A Pathophysiological Overview on Diabetes Mellitus

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1. INTRODUCTION

Diabetes Mellitus is a third World Problem(The World Health Report, 1997, WHO) globally, there were estimated to be approximately 135 million adults with diabetes in 1995. By the year 2025, it is expected to rise to 300 million, an increase of approximately 120%. More than 80% of person with diabetes will be found in the developing countries by the year 2025. In United States, there are 15.7 million people or 5.9% of the population who have diabetes and approximately 2,200 people are diagnosed with diabetes each day. Even though prevalence data for diabetes among Koreans are limited and partially available, the prevalence is likely to increase considerably with further urbanization and westernization of lifestyles. Because of its chronic nature, the severity of its complications and the means required to control them, diabetes is a particularly costly disease for the affected individual and society. However, costs vary enormously, depending on social, economic and health service factors. In United States, the total annual economic cost of diabetes was estimated at 92 billion dollars (1992)-45 billion as direct medical and treatment costs and 47 billion as the value of productivity foregone due to disability, work loss and premature death.

What is Diabetes ?

Diabetes Mellitus is a group of disease characterized by high levels of blood glucose resulting from defects in insulin secretion, insulin action, or both.

Diagnosis and Classification

The diagnostic criteria and classification of diabetes have remained essentially unchanged since they were proposed by the WHO in 1980. To bring them into line with the latest scientific information on the subject and harmony with those being proposed by the ADA(USA), a WHO consultations took place in 1996. For diagnosis of diabetes, the Group recommended the reduction of the critical value of fasting blood glucose concentration from 140mg/dl to 126mg/dl. Concerning classification, they recommended that the terms type 1 and type 2 are more appropriate than insulin-dependent and non-insulin dependent diabetes since the former terms give a pathological basis for classification. For either type, the Group proposed an optional subclassification according to severity and treatment requirement.

The Four Types of Diabetes

-**Type 1 diabetes** (insulin-dependent diabetes mellitus or juvenile-onset diabetes) may account for 5% to 10% of all diagnosed cases of diabetes

-**Type 2 diabetes** (non-insulin-dependent diabetes mellitus or adult-onset diabetes) may account for 90% to 95% of all diagnosed cases of diabetes

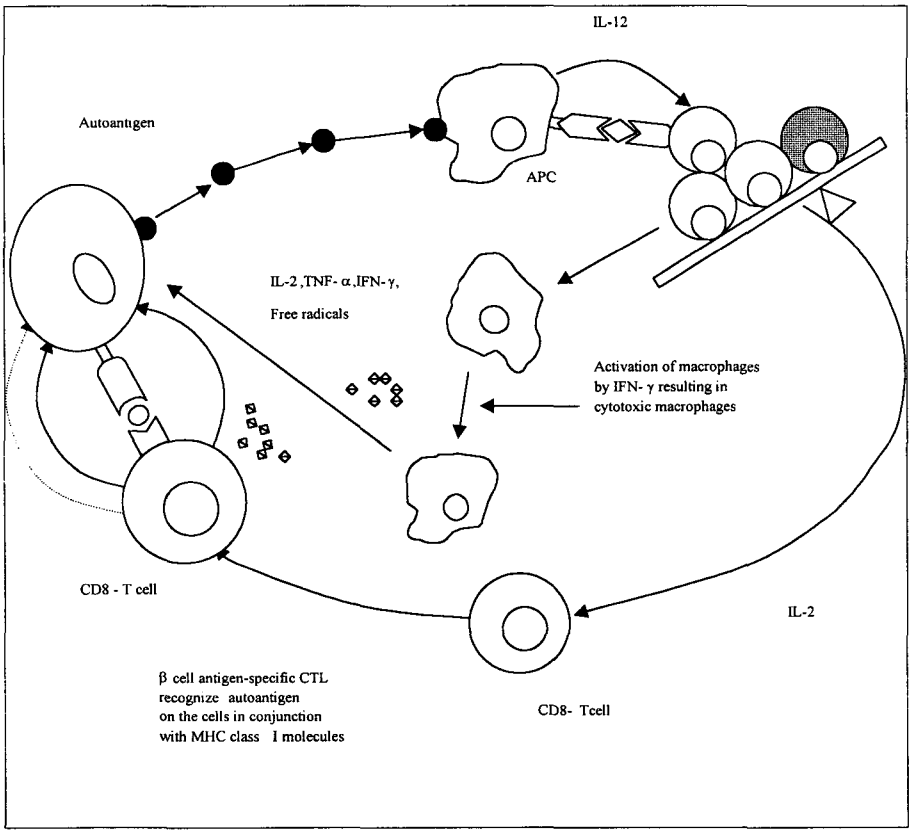
-**Gestational diabetes** develops in 2% to 5% of all pregnancies but disappears when a pregnancy is over. Gestational diabetes occurs more frequently in certain tribes and persons with a family history of diabetes. Obesity is also associated with high risk. Women who have had gestational diabetes are at increased risk for later developing type 2 diabetes.

-**Other specific types** of diabetes result from specific genetic syndromes, surgery, drugs, malnutrition, infection, and other illnesses. Such types of diabetes may account for 1% to 2% of of all diagnosed cases of diabetes.

2. TYPE 1 DIABETES MELLITUS

What is Type 1 Diabetes Mellitus ?

Type 1 diabetes mellitus is resulted from the destruction of insulinproducing beta cells. Peak incidence occurs during puberty, around 10 to 14 years of age. People with type 1 diabetes must take daily insulin injections to stay alive.



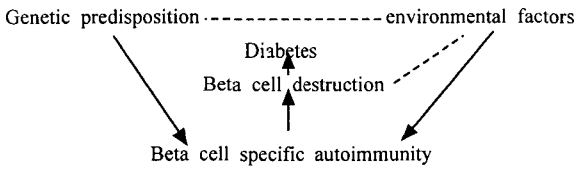
What are the Signs and Symptoms of Type 1 Diabetes ?

Hyperglycemia, Hyperglycosuria, frequent urination, extreme hunger, thirst and weight loss, weakness and tiredness, vomiting, stomachache, mood change, irritability.

Who is at Greater Risks for Type 1 Diabetes ?

Risk factors are less well defined for type 1 diabetes than for type 2 diabetes. Siblings of people with type 1 diabetes, children of parents with type 1 diabetes are at greater risk for type 1 diabetes. There is a higher incidence of diabetes in whites than other racial groups.

The Pathogenesis of Type 1 Diabetes



What causes Type 1 Diabetes ?

What causes type 1 diabetes is not exactly known yet. Type 1 diabetes appears to be a disease of autoimmunity. Genetic susceptibility may be a prerequisite for the development of type 1 diabetes and environmental factors, such as viruses, diet and toxins are also involved in the clinical expression of this diseases

Treatment of Type 1 Diabetes

Diabetes treatment and prevention strategies advance daily. Treatment requires a strict regimen that typically includes a carefully calculated diet, planned physical activity, home blood glucose testing several times a day, and multiple daily insulin injection. However, type 1 diabetes has no cure. Scientists are trying to learn how to predict the development of diabetes and how to prevent its progression.

The Prediction of Type 1 Diabetes

The predictability of type 1 diabetes continues to improve through detection of combinations of beta cell autoantigens (e.g. ICA, IAA, IA-2 and GAD-65 autoantibodies); The identifications of major histocompatibility complex (MHC)-associated predisposition genes will greatly aid such analysis.

The Prevention of Type 1 Diabetes

-Classification

Primary prevention	In normal individuals, by removal of etiological factors, dietary restrictions, changes in diet, removal of diabetogenic viruses
Secondary prevention	During the latency phase in subjects with positive markers
Tertiary prevention	At early diagnosis, to protect residual beta cell mass and function for prevention of long-term complications

-Present human preventive trial for type 1 diabetes (undertaken)

Primary prevention	Cows milk exclusion	Promising in the NOD mice
Secondary prevention	Nicotinamide Insulin (S.C., I.V., oral)	Promising only at high dose in NOD mice Promising in NOD mice and in BB rats

-Preventive approaches under investigation in animal models

T cell vaccination	under investigation
Thymic injection of beta cell autontigen(GAD65)	under investigation
Vaccination with specific insulin peptides	under investigation
Nitric Oxide inhibitors	under investigation
Gene therapy(IL-4 transgenic mouse)	under investigation
Mono/lymphocytic adherence inhibitors	effective in NOD mice
Analogues of vitamin D3	highly effective in NOD mice
Antioxidants	modestly effective in NOD mice

3. TYPE 2 DIABETES MELLITUS

What is Type 2 Diabetes Mellitus ?

Both fasting hyperglycemia and excessive increases in glucose concentration following oral glucose loading are criteria for the diagnosis of type 2 diabetes mellitus. The characteristic feature of this disease is that associated obesity is common and that its onset is over 30 years of age.

What are the Signs and Symptoms of Type 2 Diabetes?

Any of the type 1 symptoms, Tingling/numbness in the hands or feet, Cuts/bruises that are slow to heal Recurring skin, gum or bladder infections, Blurred vision, Frequent infections

Who is at Greater Risks for Type 2 Diabetes?

People over age 45, people with a family history of diabetes, obesity, low HDL or high triglycerides, impaired glucose tolerance and physical inactivity are at greater risks for type 2 diabetes. Certain racial and ethnic groups (e.g., African Americans, Hispanic Americans, Asian & Pacific Islanders, and Native Americans) show greater incidence than other racial groups. Women who had gestational diabetes, a form of diabetes occurring in 2-5 percent of all pregnancies or who have had a baby weighing 9 pounds or more at birth have greater risks.

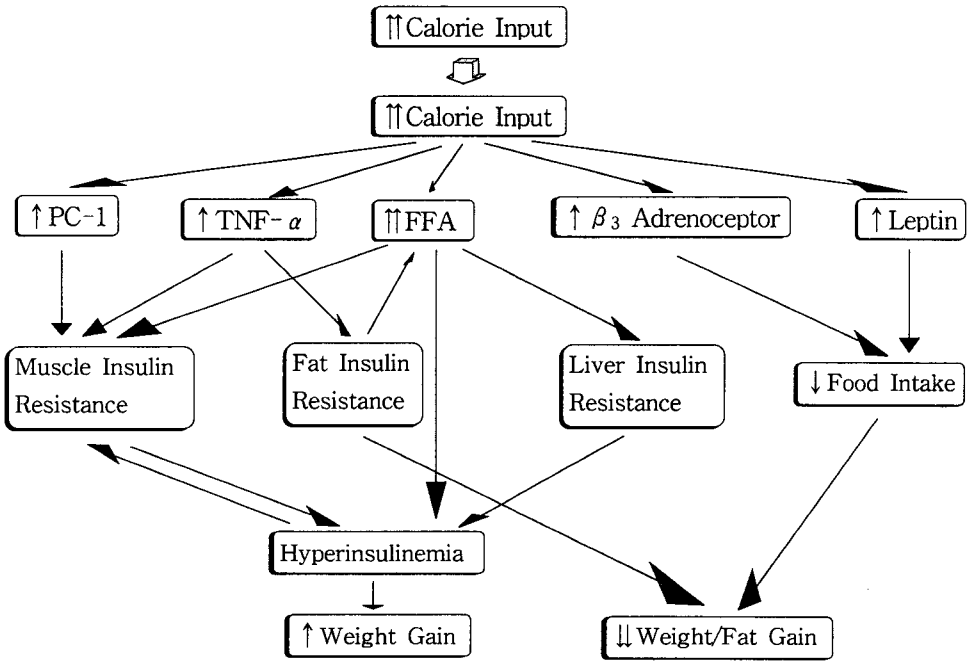
What causes Type 2 Diabetes ?

The etiology of type 2 diabetes mellitus is essentially unkown ; however, the pathogenesis of this disease involves diminished insulin actions at peripheral tissues, i.e. insulin resistance, abnormalities in insulin release from the pancreatic islet cells, as well as accelerated hepatic glucose production. This interference with the action

of insulin may be pre-receptor, receptor or post-receptor.

Pre-receptor insulin resistance is due to antibodies to insulin; receptor resistance to the action of insulin is due to changes in the shape of the insulin receptor referred to as "mutations". There were over 40 different mutations of the insulin receptor. Post-receptor insulin resistance is due to changes in responses within the cell to the message released when insulin attaches to the insulin receptor on the cell wall. The commonest form of insulin resistance which then leads to elevated insulin levels is the receptor defect; to overcome this defect in action of the receptors, insulin levels become elevated. However with continued longterm insulin resistance, the resistance changes from a receptor to a post-receptor defect. Insulin resistance often precedes obesity and obesity may be simply one of the consequences of insulin resistance. In recent studies, the possible candidates causing insulin resistance is introduced. PC-1, TNF-α, leptin is overproduced and released from fat cell and elevated glucose, lipid and insulin could display toxic effects to various tissues.

The Pathogenesis of Type 2 Diabetes



Treatment of Type 2 Diabetes

For the NIDDM patient, reduction of intake of sugars and fats and concomitant reduction of body fat levels are key. The oral hypoglycemic agents(Sulfonylurea group, Biguanide group) with diet control is essential to the patient. Sulfonylurea

group act initially by stimulating insulin production by the beta cells. Biguanide group works mainly by suppressing excessive hepatic glucose production. They also have a lesser effect on improving peripheral insulin resistance and does not cause weight gain and in some cases may lead to a loss of weight. Acarbose is an alpha glucosidase inhibitor, which works by delaying the absorption of carbohydrates in the small intestine and thus improving postprandial glucose values. Postprandial elevation in blood glucose values is a serious and commonly overlooked problem in type II diabetes that contributes to poor metabolic control. The thiazolidinediones are the fourth and newest class of anti-diabetic agents to be approved by the FDA for the treatment of type II diabetes. They work mainly by improving peripheral insulin resistance in skeletal muscle without stimulating insulin secretion. They also work to a lesser degree by reducing excessive hepatic glucose production. In addition, troglitazone was synthesized with an alpha-tocopherol substitution and has antioxidant properties, as well as being an "insulin sensitizer".

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