CHAPTER 8

RECENT DEVELOPMENTS IN THE TREATMENT OF DIABETES TYPE 2

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Abstract: Diabetes type 2 (T2DM) is a life-long metabolic disease that develops commonly in adulthood as a consequence of an unhealthy life style and genetic predisposition. T2DM is the most common form of diabetes, resulting from both insulin resistances in target organs and insufficient insulin production from pancreas beta cells. T2DM is characterized by increased plasma glucose and insulin levels as well as dyslipidemia. If left untreated chronic diseases will develop that result in a higher mortality risk.

The prevalence of type 2 diabetes worldwide has increased dramatically in recent times in part due to changes in diet and physical activity levels. Also, several genes underlying monogenic forms of diabetes as well as polymorphic variants have been identified that can contribute to the etiology of the disease.

A number of treatment strategies exist for T2DM that tackle several of the symptoms. Anti-obesity drugs and PPAR agonists are likely to become efficient pharmacological remedies to prevent further health problems in individuals with T2DM

Keywords: diabetes type 2; obesity; hyperinsulinemia; dyslipidemia; hyperglycemia; PPAR agonists; thiazolidinediones

1. INTRODUCTION

More than 150 million people worldwide suffer from T2DM, also known previously as non-insulin dependent diabetes mellitus (NIDDM). The common problem facing T2DM-affected individuals daily is that they are unable to produce sufficient amounts of insulin to stop the rise in blood glucose levels after food intake. T2DM can be defined as a state with hyperglycemia due to insulin resistance (see below) and relative insulin deficiency, showing a heterogeneous group of conditions (English and Williams, 2001; Kahn et al., 2005).

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It is expected that the number of T2DM cases will double within the next 25 years according to the World Health Organization (WHO), representing an enormous social and economic burden. It is generally believed that the dramatic surge of new T2DM cases in some Asian countries correlates with a sudden change in habits, by adopting a Western-like lifestyle characterized by physical inactivity and consumption of energy-rich foods, etc. (Yach et al., 2006; WHO, 2006). The prevalence of T2DM is highest (up to 50 percent) in American Indians and in South Pacific islanders, populations that evolved to survive caloric deprivation but who are now affluent and obese (Press, 2002).

Obesity is considered as a major T2DM risk factor evidenced by a strong correlation between the Body Mass Index (BMI) and T2DM incidence. There has been a marked increase in the percentage of overweight and obese individuals in the American population judged by the BMI index (CDC, 2006). A BMI above 25 kg/m$^2$ is a risk indicator of T2DM incidence. Risk factors that also can predict obesity include the individual’s waist circumference (abdominal fat), physical inactivity, high-blood pressure and a high-fat diet (Wild et al., 2004).

Insulin is a hormone normally made by β (beta) cells in the pancreas whose major role is to promote the conversion of excess blood glucose, into glycogen, a stored form of energy (Kulkarni, 2004). Glycogen is important for providing rapid movement to muscles and maintaining blood glucose levels during fasting (liver glycogen). Excess glycogen can be converted into stored fat in the form of tryglycerides within fat cells (adipocytes) and released as free fatty acids. Excessive accumulation of adipose tissue leads to obesity. Among the other functions of insulin are to stimulate glucose transport into cells by enhancing glucose transporters activity (i.e. GLUT4), glycolysis, glucose oxidation, lipogenesis, and many other processes (Speight and Holford, 1997) (see Figure 1).

T2DM can be divided into stages or phases according to the level of function of pancreatic β-cells. In the first stage of T2DM, a defect(s) primarily in the β cell lead(s) to a drop in insulin levels and the inability to metabolize the excess levels of blood glucose (hyperglycemia). The inability to stimulate sufficiently the cellular uptake of glucose is known as “insulin resistance” that is usually hard to diagnose, leading to a compensatory increase in the production of insulin (hyperinsulinemia). This stage 2 of T2DM can result in heart disease and many other illnesses. The impact of hyperinsulinism has been dubbed syndrome X (Reaven, 2005). Metabolic syndrome (MS) or syndrome X often refers to multiple related clinical disorders including insulin resistance, abdominal obesity, hypertension, a variety of blood sugar abnormalities, high blood levels of triglycerides (hyperlipidemia) and low HDL cholesterol that are risk factors for cardiovascular disease. The metabolic syndrome is an increasingly prevalent disease in industrialized societies (Wang et al., 2003; Kahn et al., 2005).

Eventually, the insulin-producing β cells fail to overcome the defect(s), resulting in a drop in insulin levels leading to impaired glucose tolerance. This pre-diabetic stage 3 of T2DM is often diagnosed through an oral glucose tolerance test (OGGT) and by symptom questionnaires, although measurement of fasting plasma glucose