Reduction in the incidence of Type 2 Diabetes with glipizide

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A. Study Purpose and Rationale:

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Type 2 diabetes affects approximately 8% of adults in the United States. It is characterized by variable degrees of insulin deficiency and resistance. Diabetes is diagnosed by fasting plasma glucose (FPG) at or above 126mg/dL (7.0mmol/L), a two hour value on the oral glucose tolerance test (OGTT) at or above 200mg/dL (11.1mmol/L), or a random plasma glucose concentration greater than or equal to 200mg/dL in the presence of symptoms. There is also an intermediate group of patients who do not meet the criteria for diabetes but whose glucose is too high to be considered in the range of normal. These patients are considered to have impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).   Fasting plasma glucose between 100-125mg/dL is considered too high and therefore falls under the category of impaired fasting glucose. The corresponding category of impaired glucose tolerance two hours after a glucose load is 140-199mg/dL.   These patients are an important group to consider because they do not yet have diabetes and therefore may benefit from an intervention.

Diabetes is a costly and burdensome disease. The complications resulting from the disease are a significant cause of morbidity and mortality.   Poorly controlled diabetes can lead to microvascular complications such as retinopathy, nephropathy, and neuropathy. Diabetics are also at greater risk for cardiovascular disease, stroke and peripheral vascular disease. Since there are so many complications associated with diabetes the question arises of whether further attempts should be made to prevent the onset of the disease?

There are several criteria that should be considered when deciding whether a disease is suitable for prevention. To begin with the disease must impose a significant burden on the affected population, which diabetes does.[i] Another criterion is that the early development and natural history of the disease should be understood sufficiently well to identify parameters that measure progression to the disease. Although glucose levels are not the only predictor of progression to diabetes and other risk factors such as age, BMI and family history do play an important role, plasma glucose is nevertheless a useful prognostic indicator.[ii] Furthermore, there should be tests like the fasting plasma glucose and the oral glucose tolerance test that detect the pre-disease state.   Another important criterion is that there is a safe, reliable and effective method to delay or prevent the disease from occurring. After assessing all but the final criteria it can be said that diabetes is indeed a disease that can and should be prevented if possible. The question of whether there is a safe and effective way of preventing the disease has recently been addressed in several studies.

There have been several studies in the last few years that have documented attempts to prevent diabetes by both behavioral modification and using pharmacotherapy.   There was a Finnish study entitled "Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance" that was published in the *New England Journal of Medicine* in 2001[iii] in which subjects were randomized to receive either brief diet and exercise counseling (control group) or intensive individualized instruction on weight reduction, food intake, and guidance on increasing physical activity (intervention group). After an average follow-up of 3.2 years, there was a 58% relative reduction in the incidence of diabetes in the intervention group compared with the control subjects. Another study by the Diabetes Prevention Program: "Reduction in the Incidence of Type 2 Diabetes with Lifestyle Interventions or Metformin," published in the *New England Journal of Medicine* in 2002[iv] further demonstrated that lifestyle intervention lowered the incidence of diabetes in persons with impaired glucose tolerance. This study differed from the Finnish study in that it demonstrated that metformin also decreased the incidence of Type 2 diabetes when compared to placebo, there was a 31% relative reduction with metformin

compared to the placebo with regards to progression to diabetes. Other studies that demonstrated the effectiveness of pharmacological interventions were the Troglitazone in Prevention of Diabetes (TRIPOD)[v] study and the STOP-NIDDM trial. The former demonstrated a 56% relative reduction in progression to diabetes in Hispanic women with previous gestational diabetes who received troglitazone instead of placebo. The STOP-NIDDM[vi] trial took 1,429 participants with impaired glucose tolerance and randomized them to either the α-glucosidase inhibitor acarbose or a placebo. The absolute risk reduction in the acarbose-treated group was 9%.

Since multiple drugs with different mechanisms of action have been useful in delaying the progression to Type 2 diabetes it would interesting to see if glipizide, which is currently generic and therefore the cheapest alternative, would reduce the incidence of diabetes in patients with impaired glucose tolerance.

B. Study Design and Statistical Analysis

The hypothesis of this study is that the administration of glipizide will prevent or delay the development of Type 2 diabetes in patients who do not yet meet the criteria for diabetes but who have impaired fasting glucose or impaired glucose tolerance. The subjects will be assigned to two study arms in a double blind manner: the first arm will be those receiving a placebo once a day and the second will be those receiving glipizide 5mg once a day. Both study arms will receive intensive lifestyle intervention in the form of a 16-lesson curriculum covering diet, exercise, and behavior modification. The primary outcome of the study will be diabetes.

The power analysis will be done using the chi-squared test since there is a categorical outcome (in this case incidence of Type 2 diabetes) in two groups. Using the chi-square test with a p1 of 0.11 and p2 of 0.078, an alpha of 0.05 and a power of 80% the number of participants needed in each group is 1367. The p values were derived from the Diabetes Prevention Program study "Reduction in the Incidence of Type 2 Diabetes with Lifestyle Interventions or Metformin," [vii]under the assumption that glipizide would be as effective as metformin in delaying or preventing Type 2 diabetes. Subjects will remain in their specific groups throughout the study.

C. Study Procedure

The study will last 4 years. The subjects will have semi-annual fasting glucose tests and annual oral glucose tolerance tests. They will also have testing if they demonstrate signs and symptoms of diabetes. If the study participant's fasting glucose is greater than or equal to 126, the study medication will be discontinued and the subject will be referred to his or her physician for further treatment. Neither the placebo pill nor the glipizide pill will be taken on the morning when the glucose testing is done. Measurements of glycosylated hemoglobin (HbA1C) will also be done on a semi-annual basis. All participants will be required to complete food frequency and physical activity questionnaires on a monthly basis, this is especially important to monitor once the lifestyle intervention sessions have finished.

D. Study Drugs

The first drug will be a placebo pill.

The second drug will be glipizide, which is an approved drug. Glipizide is a second generation sulfonylurea. The sulfonylurea receptor is a component of the ATP-dependent potassium channel in the pancreatic beta-cells. Sulfonylurea binding leads to inhibition of these channels, which alter the resting potential of the cell, leading to calcium influx and stimulation of insulin secretion. One of the common side effects is hypoglycemia, although the incidence of episodes of serious hypoglycemia is rare. A study published in the *Archives of Internal Medicine* in 1997, by Shorr et al. demonstrated that in 14,000 patients 65 years or older with type 2 diabetes treated with different sulfonylurea drugs, episodes of

serious hypoglycemia were rare.[viii] Shorter acting drugs such as glipizide were associated with a lower incidence than drugs like glyburide. The dosing regimen will be once a day in the morning, which is consistent with the standard use of this drug.

Patients will be instructed about the signs and symptoms of hypoglycemia including: shakiness, dizziness, sweating, hunger, headache, irritability, pale skin color, sudden moodiness or behavior changes, such as crying for no apparent reason, clumsy or jerky movements, difficulty paying attention, or confusion, tingling sensations around the mouth, seizures and coma. They will also be instructed on interventions for hypoglycemia ranging from consumption of sugar to calling for an ambulance depending on the severity of symptoms.   Subjects will also be asked to document their episodes of hypoglycemia.   Other side effects of glipizide include diarrhea, nausea, headache, flatulence, drowsiness, rash, and dizziness.

E. Medical Device

Not applicable.

F. Study Questionnaires

Not applicable.

G. Study Subjects

Several of the eligibility criteria will be consistent with the Diabetes Prevention Program: "Reduction in the Incidence of Type 2 Diabetes with Lifestyle Interventions or Metformin,"[ix] trial which required that participants be at least 25 years old, BMI of 24 or higher, a fasting glucose between 95-125mg/dL and 140-199mg/dL two hours after a 75g oral glucose load.

In order to remain consistent with the afore mentioned study, eligible persons will be excluded if they are taking medicines known to alter glucose tolerance or if they have illnesses that could seriously reduce their life expectancy or their ability to participate in the trial.[x]   Subjects with hypertension, hyperlipidemia, and previous history of gestational diabetes will not be excluded. Pregnant women will be excluded.

Subjects who develop the lab criteria for diabetes, either a fasting glucose greater than or equal to 126mg/dL or greater than or equal to 200mg/dL two hours after an oral glucose load, will be referred to their physicians and the study drug will be stopped.

Efforts will be made to include a sufficient number of women and minorities.

H. Recruitment of Subjects

Subjects will be recruited through a referral process from their primary care physicians. Physicians will be asked to make referrals on the basis of fasting plasma glucose values or glucose values after an oral glucose load. Physicians will also be asked to refer all patients with a BMI greater than or equal to 24 for further testing to determine if the patient is eligible to participate in the study.

Data Safety Monitoring Plan:
1. informed consent will be obtained.
2. glucose levels will be checked as described above.
3. potential adverse events include but are not limited to hypoglycemia, patients will be given specific instructions on how to treat hypoglycemia if it occurs.
4. adverse events will be reported to the FDA.
5. there will be a specific person who is the safety monitor for the protocol.
6. the study will be monitored on a monthly basis.

I. Confidentiality of Study Data

All study data will be coded using a unique code number that is not related to the subject's hospital unit number, social security number, initials, phone number or address.
Data will be stored in a secure location and accessible only to the investigators.

J. Potential Conflict of Interests

None.

K. Location of the Study

Columbia Presbyterian Medical Center.

L. Potential Risks

The patient has a low risk of developing some of the side effects that are associated with glipizide that were enumerated above. The most concerning of which is hypoglycemia, although the incidence of that side effect is rare.

M. Potential Benefits

The subject may benefit because glipizide may prove beneficial in delaying or preventing Type 2 diabetes. Given the large number of people with Type 2 diabetes and the morbidity and mortality associated with the disease, the potential benefit to society of delaying or preventing the onset of Type 2 diabetes is substantial.

N. References

i   American Diabetes Association National Institute of Diabetes and Digestive and Kidney Diseases: "Prevention or Delay of Type 2 Diabetes," *Diabetes Care* 2004; 27:S47.

ii   American Diabetes Association National Institute of Diabetes and Digestive and Kidney Diseases: "Prevention or Delay of Type 2 Diabetes," Diabetes Care 2004; 27:S47.

iii Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: "Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance." New England Journal of Medicine 2001; 344:1343–1350.

iv   Diabetes Prevention Research Group: "Reduction in the evidence of type 2 diabetes with life-style intervention or metformin." New England Journal of Medicine 2002; 346:393–403.

v   Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP: "Preservation of pancreatic ß-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women." Diabetes 2002; 51:2796–2803.

vi   Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, for the STOP-NIDDM Trial Research Group: "Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial." Lancet 2002; 359:2072–2077.

vii Diabetes Prevention Research Group: "Reduction in the evidence of type 2 diabetes with life-style intervention or metformin." New England Journal of Medicine 2002; 346:393–403.

viii Shorr, RI, Ray, WA, Daugherty, JR, et al. " Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas." Archives in Internal Medicine 1997; 157:1681.

ix   Diabetes Prevention Research Group: "Reduction in the evidence of type 2 diabetes with life-style intervention or metformin." New England Journal of Medicine 2002; 346:394.

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