and ARBs, like losartan and valsartan has been shown to reduce the incidence of new-onset diabetes anywhere by 14% to 34% (17). Although the exact mechanism how these agents reduce the incidence of diabetes is not known, it is well established that ACEI increases glucose uptake in skeletal muscle through increased synthesis of GLUT-4 transporter protein secondary to up-regulation of insulin receptor substrate 1 (IRS 1) activity, enhanced bradykinin and nitric oxide (NO) activity (34).

Statins

The West of Scotland Coronary Prevention Study (WOSCOPS) examined the effect of pravastatin on cardiovascular (CV) events and observed that these pharmacological interventions were associated with a 30% reduction in the incidence of diabetes as secondary outcome (35). Therapeutic agents used to treat other coexisting conditions like hypertension and dyslipidemia with agents like ACEI/ARB/statins can also help with the prevention of diabetes and CV disease (13).

In the meta-analysis systematic review of Gillies *et al.* (36), twenty one trials met the inclusion criteria and 17 of them (1979-2006) with 8084 participants were included in the meta-analyses. The trials were heterogeneous in terms of interventions, ethnicity, weight, and age. Because of the time period covered by the trials, several definitions for type 2 diabetes and

IGT were used (ADA and WHO) (37-40). The meta-analysis systematic review provides overwhelming evidence to support the benefit of interventions to prevent or delay type 2 diabetes, and the pooled effect of all forms of lifestyle interventions gave a hazard ratio of 0.51 (95% CI 0.44 to 0.60, $p<0.001$), indicating a relative 49% reduction in the risk of developing diabetes. Gillies *et al.* (36) conclude that both forms of pharmacological intervention-oral diabetes drugs and the anti-obesity drug-also showed a highly significant benefit of intervention compared with control (hazard ratios 0.70, 0.62 to 0.79 ($p<0.001$), and 0.44, 0.28 to 0.69 ($p<0.001$), respectively). The numbers needed to be treated in this systematic review were 6.4 (95% credible interval NNTB 5.0 to NNTB 8.4) for lifestyle, 10.8 (NNTB 8.1 to NNTB 15.0) for oral antidiabetic drugs, 5.4 (NNTB 4.1 to NNTB 7.6) for orlistat, and 4.0 (NNTB 16.9 to NNTB 24.8) for *jiangtang bushen* recipe (herbal remedies).

The key components of lifestyle interventions in clinical practice based on the studies analyzed by Burnet *et al.* (41) were as follows: the staff included were medical doctors, nurses, technicians, dietitians and physiotherapists. Trainings with patients were focused on nutrition, physical activity and behavioral self-management four times during the year in individualized sessions (in Diabetes Prevention Study) or small group counseling sessions weekly for one month, then monthly for three months (16). Physical activities were organized 2 times during the week as brisk walking (in Diabetes Prevention Program and Malmo Feasibility Study). Smokers were advised to stop or reduce smoking. It was a useful follow up session every 2 months with phone calls to patients between visits. In DPS study, if weight goal was not achieved in 6 to 12 months, a very low calorie diet was considered. As for social support, spouses were invited to join sessions.

The overall goal for diabetes prevention is to reach and maintain an active, healthy weight with a tendency toward a hypocaloric diet. Evidence supports limiting total calories and fat (25% of caloric intake) and

increasing dietary fiber (20 to 30 g/day). Essential skills include understanding portion sizes and reading food labels (41).

CONCLUSION AND RECOMMENDATIONS

The data derived from the trials show that intervention can reduce the risk of type 2 diabetes in people with IGT, and lifestyle intervention seems to be more effective than pharmacological interventions. Lifestyle intervention, which aims to reduce obesity and increase physical activity, help in addressing directly these risk factors. However, lifestyle interventions incur fewer and less serious side effects than drug treatment. Like in pharmacological interventions, lifestyle interventions may not be permanent and advice on diet and exercise needs to be regularly reinforced. For pharmacological interventions, adverse effects need to be fully understood to enable the potential harms and benefits to be assessed.

Clinicians should recommend behavior changes for asymptomatic patients at a high risk of diabetes such as IGT. First of all, high-risk patients can be identified through clinical characteristics augmented with careful screening by fasting glucose.

Although the diabetes prevention trials used intensive strategies for effecting lifestyle change, clinicians can translate key elements from those strategies into brief, office-based counseling on physical activity and dietary change.

As it was proved by different trials in clinical practice, lifestyle changes should be made through structured programs. These programs, proved to be successful in clinical practices from different countries, should emphasize goal setting, practice and motivational interviewing with patients, education and skills development, self-monitoring, physical activity, problem solving, behavior change (cognitive restructuring), stress and stimulus control, the importance of social support, and the utilization of community resources.

Multidisciplinary care teams consisting of nurses, clinicians, dietitians, psychologist physiotherapists and health educators may provide more intensive counseling and increase the contact that the patient has with the health care system. Printed materials or if possible interactive computer programs in offices can reinforce counseling efforts.

Implementing diabetes prevention will require significant changes for both patients and clinicians. It is needed to educate clinicians in training and in practice about the potential benefits of diabetes prevention. Appropriate programs on the prevention or delay of type 2 diabetes have to be culturally adaptive for office-based counseling and this may be challenging in diverse communities.

Successful diabetes prevention efforts will likely require involvement of family members, enhancing clinician-patient relationships, practices and broader societal changes supporting healthy lifestyles in the context of schools, communities, and workplaces.

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