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Family Physician Corner

Landmark Studies of Prevention or delay of type II diabetes

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About 5% of people with impaired glucose tolerance (IGT) progress to type II diabetes each year[1]. Several landmark trials have shown that the risk of progression from prediabetes stage (plasma glucose levels above normal (≥6.1 mmol/l) but below the diabetes (<7.0 mmol/l) threshold) to diabetes may be prevented, or at least delayed by both non-pharmacological and pharmacological measures[1,2]. In this paper, a brief background of five well designed randomized controlled trials on preventing or delaying type II diabetes will be summarized. In the next paper, the practical implications of these trials will be discussed. These trials include: Finnish diabetes prevention study (FINISH study), Diabetes Prevention Program (DPP), Troglitazone in Prevention of Diabetes (TRIPOD), the stop-non insulin dependent diabetes mellitus (STOP-NIDDM) and Xenical in the prevention of diabetes in obese subjects (XENDOS) study.

The first trial report came up in 2001 from the finish study[2,3]. In the finish trial, 522 middle-aged (mean age 55 years), obese (mean BMI 31 kg/m2) subjects with IGT, were randomly allocated into either control or intervention group. In the control group, the candidates received brief diet and exercise counseling. In the intervention group, the candidates received intensive individualized instruction on weight reduction, food intake, and guidance on increasing physical activity. At the end of follow-up period (3.2 years), there was 58% relative reduction in the incidence of diabetes in the intervention group compared with the control subjects. The success in achieving reduction in incidence of diabetes was strongly correlated with achieving one or more of the following: weight loss (goal of 5% weight reduction), fat intake reduction (goal of <30% of daily total calories), saturated fat intake reduction (goal of <10% of daily total calories), fiber intake (goal of ≥15 g/1,000 kcal), and exercise (goal of >150 min/week). No untoward effects of the lifestyle interventions were observed. In conclusion, type II diabetes can be prevented by changes in the lifestyles of high-risk subjects.

In the Diabetes Prevention Program (DPP) trial, it was hypothesized that modifying risk factors for diabetes (such as IGT, overweight, or sedentary lifestyle) with a lifestyle-intervention program or the administration of Metformin would prevent or delay the development of diabetes[2,4]. Total of 3,234 subjects were enrolled in the study. They were slightly younger (mean age 51 years) and more obese

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(mean BMI 34 kg/m 2) but had nearly identical glucose intolerance compared with subjects in the Finnish study. The mean age of the participants was 51 years, 68 percent were women, and 45 percent were members of minority groups. Subjects were randomized into three intervention groups: the intensive nutrition and exercise counseling ("lifestyle") group with the goals of at least a 7 percent weight loss and at least 150 minutes of physical activity per week, the biguanide Metformin group (850 mg twice daily) or the placebo group. The intensive lifestyle group received an individualized tailored advice and physical activity guidance. It consisted of one to one 16-lessons curriculum covering diet, exercise and behavioral modification. The control group (Metformin or placebo) was given standard diet and exercise recommendations. After an average follow-up of 2.8 years, 58% relative reduction in the progression to diabetes was observed in the lifestyle group (absolute incidence 4.8%), and a 31% relative reduction in the progression of diabetes was observed in the Metformin group (absolute incidence 7.8%) compared with control subjects (absolute incidence 11.0%). The lifestyle intervention (number needed to treat (NNT) = 6.9) was significantly more effective than Metformin (NNT= 13.9) to prevent diabetes. No serious side effects were seen in any group.

The third study was Troglitazone in Prevention of Diabetes (TRIPOD)[2,5]. The aim of the trial was to test whether long term amelioration of insulin resistance would preserve pancreatic beta-cell function, and delay or prevent the onset of type II diabetes in high-risk Hispanic women. Two hundred and thirty six (236) women with previous gestational diabetes were randomized to either placebo (n = 133) or the insulin-sensitizing drug Troglitazone (400 mg/day; n = 133, the drug now is withdrawn from commercial sale, but belongs to the thiazolidinedione class, of which two related drugs are currently available) administered in double-blind fashion. After a median follow-up of 30 months on blinded medications, annual diabetes incidence rates were 12.1 and 5.4% in women allocated to placebo and Troglitazone groups, respectively. Thus, Troglitazone treatment was associated with 56% relative reduction in progression to diabetes. The protection from diabetes in the Troglitazone group was found to be closely related to the degree of reduction in endogenous insulin requirements and was associated with preservation of beta-cell compensation for insulin resistance.

The trial was scheduled to continue until 1st of August 2000 but was terminated on 24th of March 2000 due to hepatotoxicity reports in patients taking the drug. During the course of the trial, nine women had the medication discontinued when serum transaminase concentrations exceeded three times the upper normal limit with no clinical explanation. When the blind was broken, it was revealed that six of the nine women had been assigned to Troglitazone.

The fourth study is STOP-NIDDM trial[2,6]. The aim of this study was to assess the effect of Acarbose in preventing or delaying conversion of impaired glucose tolerance to type II diabetes. A total of 1,429 participants, aged 55 years, had BMI of 31 kg/m2 and IGT, were randomized in a double-blind fashion to receive either the alpha-glycosidase inhibitor Acarbose (100 mg three timed daily) or a placebo (three times daily). Development of diabetes was determined on the basis of a yearly oral glucose tolerance test (OGTT). After a mean follow-up of 3.3 years, 25% relative risk reduction in progression to diabetes was observed in the Acarbose-treated group compared with the placebo group. When the second OGTT was repeated to confirm the diagnosis, a 36% relative risk reduction was observed in the Acarbose group compared with the placebo group. There was no difference in Acarbose effect on different age groups, gender, and BMI values. No serious adverse

events were related to the study drug. The most common side effects were gastrointestinal symptoms, which were more frequent in those given Acarbose than in those given placebo ($p<0{\cdot}0001$). In conclusion, Acarbose could be used, either as an alternative or in addition to changes in lifestyle, to delay development of type II diabetes in patients with impaired glucose tolerance.

In the last study, the most recent one, Xendos trial, the primary objective was to determine if Xenical in addition to lifestyle changes, can reduce the incidence of type II diabetes in obese patients and the weight control effect of Xenical in combination with dietary counselling for up to 4 years[7]. The secondary objective was to determine the effect of Xenical on other aspects of the metabolic syndrome, and the tolerability of Xenical administered for up to 4 years. A group of 3,305 patients were randomized on double blind fashion to lifestyle changes plus either Xenical 120 mg or placebo, three times daily. Participants were males and females, aged 30-60 years, had a BMI of ≥ 30 kg/m2, and either normal (79%) or impaired (21%) glucose tolerance test (IGT). After 4 years of treatment, Xenical was found to prevent the progression to type II diabetes. The Cumulative incidence rate of diabetes was significantly lower in the Xenical group than placebo (6.2% *vs*. 9.0%; p=0.0032). The hazard ratio showed 37.3% decrease with Xenical. The difference in diabetes incidence was detectable only in the IGT subgroup. Furthermore, Xenical treatment resulted in a significant and sustained reduction in body weight. Mean weight loss was significantly greater with Xenical (5.8 vs. 3.0 kg with placebo; $P < 0.001$) and similar between Xenical recipients with impaired (5.7 kg) or normal glucose tolerance (NGT) (5.8 kg) at baseline. The improvement in body weight resulted in long-term improvement of glycaemic parameters, and reduction of LDL-cholesterol, systolic and diastolic blood pressure. Xenical was found to be safe and well tolerated. Gastro intestinal (GI) events were more frequent in Xenical-treated patients, but decreased progressively from year 1 to year 4. Xenical was found to have a safety profile similar to placebo. In conclusion, Xendos study has demonstrated that combined lifestyle changes and Xenical intervention is significantly better than lifestyle intervention alone in preventing the progression to type II diabetes in obese patients with IGT. In addition, weight loss with Xenical was significantly greater than with lifestyle intervention alone, but this was similar in subjects with IGT and or NGT. Long-term treatment with Xenical was found to be both effective and safe.

Based on the finding of the above-mentioned studies, many issues and strategies on the prevention of type II diabetes developed. The practical implications of these studies and the approaches toward the prevention of type 2 diabetes will be discussed in the next paper[2].

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