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Effect of the novel GLP-1 receptor agonist, exenatide, in reducing the development of type 2 diabetes mellitus in high risk patients with impaired glucose tolerance as marked by incremental increase in glycosylated hemoglobin A1c

A. **Study Purpose and Rationale:** The health care system of the developed world is now up against one of its most destructive foes: diabetes mellitus. Currently, more than 21 million people in the USA and 194 million people worldwide are afflicted with this disease and this number is expected to double by 2025 [1]. This is a disease that disproportionately affects minority racial groups, with African Americans, Hispanics, and Native Americans 2-4 times as likely than Caucasians to be afflicted [2]. Persons with diabetes are many times more likely to develop heart disease or stroke within their lifetimes. Sadly, diabetes mellitus accounts as the biggest cause of end stage renal disease, blindness, and non-traumatic loss of limbs. These add up to health care costs of greater than $174 billion per annum [1].

Diabetes mellitus is caused by a failure of insulin to properly regulate carbohydrate metabolism leading to hyperglycemia. This can be the result of the complete lack of insulin, such as in type 1 diabetes mellitus (DM1), also termed insulin dependent diabetes. The development of insulin resistance in peripheral target organs with subsequent beta-cell decompensation over time is known as type 2 diabetes mellitus (DM2). While DM1 accounts for 5-10% of total cases, DM2 is the most common metabolic disease in the world accounting for the majority of all diabetes cases [2]. That DM2 was once known as “adult-onset diabetes” this term is no longer accurate, as nearly half of the newly diagnosed cases of diabetes in children are DM2 due to the increasing prevalence of childhood obesity [3].

While DM2 is caused both by genetic [4] and environmental factors, the recent increases in the prevalence of DM2 to “epidemic” proportions is mainly attributed to a corresponding increase in the overall rate of overweight and obesity. Currently in the United States nearly two-thirds of adults are considered overweight or obese [5,6]. Unfortunately, the increased obesity rate among adults has been carried over to children, with children showing a further increase in the incidence of overweight during the past six years [6]. Obesity not only increases the risk for impaired glucose tolerance and ultimately DM2, but also plays an important and causative role in the development of coronary artery disease, hypertension, and other metabolic diseases [7]. These trends are frightening and must be reversed, but the links between obesity and insulin resistance are as many as they are elusive.

What is it about obesity that leads to DM2? It is clear that a better understanding of the mechanisms involved in the downward spiral leading from obesity to outright diabetes is needed in order to more efficiently prevent this progressively destructive disease. Several factors have been figured to play key

roles in the development of insulin resistance in the obese human [8]. For one, it is known that the elevations in circulating free fatty acids (FFA) as seen in obesity can induce insulin resistance. The lipotoxicity model states that increased levels of circulating FFA eventually leads to insulin resistance in muscle and liver, as well damage to the islet cells in the pancreas, and thus a limited compensatory ability to overcome insulin resistance with increases in circulating insulin. For the majority of obese patients, the pancreas is able to successfully compensate for the obesity-associated peripheral insulin resistance by increasing the circulating insulin concentration, matched by an increase in total b-cell mass and total insulin secretion [9]. This accounts for the clinically apparent hyperinsulinemia associated with obesity. Persons that are able to maintain the increased b-cell mass and elevated insulin levels have compensated for their peripheral insulin-resistance and usually avoid the development of outright DM2. b-cell mass is a product of several independent factors - replication, size, neogenesis, and apoptosis - and it is known that b-cell mass is able to make adaptive changes to metabolic status, such as in pregnancy [10,11]. The effective balance between these factors ultimately determines and maintains overall b-cell mass. The fact that not all obese persons develop DM2 alludes to a complex genetic predisposition for this disease, as has been shown in rodents [12]. It is thought by some clinicians that in the development of DM2, the major genetic factors may be those influencing overall b-cell function, while the acquired factors mainly define insulin resistance [13]. It is known that although the detrimental effects of hyperglycemia on b-cell survival have been well researched, it is not established, however, what is the primary insult that tips the balance of b-cell function.

Are our efforts to treat diabetes initiated too late in the progression of the disease? Unfortunately, it has been found that by the time the initial diagnosis of DM2 is made, b-cell function is already 50% of non-diabetics with the thought that the process has probably accumulated over the past 5-10 years prior to outright DM2 [13,14]. Recently, a new class of pharmacotherapeutics, the glucagon like peptide 1 (GLP-1) receptor agonists, has been discovered that not only improve overall indices of hyperglycemia (marked by decreased HbA1c, fasting glucose, and OGTT) but has also been shown to promote increased b-cell function [15,16,17,18,19]. Exenatide, trade name Byetta, is the prototype drug in this novel class of compounds. Exenatide is a GLP-1R agonist that was discovered while screening the saliva of *Heloderma suspectum*, the Gila Monster. It shares 53% homogeneity to human GLP-1, but has a longer half life in serum of roughly 2 hrs prior to degradation by dipeptidyl peptidase IV (DPP4). GLP-1 is an incretin hormone released from the enteroendocrine L cells in the distal ileum and colon that augments the magnitude of meal-stimulated insulin secretion from b-cells in a glucose-dependent manner. Additionally, GLP-1 has been shown to slow gastric emptying, facilitate glucose uptake into peripheral tissues, decrease alpha-cell release of glucagon, promote cAMP-mediated expansion of b-cell mass and decrease mechanisms of b-cell apoptosis [13,20,21].

Exenatide has been approved by the FDA as an agent to be used in combination with metformin, sulfonylureas or both. Multiple studies have shown the efficacy and relative safety of exenatide in short-term human clinical trials [14,15,16,17,18,19], with a multicenter long-term study currently underway [22]. However, the ability of exenatide to promote b-cell expansion and preservation in the setting of impaired glucose tolerance, or pre-diabetes, with subsequent reduction in progression from impaired glucose tolerance to outright DM2 has not been studied. This study aims to compare the effects of exenatide treatment vs placebo for 52 weeks in obese, pre-diabetic humans in terms of moderate but significant decreases or stabilization of HbA1c thus identifying GLP-1R agonist therapy as a potential adjunct therapy to prevention of DM2 in high-risk patients.

B. **Study Design and Statistical Procedures:** Eligible study subjects will be randomized to two separate groups, those receiving exenatide and those receiving placebo. All patients will have a 2 week run-in following initial randomization to practice twice-daily administration and use of glucometers. Following initial 2 week run-in, patients will be supplied with appropriate medication or placebo. All patients will be counseled to maintain pre-trial diet and exercise regimens although literature with proper guidance for healthy diet and nutrition will be provided during initial screen. Those patients receiving exenatide will start with 5 ug SC given 15 minutes prior to breakfast and dinner. Journals with finger stick glucose measurements will be kept with AM and at least one 1 hr post-prandial value daily. These journals will be brought in on subsequent clinic visits for review by nursing staff for safety. Following the initial month, pts receiving exenatide will increase their daily dose to 10 ug SC BID as tolerated. Follow up with be at 1 month, 3 month, 6 month, and 12 month for monitoring of glucose logs and safety. Blood measurements of HbA1c will be made at initial screening, 6 months and 12 months.

Primary outcome will be HbA1c (mean +/- standard deviation) at the end of the 52 week study period. An unpaired t-test was used to determine the number of participants needed for this study assuming that alpha is 0.05 and the power is 0.80. Assuming that the mean HbA1 will differ by 0.5 in treated vs untreated, HbA1c 6.5 vs 7.0, the sample size for each group will need to be at least 64. Prior studies have shown drop out rates from exenatide administration on the order of 5-10%, with another 5% adjustment needed for other attenuating factors effecting follow-up. Thus a total of 150 pts (75 per group) will be studied.

C. Study Drugs / Medical Devices

a. Drugs

i. Exenatide: supplied as prefilled pens for 5 ug SC BID and 10 ug SC BID dosing. Dose can be administered to the upper arm, thigh or abdomen as each of these areas have been found to exhibit the same bioavailability of drug [18]. Exenatide (trade name Byetta) manufactured by a joint collaboration between Amylin Pharmaceuticals Inc. and Lilly USA, LLC.

ii. 0.9% Saline Solution: supplied as prefilled pens with equal volume as experimental drug (exenatide, as above).

b. Medical Devices

i. Glucometer and test strips: home glucose monitoring kits and test strips will be provided to all patients with education on proper use during the 2 week run-in period.

D. **Study Questionnaire:** No questionnaires will be utilized during this study.

E. Study Subjects

a. Inclusion Criteria:

Men and women
All ethnic groups
Age 35-65
BMI 30-50
IGT (2 hr plasma glucose 140-199 following 75 mg OGTT) with Fasting glucose of 95-125
One of the following: HDL < 40 (females), < 35 males; TG > 150, BP > 135/85 or on antihypertensives
Family history of DM2

b. Exclusion Criteria

DM2 (FPG > 126)
Previously treated (within 3 mos) or currently on TZD, metformin or sulfonylurea
Clinically significant cardiac, liver or renal disease
Excessive alcohol intake
Pregnancy or expectation to be pregnant during study
Currently taking glucocorticoids

F. **Recruitment of Study Subjects:** Enrollment of patients to this study will be completed by study coordinators using local media advertisements and networking with outpatient clinics affiliated with the New York Presbyterian Hospital System.

G. **Confidentiality of Study Data:** All patients enrolled in this study will be identified by the investigators using a unique alphanumerical code without reference to name, address, date of birth or social security number. Data will be securely stored throughout the study with all access recorded. All identifying data will be destroyed following study review.

H. **Potential Conflict of Interest:** The investigators have no scientific or monetary conflicts of interest with this study's design, interventions or outcomes.

I. **Location of Study:** This study will be conducted solely within the outpatient clinical facilities of the Columbia University Medical Center, New York, NY.

J. **Potential Risks:** Exenatide use has been associated with < 10 cases of hemorrhagic pancreatitis and acute pancreatitis in < 1 in 10,000 (< 0.01%) of subjects taking the medication [14]. It should be pointed out, however, the risk of pancreatitis in persons with DM2 is already 3 times as high. However, complete liver enzymes (including amylase and lipase) will be measured at 3 months. Mild hypoglycemia has been shown in the setting of exenatide monotherapy in 4-5% of subjects but zero severe episodes [18].

K. **Potential Benefits:** Enrolled subjects in the exenatide arm may be protected against development of frank DM2. All subjects will have complete blood work and physical exam at the beginning and end of this study.

L. **Alternative Therapies:** Diet and exercise remain the most beneficial intervention in the prevention of DM2. Each patient will be counseled on the outset of this study about proper nutrition and benefits of exercise.

M. **Compensation to Subjects**: Subjects will receive $500 on completion of this study.

N. **Cost to the Subjects:** There will be no out of pocket expenses to be covered by the study subjects. All drugs and supplies will be provided by the study team and reimbursement for transportation (public transit, parking, gas) costs will be managed by study coordinators.

O. **Minors as Research Subjects:** As per protocol, see "*Inclusion Criteria*" above, no minors will be enrolled in the current study.

P. **Radiation Exposure:** No radioactive materials will be utilized during this study.

Q. References

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