CHAPTER II

BACKGROUND

Diabetes mellitus

Diabetes mellitus is a heterogeneous syndrome. Its primary manifestation, hyperglycemia, can arise from various causes. It is characterized by a lack of insulin secretion and/or increased cellular resistance to insulin resulting in hyperglycemia and other metabolic disturbances. Symptoms of uncontrolled diabetes include excessive thirst and hunger, frequent urination, weight loss, blurred vision, and recurrent infections. However, many patients have no symptoms in early stages of the disease. Diabetes mellitus is associated with severe neurological, cardiovascular, ophthalmologic and renal complications.

Types of diabetes mellitus

Diabetes mellitus is a group of disease states that may be classified as follows.

Insulin-dependent diabetes mellitus(IDDM) or Type I diabetes

IDDM usually appears before the age of 30 years and has an abrupt onset of symptoms that requires prompt medical treatment. Patients with IDDM need insulin injection to control blood glucose levels. Patients can develop severe and abrupt symptoms of hyperglycemia, dehydration, and ketoacidosis if they do not get adequate insulin treatment.

Non-insulin-dependent diabetes mellitus(NIDDM) or Type II diabetes

NIDDM appears primarily in adults over 30 years of age but can occur at any age. It may not be associated with any symptoms for many

years. The majority of patients with NIDDM are obese. The disease may be controlled satisfactorily by dietary treatment and exercise. Many patients with NIDDM need some forms of oral hypoglycemic agents to control blood glucose level and some patients need insulin treatment.

Diabetes associated with certain conditions or syndromes

These are hyperglycemic states occurring in relation to other disease states. Pancreatic diseases, drug or chemical-induced diabetes, endocrinopathies, insulin-receptor disorders, and certain genetic syndromes(e.g.Laurence-Moon-Biedl syndrome, Werner syndrome, etc.) may be associated with hyperglycemic states.

Gestational diabetes mellitus(GDM)

Gestational diabetes mellitus is a disorder with onset or first recognition of symptoms during pregnancy. It is estimated to occur in ~ 3% of pregnancies and usually disappears after delivery. Women with gestational diabetes are at increased risk for developing diabetes at a later date. Hyperglycemia during pregnancy and labor is associated with increased fetal morbidity.

Impaired glucose tolerance(IGT)

People with impaired glucose tolerance have high blood glucose level but at a level lower than that which qualifies as a diagnosis of diabetes. Symptoms of diabetes are absent.

Diagnosis of diabetes mellitus

The criteria for diagnosis of diabetes mellitus are as followed:

A. Diabetes mellitus-adult

1. Unequivocal elevation of plasma glucose(random plasma glucose ≥ 200 milligrams/deciliter(mg/dl)) and classic symptoms of

diabetes, including polydipsia, polyuria, polyphagia, and weight loss.

2. Fasting plasma glucose(FPG) ≥ 140 mg/dl on two occasions.

3. Fasting plasma glucose < 140 mg/dl and two oral glucose tolerance tests(OGTT's) with the 2-h plasma glucose ≥ 200 mg/dl and one intervening value ≥ 200 mg/dl after a 75-g OGTT.

B.Impaired glucose tolerance

Fasting plasma glucose < 140 mg/dl and 2-h plasma glucose ≥ 140 and < 200 mg/dl with one intervening value ≥ 200 mg/dl after a 75-g glucose load.

C.Gestational diabetes mellitus(GDM)

When the above criteria for diabetes mellitus is established, no additional tests are needed. In some cases it is necessary to do oral glucose tolerance test to diagnose gestational diabetes mellitus. The criteria for a positive diagnosis for gestational diabetes mellitus are: fasting plasma glucose 105 mg/dl; 1-h plasma glucose 190 mg/dl; 2-h plasma glucose 165 mg/dl; 3-h plasma glucose 145 mg/dl., after 100-g glucose load.

Complications of diabetes

People with diabetes mellitus suffer from increased morbidity and early mortality related to cardiovascular, microvascular, and neuropathic complications. Microvascular diabetic complications result in diabetic retinopathy and diabetic nephropathy. Diabetic retinopathy is very common. By 10 years, approximately 50 per cent and by 20 years, approximately 90 per cent of diabetics have nonproliferative retinopathy. In a small percentage of diabetics, nonproliferative retinopathy progresses to proliferative retinopathy that may lead to severe visual loss or blindness. Diabetic retinopathy is the most common cause of blindness in developed countries. Diabetic nephropathy usually occurs between 15 and 20

years after the onset of diabetes in approximately 50 per cent of Type I diabetics. The first major clinical manifestation of diabetic nephropathy is persistent proteinuria(> 500 mg/24 hr). On the average, azotemia occurs three years after the onset of persistent proteinuria, and end-stage renal failure develops three years after the azotemia. Diabetic patients with renal failure are treated with either hemodialysis, peritoneal dialysis, or renal transplantation.

Arteriosclerosis is a common problem in diabetics and occurs more extensively and earlier than in the general population. The causes of the accelerated atherosclerosis are probably multifactorial. Atherosclerotic vascular disease in diabetic patients affects the coronary, cerebral, and peripheral vessels leading to significant mortality and morbidity from coronary heart disease, stroke, claudication and amputation.

Diabetic neuropathy is a common disabling complications of diabetes, resulting in a great deal of morbidity and a reduced quality of life. Peripheral diabetic neuropathy may result in pain, loss of sensation, and muscle weakness. Autonomic involvement can affect gastrointestinal, cardiovascular, and genitourinary function.

Therapeutic treatment of diabetes mellitus

The goal of treatment of diabetes mellitus are to normalize abnormal carbohydrate, protein and lipid metabolism in order to alleviate and prevent acute and chronic complications. The Diabetes Control and Complications Trial(DCCT) convincingly demonstrated the relationship of hyperglycemia to the development and progression of microvascular and neuropathic complications in people with insulin-dependent diabetes mellitus and showed that improved glycemic control achieved through an intensive insulin treatment regimen reduced these complications(DCCT Research Group. 1993). In the DCCT, a 50% reduction in microvascular complications was achieved with a mean HbA1c of 7.2% in the intensive insulin treated cohort. The data

suggest that any improvement in the degree of blood glucose control will postpone development and slow the progression of microvascular complications. The American Diabetes Association(1995) has recommended treatment goals for people with diabetes that emphasize glycemic control(Table 2).

Table 2 Glycemic control for people with diabetes

Biochemical index	Nondiabetic	Goal	Action suggested
Preprandial glucose (mg/dl)	< 115	80-120	< 80 > 140
Bedtime glucose (mg/dl)	< 120	100-140	<100 > 160
HbA1c(%)	< 6	< 7	> 8

Medical nutrition therapy and exercise are integral to total diabetes care and management. However, a large proportion of people with diabetes mellitus needs pharmacological treatment. The choice of pharmacological agents in Thailand is limited to insulin, sulfonylureas, the biguanide metformin, and the α-glucosidase inhibitor acarbose. Although these agents have been effective in many patients, the difficulty of achieving near-normal glycemia in the majority of NIDDM patients emphasizes the need for additional therapeutic options. Search for more effective agents with fewer side effects is under way in various sites around the world. One important source of agents with hypoglycemic effect is herbal medicine.

People in different regions use a wide varieties of plants which are believed to have hypoglycemic effect. One of the plants, Aloe vera, is widely used for many medical purposes since ancient times.

The Aloe vera plant

There are more than 300 species of Aloe plants. Aloe Barbadensis is now referred to by taxonomists as Aloe vera. The Aloe plant has yellow flowers. The leaves are arranged in a rosette configuration; they are triangular and spear-like and have thorny ridges. They are meaty if filled with get that arises from the clear central mucilaginous pulp. The peripheral bundle sheath cells give rise to a bitter, yellow exudate that is responsible for the cathartic effect.

Chemical components of Aloe vera

The different species of Aloe have different chemical compositions. Many organic compounds and inorganic elements have been found and are listed in Table 3(Shelton, 1991).

Table 3 Chemical composition of Aloe vera

Anthraquinones	Aloin, barboloin, isobarbaloin, anthranol, aloetic acid, anthracene, ester of cinnamic acid, aloe-emodin, emodin, chrysophanic acid, ethereal oil, resistannol
Inorganic	Calcium, sodium, chlorine, manganese, magnesium, zinc, copper, chromium, potassium sorbate
Saccharides	Cellulose, glucose, mannose, l-rhamnose, aldopentose
Enzymes	Oxidase, amylase, catalase, lipase, alkaline phosphatase
Vitamins	B1, B2, B6, choline, folic acid, C, alpha-tocopherol, beta carotene
Essential amino acids	Lysine, threonine, valine, methionine, leucine, isoleucine, phenylalanine
Nonessential amino acids	Histidine, arginine, hydroxyproline, aspartic acid, glutamic acid, proline, glycine, alanine, tyrosine
Miscellaneous	Cholesterol, triglycerides, steroids, beta-sitosterol, lignins, uric acid, gibberellin, lectin-like substance, salicylic acid

The constituents that have hypoglycemic effects are polysaccharides(Hikino et al, 1985, Hikino et al, 1986) and anthraquinones(Ghannam, 1985, Mossa, 1985). The polysaccharide constituent lowered blood glucose levels in mice and in human (Ghannam, 1985, Hikino et al, 1986). The anthraquinone constituent showed hypoglycemic activity in non-insulin-dependent diabetes patients and diabetic mice. Both polysaccharides and anthraquinones may mediate their hypoglycemic activity through stimulating the pancreatic β-cells to synthesize and/or release more insulin(Ghannam, 1985, Ajabnoor, 1990). However, the mechanism of action of Aloe vera in lowering blood glucose is controversial.

This study intends to evaluate the effect of the Aloe vera on blood glucose and blood lipid levels in Thai diabetic patients. Once the efficacy of the Aloe vera in lowering blood glucose level is established, its effectiveness may be evaluated in clinical settings and dose-response relationship may be explored.