

# **“New Frontiers in Diabetes Treatment and Prevention”**

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**Wednesday, October 19, 2005 at 7:00 p.m. in the Garren Auditorium**

**Basic Science Building**

**Sponsored by the Sam & Rose Stein Institute for Research on Aging,UCSD**

## **Educational Objectives:**

1. Discuss the key role of insulin resistance and impaired beta-cell function in the pathogenesis of type 2 diabetes
2. Describe management strategies for optimizing glucose control in patients with diabetes using the various oral anti-diabetic agents and insulin
3. Provide an update of newer agents now available and in development for the treatment of diabetes
4. Present an overview of diabetes prevention strategies

## **Outline of Presentation:**

Type 2 diabetes is a disabling metabolic disease which affects more than 16 million people in the US and about 150 million people worldwide. Diabetes is a chronic disease which is characterized not only by high blood glucose, but also numerous other metabolic abnormalities including high cholesterol, high blood pressure and a pro-thrombotic (pro-clotting) state. Patients with diabetes suffer from several complications of diabetes which can lead to blindness, kidney failure and limb amputations. But the majority of patients with diabetes suffer from accelerated atherosclerosis and premature cardiovascular disease and ultimately die from a heart attack or a stroke. There is now strong evidence from large studies that intensive control of blood glucose, blood pressure and high cholesterol can significantly reduce and retard the complications of diabetes. To assist in the task of achieving and maintaining tight blood glucose control, we now have 5 classes of oral anti-diabetic agents in our therapeutic armamentarium. These include agents which increase insulin secretion (sulfonylureas and meglitinides); agents which suppress excessive liver glucose production (metformin); drugs which improve insulin sensitivity (rosiglitazone and pioglitazone); agents which delay gastrointestinal glucose absorption (acarbose and miglitol) and injectable insulin. Using these agents, alone and in combination, makes the task of lowering blood sugars more readily achievable. Recently, two new anti-diabetic agents (both injections) have been introduced. They are Pramlinitide - Symlin® which is a synthetic analog of a hormone (Amylin) secreted by the pancreatic beta cell and which is deficient in patients with diabetes. Pramlinitide is postulated to work by inhibiting the secretion of the insulin-antagonist, glucagon; by modulating gastric emptying; and by suppressing one's appetite. The other new drug is exenatide or Byetta® (a synthetic analog of a hormone discovered in the saliva of a lizard). Exenatide is an insulin stimulating hormone and is not only a very potent

stimulator of glucose-mediated insulin secretion, but also has effects to suppress one's appetite and in animal studies has even been shown to cause regeneration of the pancreatic insulin producing cells.

The last few years has seen the introduction of several newer insulins with attractive advantages over the older insulins. These include the rapidly acting insulins: Lispro insulin (Humalog ®) and Aspart insulin (Novalog ®). Among the new long acting basal insulins are: Glargine insulin (Lantus ®) and Insulin detimer (NN304). Despite the demonstrated benefits of the newer insulins however, intensive insulin therapy has not gained widespread clinical acceptance since multiple daily injections are inconvenient and many patients would prefer a less invasive method of insulin administration. This has led to the development of inhaled insulins. Clinical trials have shown that inhaled insulin is equivalent to subcutaneous insulin in lowering blood glucose in patients with both Type 1 and 2 diabetes mellitus. When administered before a meal, the physiological profile of inhaled insulin more closely mimics endogenous insulin secretion than subcutaneously injected regular insulin. It is well-tolerated and, to date, there appears to be no evidence of an increased risk of hypoglycemia or adverse pulmonary effects. Compared to other non-invasive insulin delivery systems like buccal, oral and dermal insulin, inhaled insulin currently represents the most viable alternative to insulin delivery by preprandial injections.

In addition to the above clinical compounds which lower blood sugars, there have also been technologic advances in insulin pump delivery systems and blood glucose monitoring devices. Continuous subcutaneous insulin delivery with an insulin pump represents a major advance over intermittent subcutaneous injections and on the horizon are implantable insulin pumps which deliver insulin directly into the portal system (similar to the body's own method of insulin secretion). In the field of blood glucose monitoring, we now have devices which enable us to measure blood glucose relatively painlessly for continuous periods up to several days. Under development are implantable devices which will be able to measure blood glucose continuously for up to 6 months.

Ultimately however, prevention is better than cure and we should focus our efforts towards the prevention of diabetes. In the Diabetes Prevention Program one group of participants were assigned to an intensive lifestyle program and were encouraged to achieve and maintain a weight reduction of at least 7 percent of initial body weight through consumption of a healthy low-calorie, low-fat diet and to engage in physical activity of moderate intensity, such as brisk walking, for at least 150 minutes per week. This intensive diet and lifestyle regime resulted in a 58% reduction in the incidence of diabetes as compared to people in the placebo group who got standard lifestyle advice.