

Evaluation of Various Pharmacological Interventions in Preventing the Development of New Onset Diabetes Mellitus

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Introduction

Diabetes is an illness that ranks as one of the more costly chronic diseases and is increasing at epidemic proportions globally.¹ Morbidity and mortality of diabetes mellitus is associated with complications that are associated with damage or failure of various organs, particularly eyes, kidneys and nervous system. Persons with type 2 diabetes mellitus are also at greater risk for cardiovascular disease² and have a greater incidence of hypertension, dyslipidemia and obesity³.

There is also growing evidence that patients discovered to have elevated blood glucose concentrations (what is now termed pre-diabetes) have a substantially increased risk for cardiovascular disease and death⁴. Given this evidence in addition to the established evidence regarding the morbidity and mortality of type 2 diabetes mellitus, delaying or preventing the onset of frank type 2 diabetes mellitus is a worthwhile goal.

The purpose of this paper is to review five studies that investigated early pharmacological interventions in patients at high risk of developing diabetes mellitus to determine if these interventions could reduce the rate of the development of new cases of diabetes mellitus.

Evaluation of Studies

The DPT-1⁵ was the only study that addressed the possibility of affecting the development of Type 1 Diabetes. The goal of this study was to determine if low dose of insulin in persons at high risk for developing type 1 diabetes mellitus had an effect on the onset of the disease. The trial was randomized and not blinded. The subjects recruited were first degree relatives of patients with Type 1 Diabetes. Islet cell antibody positive subjects were deemed at high risk and eligible for participation. ISA negative subjects were excluded. Subjects were stratified according to glucose tolerance status prior to randomization. Subjects who were identified at high risk were randomized into two groups. One group received parenteral insulin while the control group underwent close monitoring. The results were analyzed using Kaplan-Meier Curves. The results showed that low dose insulin in high risk relatives of patients with diabetes had no effect in halting the rate of development of the disease. The cumulative incidence of diabetes was similar in the two groups (hazard ratio in the prevention group as compared with the observation group, 0.96; 95% CI, 0.69 to 1.34; P=0.80).

The DPP⁶ was a randomized, double blind, placebo controlled, and multicenter study performed by the Diabetes Prevention Program Research Group (DPPRG). It studied a total of 3234 patients deemed at high risk for the development of diabetes. The 3234 subjects with elevated fasting and post-load plasma glucose were randomly assigned to either a placebo, metformin (850 mg. BID), or intensive lifestyle modification group (with goals of 7% weight loss and 150 minutes of physical activity daily). The mean age of the participants was 51 years. The mean BMI was 34.0. 68% of the study group were women and 45% were members of a minority group. The average follow up was 2.8 years. The study design provided 90 percent power to detect a 33 percent reduction from an incidence

of 6.5 cases of diabetes per 100 person-years, with a 10 percent rate of loss to follow-up per year. The primary endpoint was the development of type 2 diabetes mellitus. The study originally had a troglitazone treated arm but that was discontinued when the troglitazone was removed from the market. The goal of the study was to determine the effect of these interventions on the onset of frank diabetes mellitus.

The incidence of diabetes was 11.0, 7.8 and 4.8 per 100 person years in the placebo, metformin and lifestyle group respectively. The cumulative reduction in incidence was 58% (95%CI =48-66) in the lifestyle group and 31% (95%CI = 24-51). These data suggest that to prevent one new case of DM in three years, 6.9 persons would have to participate in a healthy living program and 13.9 would have to receive metformin.

The STOP-NIDDM⁷ trial was a randomized, double blind, placebo controlled, and multicenter study including a total of 1429 patients in Canada and Europe. The enrollees were persons with impaired glucose tolerance and were randomly assigned to receive 100 mg acarbose or placebo TID. The exclusion criteria were minimal and concerned primarily absence of baseline data. The primary endpoint was the development of diabetes as evidenced by OGTT. Analyses were made on an intend to treat basis. Analysis employed the Cox proportional hazards model. The Kaplan-Meir method was employed to calculate probability of survival. Almost 25% of patients discontinued early primarily due to gastrointestinal complaints. The magnitude of RR reduction was less than seen in the DPP (58% vs. 25%). The authors state that the efficacy of acarbose may have been diluted by the drop out rate. The results suggest that 11 patients with impaired glucose tolerance would need to be treated for 3.3 years to prevent the development of one new case of DM.

The TRIPOD⁸ study was a randomized, double blinded, placebo controlled, and single center study that followed the development of type 2 diabetes mellitus in 266 Hispanic women who previously experienced gestational diabetes mellitus (GDM). The goal of this study was to determine if reducing insulin resistance affected the development of type 2 diabetes mellitus. The enrollees were women >18 years of age who had gestational diabetes mellitus in the previous 4 years and agreed to use effective contraception. The enrolled subjects received dietary advice and were advised to walk 30 minutes three times a week. All were administered a frequently sampled OGTT within 4 weeks of screening and then randomized to receive troglitazone 400 mg or placebo once daily in a double blinded fashion. Women who became pregnant were given the option of learning their treatment status. Three became pregnant. Of these the one who chose to learn treatment status was a placebo subject and was followed through the trial. Two others chose not to be unblinded and discontinued participation till at least 4 months postpartum and 1 month after cessation of breast feeding. Development of type 2 diabetes mellitus by the criteria of the ADA was the primary study end point. Cumulative DM incidence rates were calculated by life table analysis. Incidence rates of treatment groups were compared by log rank tests. HR for development of type 2 diabetes mellitus were calculated using Cox proportional hazards regression analysis with and without adjustments for difference in baseline variable. Life table analysis showed a significantly lower incidence of type 2 diabetes mellitus in the troglitazone group (12.1% in placebo group and 5.4 % in the troglitazone group). The HR for the troglitazone group was 0.5 (95% CI 0.28-0.89) without

adjustment for baseline differences and 0.44 with adjustments. This protection from diabetes persisted for 8 months after treatment was stopped indicating that treatment altered the natural history of the disease rather than just masking the deterioration through acute effects on circulating glucose levels.

The XENDOS⁹ study was a 4 year double blind, randomized, placebo controlled prospective study carried out at 22 medical centers in Sweden. The purpose of this study was to determine if orlistat could help prevent or delay the development of type 2 diabetes mellitus in high risk patients. Eligible participants were persons with a BMI > 30 and between the ages of 30 and 60 years who had a non-diabetic oral glucose tolerance. Patients who had type 2 diabetes mellitus, ongoing or active cardiovascular disease and gastrointestinal disease were excluded. The enrollees were randomized to orlistat 120 mg or placebo TID. The participants were prescribed a reduced calorie diet (~800 kcal/day) with 30% from fat. The prescribed energy intake was readjusted every 6 months according to account for any weight loss. The patients received dietary counseling every 2 weeks for 6 months then monthly thereafter. The subjects were also encouraged to walk an additional Km per day in addition to other physical exercise. The primary outcome measures were time to onset of type 2 diabetes mellitus and change in body weight after 4 years of treatment. A review of previous literature was analyzed to provide a study size that would be unaffected by dropout rate and have a 90% power at $\alpha=0.05$. Based on ITT population cumulative incidence rates of diabetes were calculated using Kaplan-Meir estimate of survival function. Statistical significance of the difference between treatment groups was determined using the log rank test (PROC LIFETEST; SAS/STAT vs. 8). The HR (0.627 [95% CI 0.455 – 0.863]) corresponds to a 37.3% risk reduction in development of diabetes in the orlistat group as compared with the placebo group.

Critique/Analysis

The DPT-1, out of necessity, could not be blinded. Insulin is a potent hormone and proper precautions had to be taken regarding possible hypoglycemia. The study results showed development of type 1 diabetes mellitus to be the same in both groups. The study is still of value because it addresses the possibility that low insulin doses may reduce the workload of the pancreas and may delay onset of type 1 diabetes mellitus. These results show this not to be the case. Parenteral insulin therapy has been shown to prevent diabetes in animal models¹⁰. The inclusion and exclusion criteria may have been too stringent to discern a difference. Further investigation would be required to ascertain whether this or other intervention in pre-type 1 diabetes mellitus would be effective in delaying or preventing the onset of the disease.

The other four studies all evaluated groups at high risk for development of type 2 diabetes mellitus. While the STOP-NIDDM and the TRIPOD did not have BMI as an inclusion criterion, the patient demographics indicate that the BMI of the participants in these studies did have a BMI > 30 making these populations comparable. The primary endpoint was similar in all these trials and the proper statistics were applied.

The STOP-NIDDM was weak because of the high drop out rate due to gastrointestinal adverse events. The authors claimed that this may have diluted the RR reduction. Additionally the groups were started on lower doses prior to the actual start of the study to minimize this event. Particular attention to the effect of drop out rate, titrating enrollees to study dose and that this study was entirely funded by the manufacturer of acarbose give the appearance of a funding bias.

The TRIPOD has a relevance issue because the studied intervention is a drug that has been removed from the market because of hepatotoxicity. The promising results of this trial (50% risk reduction and apparent preservation of β -cell function) mandated that studies be performed to assess the efficacy of the drugs of this class (TZD's) that are currently available (rosiglitazone and pioglitazone). Studies, published too recently to be included in this review, indicate that these promising results may indeed be a class effect^{11,12}.

The XENDOS is the only one of the four studies that addresses reducing risk for the development of type 2 with an intervention not affecting glucose levels directly. It did demonstrate the long term safety of the drug. Its effect was primarily on the persons with impaired glucose tolerance. No treatment difference was discernable in the normal glucose tolerance subgroup.

Summary

The studies presented in Table 1 provide encouraging information regarding the efforts to prevent the onset of diabetes mellitus. While the DPT-1 showed no effect of low dose insulin in reducing the rate of progression, it is encouraging that venues that may prevent Type 1 DM are being studied. The inclusion criteria in the DPT-1 required the presence of islet cell antibodies which indicates immune system involvement. Perhaps an immunological approach similar to the use of etanercept in RA may be effective. An update in the status of preventing Type 1 diabetes is scheduled to be presented at the American Diabetes Association's 54th Annual Postgraduate Course in New York on February 24, 2007.

The four studies pertaining to the prevention of Type 2 diabetes pair up with two studies investigating the effect of agents that modify nutrient absorption (STOP-IDDM and XENDOS) and two that study the effect of the utilization of glucose (DPP and TRIPOD). All had a degree of emphasis on behavior modification regarding diet and physical activity with the greatest emphasis in the DPP study where intense modification was an intervention unto itself and proved to be the most effective single intervention. The studies involving sensitizing agents appear to be more promising than those that studied nutrient modulation.

Clinical Recommendations

The DPPRG conclude their article: "...thus it should be possible to delay or prevent the development of complications, substantially reducing the individual and public health burden of diabetes"¹³.

This is a worthwhile goal and suggests that treatment of pre-diabetes may shift the paradigm for the treatment of complications of diabetes. Published studies have reported that persons with pre-diabetes are at greater risk for CVD⁴ indicating that currently complications are being reactively treated. Treating pre-diabetes could result in a proactive approach making the above possibility a reality. These studies warrant that the clinician prescribe therapy cognizant of this apparent risk reduction.

Conclusions:

The data presented in the four studies on preventing the progression of pre-diabetes to diabetes indicate that progression to frank diabetes may be blunted by affecting either the supply of nutrient/glucose (acarbose, orlistat) or utilization of glucose by addressing the sensitivity of the receptors (metformin, troglitazone or exercise). Additionally all the studies were very positive on the role of lifestyle intervention including dietary changes and exercise. A community pharmacist can help identify patients who may benefit from early intervention and positively reinforce lifestyle intervention.

Table 1

Study/Author	Number of Subjects	Study Design	Location	Regimens Evaluated	Inclusion Criteria	Exclusion Criteria	Results	Duration
DPT-1 J.S. Skylar et al Insulin in Relatives at Risk for Diabetes (5)	339	Randomized, not blinded	Multi-centered, US and Canada	Insulin therapy Closely monitored	Ages 3 to 45 with brother sister child or parent with 250.01 Or Ages 3-20 with uncle nephew niece grandparent or half-sibling with 250.01	All who tested negative for ICA FBG > 126 BG > 200 2h after glucose challenge.	Development of Type 1 Diabetes was the same for both groups.	Median of 3.7 years
DPP William Knowler et al Reduction in the incidence of Diabetes with Lifestyle Intervention or Metformin (6)	3234	Randomized Double blinded Placebo controlled	Multicentered US	Metformin Lifestyle modifications Troglitazone (d/c when w/d)	>25 YO with IGT (BG= 95-125mg/Dl) BMI >24	Taking medications that alter BG Had illness that would affect long term participation	Cumulative incidence of diabetes was 58% lower in lifestyle modification group (95% CI=48-66) 31% lower in metformin group(95% CI = 24-51)	Median of 2.8 years
STOP-NIDDM Chiasson, JL et al Acarbose for prevention of type 2 diabetes mellitus (7)	1429	Randomized double blind placebo control	Multicentered(Canada and Europe)	Acarbose Placebo	40-70 years old IGT or FPG= 5.6-7.7	No IGT No postrandomization data.	RR 0.75 95% CI = (0.63-0.90)	3.3 years
TRIPOD Buchanan, TA et al Prevention of Type 2 Diabetes in High Risk Hispanic Women (8)	266	Random double blind placebo control	LA County Women's and Children's Hospital, US	Troglitazone Placebo	> 18 yo Hispanic women with gestational diabetes GTT predicting 70% risk of diabetes in 5 yrs.	Evidence of chronic disease, diabetes	RR= 0.45 95% CI= 0.28-0.89	2.5 yrs
XENDOS Torgeson, JS et al XENical in the Prevention of Diabetes in Obese Subjects (9)	3305	Random double blind placebo control	Multicenters in Sweden	Orlistat Placebo	BMI > 30 30-60 yo Nondiabetic GTT	Diabetes Ongoing and active CVD and GI disease	RR = 0.63 95% CI = 0.46-0.86 (37.3% reduction in RR)	4.0 years

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