CHAPTER TWO:

REVIEW OF LITERATURE
SECTION ONE:

2.0. REVIEW: DIABETES OVERVIEW
2.1.1. Definition

The term diabetes mellitus (DM) describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism that are associated with absolute or relative deficiencies in insulin action and/or insulin secretion\textsuperscript{\textsuperscript{200}}.

2.1.2. Classification

The classification of diabetes mellitus and other forms of glucose tolerance was published by WHO in 1980\textsuperscript{\textsuperscript{251}} and in modified form in 1985\textsuperscript{\textsuperscript{201}}. The 1980 and 1985 classification of diabetes mellitus and allied categories of glucose intolerance included clinical classes and two statistical risk classes.

I-Clinical Classes\textsuperscript{\textsuperscript{201,251}}

A. Diabetes mellitus (DM)

1. Insulin-dependent diabetes mellitus (IDDM) (Type 1 diabetes)

2. Non-insulin-dependent diabetes mellitus (NIDDM) (Type 2 diabetes)
   - Non-obese
   - Obese

3. Malnutrition related-diabetes mellitus (MRDM)

4. Other types of diabetes associated with certain conditions and syndrome such as:
   - Pancreatic disease
• Disease of hormonal etiology
• Drug induced or chemical induced condition
• Abnormalities of insulin or its receptors
• Certain genetic syndromes and miscellaneous

B. Impaired glucose tolerance (IGT)

• Non-obese
• Obese
• Associated with certain conditions and syndromes

C. Gestational diabetes mellitus (GDM)

II-Statistical Risk Classes

(Subjects with normal glucose tolerance but substantially increased risk
of developing diabetes):

A. Previous abnormality of glucose tolerance
B. Potential abnormality of glucose tolerance

I-Clinical Classes

A. Diabetes mellitus (DM)

1. Type 1 diabetes

Type 1 diabetes (previously called insulin dependent diabetes mellitus
(IDDM)) or juvenile-onset diabetes mellitus, accounts for 5-10% of all
cases in the USA\textsuperscript{174,175}. Type 1 diabetes usually occurs before the age of 30 years, but can occur at any age\textsuperscript{20}. Type 1 diabetes encompasses the majority of cases which are primarily hormone deficiency disease due to autoimmune destruction of pancreatic islet β-cells\textsuperscript{200}. Patient with Type 1 diabetes have classical symptoms of hyperglycemia\textsuperscript{20}. Patient becomes dependent on administered insulin for survival\textsuperscript{281}.

2. Type 2 diabetes

Type 2 diabetes (previously called non-insulin dependent diabetes mellitus (NIDDM) or adult-onset diabetes is by far the more common form of diabetes, accounting for 90-95% of all cases in USA\textsuperscript{123,175}. Type 2 diabetes usually occurs after the age of 30 years but can occur at any age\textsuperscript{20}. Through the past decade, it has become clear that resistance to insulin mediated glucose disposal in the muscle, liver and adipose tissue, along with defective insulin secretion from the pancreatic β-cell, characterizes Type 2 diabetes\textsuperscript{197}. There are marked differences in the phenotypic expression of Type 2 diabetes with affected individuals exhibiting varying levels of insulin resistance and impairments in insulin secretion\textsuperscript{197}. This range of abnormalities includes metabolic derangements characterized by predominant defects in insulin sensitivity with relative β-cell dysfunction to metabolic derangements characterized by severe β-cell dysfunction accompanied by mild insulin resistance\textsuperscript{52}. Although the pathophysiologic
causes of insulin resistance and β-cell dysfunction are unknown, it clearly indicates that there are genetic and environmental factors leading to the development of each of these abnormalities\textsuperscript{197}.

3. Malnutrition related-diabetes mellitus (MRDM)

Malnutrition related diabetes mellitus occurs in certain parts of the world and may be more frequent than Type 1 diabetes and may approximate the frequency of Type 2 diabetes\textsuperscript{172}. It is seen with particular frequency in India and certain parts of Africa\textsuperscript{172}. It is usually found in young people and is characterized by severe protein malnutrition and emaciation and in some patients by evidence of pancreatic calcification on X-ray films of the abdomen\textsuperscript{172}. The diabetes of these patients is characterized by severe hyperglycemia unaccompanied by ketosis\textsuperscript{172}. These individuals require insulin for health and life, although they are not dependent on insulin for prevention of ketosis\textsuperscript{172}. It was shown that the C-peptide concentrations (explained below), were lower in patients with this type of diabetes than inpatient with Type 2 diabetes, but were significantly higher than those seen in Type 1 diabetes\textsuperscript{172}. It is quite likely that the higher insulin secretion capacity reflected by the higher C-peptide concentrations is responsible for the absence of ketosis in these patients\textsuperscript{172}. 

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4. Other specific types

Diabetes of other types is seen in less than 3% of individuals with diabetes\(^{20}\). The development of diabetes is associated with certain conditions and syndromes such as genetic defects of pancreatic β-cell function, genetic defects of insulin action, disease of exocrine pancreas, endocrinopathies, drug or chemical induced diabetes, uncommon forms of immune-mediated diabetes and selected genetic syndromes associated with diabetes\(^{20,151,257}\).

B. Impaired glucose tolerance (IGT)

Impaired glucose tolerance is not diabetes \textit{per se}, but denotes hyperglycemia during an oral glucose test\(^{218}\). The blood glucose value is above the normal range after glucose challenge but below the diabetic range\(^{218}\). About 3 to 5% of patients with impaired glucose tolerance progress to overt diabetes every year\(^{218}\). This category represents a risk factor for development of diabetes and cardiovascular disease\(^{20}\).

C. Gestational diabetes mellitus (GDM)

Gestational diabetes usually occurs during pregnancy, usually in the 2\(^{\text{nd}}\) or 3\(^{\text{rd}}\) trimester\(^{20}\). It complicates 2%-4% of all pregnancies\(^{20}\). After delivery, blood glucose levels generally return to normal range, although one-third to one-half of these women develop Type 2 diabetes within 10 years\(^{86}\).
II-Statistical Risk Classes

1. Previous abnormality of glucose tolerance

The classification of previous abnormality of glucose tolerance is restricted to individuals with previous diabetic hyperglycemia or impaired glucose tolerance but who presently have normal glucose levels\textsuperscript{86}. Individuals who have gestational diabetes but returned to normal glucose tolerance after parturition are examples, as are individuals who were obese and who have developed diabetes or impaired glucose tolerance after loss of weight\textsuperscript{86}.

2. Potential abnormality of glucose tolerance

Individuals in the class of potential abnormality of glucose tolerance have never exhibited abnormal glucose tolerance but have a substantially increased risk for the development of diabetes\textsuperscript{86}.

2.1.3. Aetiology

1. Type 1 diabetes

A. Autoimmune diabetes mellitus

Type 1 diabetes, or juvenile-onset diabetes, results from autoimmune mediated destruction of the beta cells of the pancreas\textsuperscript{200}. The rate of destruction is variable, being rapid in some individuals and slow in others\textsuperscript{260}. The rapidly progressive form is commonly observed in children, but also may occur in adults\textsuperscript{260}. The slow progressing form generally occurs
in adults and is sometimes referred to as latent autoimmune diabetes in adults (LADA)\textsuperscript{260}. Some patients, particularly children and adolescents, may present with ketoacidosis as the first manifestation of the disease\textsuperscript{200}. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis in the presence of infection or other stress\textsuperscript{200}. Still others, particularly adults, may retain residual beta-cell function, sufficient to prevent ketoacidosis, for many years\textsuperscript{261}. Individuals with this form of Type 1 diabetes often become dependent on insulin for survival and are at risk for ketoacidosis\textsuperscript{252}. At this stage of the disease, there is little or no insulin secretion as manifested by low or undetectable levels of plasma C-peptide\textsuperscript{130}. Markers of immune destruction, including islet cell autoantibodies and/or autoantibodies to insulin and autoantibodies to glutamic acid decarboxylase (GAD) are present in 85-90\% of individuals with Type 1 diabetes mellitus when fasting diabetic hyperglycemia is initially detected\textsuperscript{200}. The peak incidence of this form of Type 1 diabetes occurs in childhood and adolescence, but the onset may occur at any age, ranging from childhood to the ninth decade of life\textsuperscript{200}. There is a genetic predisposition to autoimmune destruction of beta cells, and also environmental factors that are still poorly defined\textsuperscript{200}. Although patients are usually not obese when they present with this type of diabetes, the presence of obesity is not incompatible with the diagnosis\textsuperscript{200}. These
patients may also have other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis and Addison's disease. 

B. Genetic factors

It is believed the Human Leukocyte Antigen (HLA) region on the short arm of chromosome 6 is responsible for the majority of the genetic susceptibility to Type 1 diabetes. The strongest associations are to be found in the DQ and DR regions of the major histocompatibility complex (MHC) with 95% of patient with Type 1 diabetes having either DR3 or DR4 alleles compared to 40% in a control population. In addition, certain DQ alleles, which code for amino acid other than aspartame at position 57 of the β-chain and/or arginine at position 52 for the α-chain of insulin are significantly more common in the diabetic population. Interestingly, DR2 is protective against Type 1 diabetes. There are also associations with certain HLA class 1 antigens, for example B8 and B15.

C. Idiopathic

There are some forms of Type 1 diabetes, which have no known aetiology. Some of these patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity. This form of diabetes is more common among individuals of African and Asian origin. In another form found in Africans, patients present an absolute
but intermittent requirement for insulin replacement therapy and may periodically develop ketoacidosis.

D. Viruses

Certain viruses have been found responsible for beta-cell destruction. Diabetes occurs in some patients with congenital rubella. In addition, Coxsackie B, cytomegalovirus and other viruses (e.g. adenovirus and mumps) have been implicated in inducing the disease.

E. Cows milk

It has been observed that diabetic children are breast fed for a significantly shorter period than controls suggesting that breast feeding may be a protective factor for diabetes. The incidence of diabetes in murine models can be modified by diet including the exclusion of cow's milk. Bovine serum albumin (BSA) in cow's milk resembles a protein in beta-cells. These observation and others have led to the suggestion that early exposure to cows’ milk protein may be important in the aetiology of Type 1 diabetes.

2. Type 2 diabetes

A. Genetic factors

Investigation on genetic factors for the development of Type 2 diabetes is complicated, since both impairment of beta cell functions and abnormal
response to insulin are involved\textsuperscript{197}. A small number of cases of Type 2 diabetes are caused by single gene defect. These cases include maturity-onset diabetes in youth (mutated MODY gene), syndrome of insulin resistance (insulin receptor defect), maternal inherited diabetes and deafness (Mitochondrial gene defect)\textsuperscript{134}. In the recent years there have been numerous studies on the relationship of genetic markers to the development of Type 2 and Type 1 diabetes. Recently genome scan studies have been conducted to identify susceptibility loci that are linked with Type 2 diabetes that hopefully will shed light on the polygenetic nature of this disease\textsuperscript{222}.

B. Family history

Family history is an established risk factor for the development of Type 2 diabetes\textsuperscript{12}. Twin studies have demonstrated that Type 2 diabetes is more highly concordant in monozygotic twins than in dizygotic twins\textsuperscript{177}. This concordance was demonstrated in a study of 250 monozygotic and 264 dizygotic white male twin pairs who had a history of genetic predisposition to Type 2 diabetes\textsuperscript{177}. This study concluded that the concordance rate for monozygotic twins was 58%, as compared with the concordance rate of 17% for dizygotic twins\textsuperscript{177}. The concordance rate of 58% as opposed to 100% supports the fact that there are environmental and genetic factors involved in the genesis of Type 2 diabetes\textsuperscript{197}. 

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D. Race/Ethnicity

Type 2 diabetes occurs in all races, but the prevalence tends to be high among certain ethnic group than other\textsuperscript{197}. The prevalence of Type 2 diabetes is higher in the black population, when compared with non-Hispanic white population at all ages\textsuperscript{197}. In 1993 estimates of diabetes prevalence in non-Hispanic whites compared to blacks, respectively, were 0.7\% and 0.9\% for individuals less than 45 years of age, 5.4\% and 8.2\% for individuals between 45 and 64 years of age and 10.2\% and 19.9\% for individuals 65 years of age or older\textsuperscript{197}. In addition, data from the Third National Health and Nutrition Examination Survey, 1994-1998 (NHANE III)\textsuperscript{123}, estimated that age and sex standardized prevalence rates of physician-diagnosed diabetes for non-Hispanic whites, non-Hispanic blacks and Mexican-Americans 20 years of age and older were 4.8\%, 8.2\% and 9.3\% respectively. Age and sex standardized prevalence rates for undiagnosed diabetes among non-Hispanic whites, non-Hispanic blacks and Mexican-American 20 years of age or older were estimated to be 2.5\%, 3.6\% and 4.5\% respectively\textsuperscript{123}. In addition, age and sex standardized prevalence rate for IGT among non-Hispanic whites, non-Hispanic blacks and Mexican-Americans were 6.8\%, 7.0\% and 8.9\% respectively\textsuperscript{123}. These differences, however, were most pronounced between Mexican-American men and women, at 7.7\% and 10.9\% respectively\textsuperscript{123}. In addition,
increasing age was associated with increased prevalence of diabetes. In individuals 64 years of age or older the prevalence of diabetes was 13.2%\textsuperscript{123}. The highest rates of diabetes in the USA and the world are in the Pima Indians of Arizona\textsuperscript{123}. Pima Indians between the ages 30 and 46 years have prevalence rates of Type 2 diabetes of approximately 50%\textsuperscript{13}.

E. Socioeconomic status

Certain key factors that account for these marked geographic and ethnic differences in diabetes have been suggested. One of the critical risk factors appears to be change in socioeconomic status\textsuperscript{12}. In communities where there has been rapid economic development status, there appears to be a marked and rapid increase in the incidence and prevalence of Type 2 diabetes\textsuperscript{12}. The data suggested that individuals in the lowest brackets have the highest risk for Type 2 diabetes\textsuperscript{12}. In addition, education was also found to be inversely related to diabetes risk in the USA\textsuperscript{12}.

F. Diet

There is association between the amount of caloric intake and development of Type 2 diabetes\textsuperscript{197}. The dependent effects of caloric restriction on prevention of Type 2 diabetes, however, are difficult to discern. The exact composition of diet in the prevention of Type 2 diabetes is also not clear\textsuperscript{197}. High carbohydrate and low fat diets seem to deteriorate insulin sensitivity,
but high fat and low carbohydrate diets may decrease satiety, induce low
leptin levels and lead to higher energy consumption, obesity and more
insulin resistance^{118}.

G. Obesity
It has long been established that total body obesity is a risk factor for
development of Type 2 diabetes^{12}. When sugar and saturated fat become a
regular part of the diet, a rapid rise in body weight of the population has
been noted. There is a strong correlation between degree of obesity and risk
of Type 2 diabetes. Approximately 80% of patients of Type 2 diabetes are
obese^{197}. Obesity probably acts as a diabetogenic factor through increasing
the resistance to action of insulin. The impact of regional adipose tissue
distribution has been documented in the literature for several decades.
Krotkiewski et al^{147} evaluated women with upper and lower body obesity
and found that central body obesity is an important prognostic marker for
glucose intolerance, hyperinsulinemia and hypertriglyceridemia. In
addition, Kissebah et al^{143} noted that men and women with a male
abdominal type of obesity are more susceptible to the detrimental effects of
excess body fats.

H. Physical inactivity
A number of studies have demonstrated that high levels of physical activity
A number of studies have demonstrated that high levels of physical activity protect against the development of Type 2 diabetes\textsuperscript{124, 161, 162}. In a study of former male college students from the University of Pennsylvania, an inverse relationship between energy expenditure in leisure time physical activity and the development of Type 2 diabetes was demonstrated\textsuperscript{124}. In a study of female registered nurses, women who engaged in vigorous physical activity at least once per week had significantly less risk for development of diabetes than those who exercised less frequently and less vigorously\textsuperscript{162}. In this study, however, a dose response was not observed between the frequency of exercise per week and decrease in risk of development of diabetes mellitus. In another study of US adult male physicians, a similar protective effect of vigorous exercise, performed at least once weekly was noted\textsuperscript{161}.

**M. Urbanization**

It has been noted that when certain populations migrate from rural to the urban setting they have an increased prevalence of Type 2 diabetes when compared with those who remain in the original setting\textsuperscript{197}. This is primarily because urbanization is associated with change in diet, physical activity, socioeconomic status and obesity. The relationship between diabetes and urbanization is best exemplified by the Pima Indians of the Southwestern United States, who have a greater than 50% chance of developing Type 2
diabetes in their lifetime, but whose ancestors in Mexico have a low risk for diabetes. In addition, the migration of populations from non-Westernized to Westernized settings often increases the risk of Type 2 diabetes. This increase is best exemplified by Japanese-Americans living in Seattle who have much greater incidence of Type 2 diabetes than their counterparts in Tokyo.

N. Intrauterine Environment

Intrauterine environment is a possible factor that may increase the risk for Type 2 diabetes. Low birth weight has been associated with increased risk for developing diabetes. It was hypothesized that this relationship is the result of under nutrition in utero that causes limited development of pancreatic β-cells, whose number is fixed at birth. In addition, it has been reported that the offspring of mothers who had Type 2 diabetes during pregnancy have an increased risk of development of diabetes. However, those born to mothers before the development of Type 2 diabetes have a much lower risk than those born after the mother develops diabetes.

2.1.4. Clinical manifestations of diabetes mellitus

The clinical presentation of diabetes mellitus includes a variety of signs and symptoms that are polydipsia, polyphagia, polyurea, weight loss, blurring of vision, fatigue and weakness. In severe forms, ketoacidosis
or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and in absence of effective treatment, death. Often symptoms are not severe or may be absent and consequently hyperglycemia sufficient to cause pathological and functional changes may be present for a long time before diagnosis is made. Other symptoms reported are as follows. In women with diabetes, vaginal yeast infections are common and fungal infection may occur under the breast. Severe gum problem, itching, and unusual sensation such as tingling or burning in the extremities may also be sign of Type 2 diabetes. In men Type 2 diabetes may be associated with impotence.

2.1.5. Diagnostic criteria for diabetes mellitus and other categories of glucose intolerance

The diagnostic criteria of diabetes mellitus and other categories of glucose intolerance are presented in Table 1. Some individuals are symptomatic and are diagnosed during routine medical examination. However, others may have fully developed acute and chronic complications at diagnosis. According to WHO the diagnosis of diabetes can be made from any three of the following:

1. Fasting plasma glucose

In patients with clinical symptoms of diabetes such as polyuria, polydipsia
and polyphagia, a fasting plasma glucose greater than or equal to 140 mg/dL after eight hours of fasting.

2. Random plasma glucose

Random plasma glucose greater than or equal 200mg/dL on more than one occasion in consequent days is often sufficient diagnosis of diabetes mellitus.

3. Oral glucose tolerance test (OGTT)

If a person has normal levels but has symptoms of diabetes and a family history or other risk factors, oral glucose test should be done. The OGTT is done on the morning after 10 to 16 hours of overnight fast (water may be taken) following at least three days of unrestricted diet (more than 150 gm of carbohydrates). A fasting blood sample is taken before glucose load. The subject is made to drink 75gm of glucose in 250 to 300 ml of water. Children receive glucose at 1.75g/kg body weight to a maximum of 75gm. The glucose load has to be consumed over a period of 5 minutes. A further blood sample must be collected two hours after glucose load. Blood sample has to be collected in fluoride-oxalate tubes, which prevent the red blood cells from metabolizing glucose. Table-1 depicts the diagnostic values of various tests.
Table 1. Diagnostic value differentiating diabetes mellitus from impaired glucose tolerance

<table>
<thead>
<tr>
<th>Category</th>
<th>Whole blood glucose (mg/dL)</th>
<th>Plasma glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Venous</td>
<td>Capillary</td>
</tr>
<tr>
<td>1-Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fasting</td>
<td>≥120</td>
<td>≥120</td>
</tr>
<tr>
<td>• 2-hours after 75% Glucose load</td>
<td>≥180</td>
<td>≥200</td>
</tr>
<tr>
<td>2-Impaired glucose tolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fasting</td>
<td>&lt;120</td>
<td>&lt;120</td>
</tr>
<tr>
<td>• 2-hours after 75% Glucose load</td>
<td>120-180</td>
<td>140-200</td>
</tr>
</tbody>
</table>

Change in diagnostic criteria for fasting plasma/blood glucose concentrations

The major change recommended in the diagnostic criteria for diabetes mellitus is the lowering of the diagnostic value of the fasting plasma glucose concentration to 7.0 mmol/L (126mg/dL) and above, from the former level of 7.8 mmol/L (140mg/dL) and above. For whole blood the proposed new level is 6.1 mmol/L (110mg/dL) and above, from the former 6.7 mmol/L (120mg/dL) and above.

2.1.6. Management of diabetes mellitus

Diabetes cannot be cured but in many cases can be controlled. The components of diabetes management are:
A. Dietary management

B. Exercise

C. Pharmacological therapy
   - Insulin
   - Oral hypoglycemic agents

D. Self-monitoring of blood glucose

The choice for initiation of therapy depends on: (1) Age of onset, (2) type of diabetes (i.e. proneness to ketosis), (3) body weight, (4) presence of any additional health risk (diabetes in childhood with proneness to ketosis requires insulin therapy). Adults over 30 years of age with insidious onset and overweight may be initially treated by diet and exercise. When diet and exercise fail to achieve therapeutic target, oral hypoglycemic agents are prescribed.

A. Dietary management

Dietary management is required in the treatment of all diabetic patients to achieve the overall therapeutic goal of normal metabolism. There are a host of intervention strategies that can be selected, since no one particular intervention strategy will achieve success in reaching established goals.

Objectives of nutrition therapy

There are specific goals that need to be considered when designing nutritional interventions that include...
1. Maintenance of near-normal blood glucose levels as possible by balancing food intake with medications (i.e., oral hypoglycemic agents or insulin) and exercise

2. Achievement of optimal serum lipid levels

3. Prevention and treatment of the acute complications of diabetes

4. Maintenance of optimal body weight

5. Ensuring consistency and compatibility with other forms of treatment if used, such as oral hypoglycemic agents and insulin

6. Prevention and treatment of long-term complications of diabetes

7. Improvement of overall health through optimal nutrition

**Designing nutrition therapy**

There are four-steps in designing nutritional therapy for diabetic patients\textsuperscript{19,202}

1. **Assessment**\textsuperscript{19,202}

Nutritional assessment involves examination of the patient's clinical data, diet history and usual nutrition intake. The clinical data includes anthropometric measurements i.e., height, weight, body mass index and body frame. Laboratory data e.g., lipid profile, glycated hemoglobin, electrolytes and liver, renal, thyroid function profiles are evaluated for abnormalities that may need to be considered in the design of nutrition therapy. The patients daily energy needs are determined based on activity
levels in the daily routine of the patient i.e., type of work, activities, after work activity. It is important to assess the individuals' attitude toward nutrition and health and to assess previous dietary education and outcomes. Furthermore, the health care provider should assess the patient for ethnic, cultural, religious and philosophic practices that determine what or how a patient may or may not eat. Identifying the established eating habits of a patient is essential so that as many of the habits as possible can be incorporated into the nutrition therapy goals. This identification will assist patients in being more successful in diabetes self-management. A diet history can identify usual food intake. There are various ways that the dietary history can be obtained depending on the educator's skill in interviewing or assessing the data obtained. Multiple daily food diaries, food frequency data and previous-day food intake history are methods that can be used to obtain usual food intake information.

2. Goal setting \textsuperscript{19,202}

The ability of the patient to meet this goal can be evaluated over a period of time as a measurable outcome. The goal setting involves setting realistic measurable outcomes such as change in waist circumference, weight loss and blood glucose level. When identifying nutrition therapy goals, it is important to formulate goals that realistically can be reached by person with diabetes. The patients should not be set for failure but success. The
nutrition goals should be specific, not global. A goal of improving nutritional intake is too global and unacceptable. A goal of inclusion of three servings of fruits and two servings of vegetables per day is specific and measurable. Most importantly, the ability of the patient to meet this goal can be evaluated over a period of time as a measurable outcome is a change in waist measurement in 3 months from 47 inches to 46 inches. Working with the patient mutually to agree on a desirable weight is important if the patient is overweight. The weight goal should be reasonable to achieve and maintain. Even 10 to 15 lb weight loss can improve insulin sensitivity so that other management factors can be modified. Nutrition goals need to be determined by the patient with consultant from the dietitian or health care provider.

3. Intervention

Nutrition intervention is designed to promote success in achieving each patient’s nutrition therapy goals. Nutrition intervention provides the nutritional guidelines that a patient needs to follow on a daily basis. The intervention also provides practical information that can be applied to daily living skills for the person with newly diagnosed diabetes. The information initially provided may be basic. Subsequently the patient requires more in-depth information to fine tune his or her diabetes management. At this time meal planning may become more structured with more attention to
details, necessitating greater care in meal planning and more attention to cause and effect of eating practices on the part of the patient. More in-depth information may be provided as a patient is followed over time because of life experiences that the patient encounters. There are some people with diabetes who do not advance beyond survival skill knowledge or who are in that mode for years before nutrition therapy evaluation will help to assess the patient's level of need for information.

4. Evaluation\textsuperscript{19,202}

Evaluation of nutrition therapy intervention is done through the assessment of clinical data (i.e., serum lipids, glycated hemoglobin, self-monitoring of blood glucose and urine for ketones, weight, waist measurements and blood pressure) and non-clinical data such as change in dietary habits and dietary compliance. Evaluation of therapeutic outcomes is the only step that determines successful nutrition therapy intervention. The patient should be involved with the problem-solving process so that self-management skills can be developed. Redefined nutrition goals and interventions may need to be formulated. Success in reaching nutrition therapy goal also may stimulate a patient's desire to refine the goals so as to reach more finely tuned metabolic control. Maintaining follow-up with the dietitian in diabetes health care team likely will promote more consistent blood control over time.
Nutritional requirement

1. Carbohydrate

The amount of carbohydrate in the eating guidelines is dependent on each patient’s eating habits, blood glucose and lipid management goals. Eating guidelines suggest that 40% to 60% of total daily calories be derived from carbohydrates. This number may be influenced by elevated triglycerides, cultural practices (e.g., Hispanic, Asian) or philosophic practices (i.e., vegetarianism). The source of carbohydrates is not longer considered to be of primary concern as it was in the past. The total amount of carbohydrates consumed is the current focus. Carbohydrate is the macronutrient that has the greatest and most immediate influence on post-prandial blood glucose excursions. It affects pre-meal endogenous or exogenous insulin requirements more than the amount of protein and fat in a meal. Carbohydrate diet restriction impairs insulin sensitivity and is reversed by high carbohydrate diet. High carbohydrate and high fiber diet improves insulin binding and increase monocyte insulin receptor binding. Rapidly absorbed mono and disaccharide such as sweets and sweetened drink are of less use than polysaccharide sources. Therefore, dietary control and manipulation of carbohydrate intake in the form of carbohydrate counting may bring about the greatest change in blood glucose levels toward the established goals.
2. Protein

A diet high in protein is good for health of diabetics because it supplies the essential amino acids needed for tissue repair\(^\text{202}\). Protein does not raise blood glucose during absorption as do carbohydrate and it does not supply as many calories as fats\(^\text{225}\). Presently, research supports the recommendation that people with diabetes consume the same amount of protein as the general population\(^\text{202}\). This finding is reflected in a nutrition plan incorporating 10% to 20% of the total calorie intake as the protein animal and vegetable sources\(^\text{225}\). This amount coverts to about 0.8 to 1 g protein/kg body weight per day\(^\text{202}\).

3. Fats

Low fat diet increase insulin binding, reduces LDL and VLDL levels and reduces the incidence of atherosclerosis\(^\text{225}\). The National Cholesterol Education Program (NCEP) recommendations\(^\text{176}\) provide appropriate guideline for patients who have an appropriate weight with no abnormal serum lipid levels. These guidelines recommend that less than 30% of total caloric intake be derived from fat. Of this 30%, it is recommended that less than 10% of calories are derived from saturated fats, less than 10% of calories are derived from polyunsaturated fats and 10% to 15% of calories are derived from monounsaturated fats. In addition, it recommends that less than or equal to 300mg of dietary cholesterol consumption per day. When
serum low-density lipoprotein (LDL) cholesterol levels are elevated, saturated fat should provide no more than 7% of the total caloric intake with less than 200 mg dietary cholesterol consumption per day. Elevated triglycerides may improve with a moderate increase in monounsaturated fats, a maintenance of less than 10% of total calories from saturated fats and a more moderate intake of carbohydrate. Triglyceride levels greater than or equal to 1000mg/dL require the addition of pharmacological agents to reduce the risk for developing pancreatitis.

4. Fiber

High fiber intakes lower insulin requirement, increase peripheral tissue insulin sensitivity, decrease serum cholesterol\textsuperscript{202} and triglyceride values, lower blood pressure, aid in weight control\textsuperscript{19,202} and delay gastric emptying by releasing certain hormones\textsuperscript{225}. The recommendation for individuals with and without diabetes is the same, that is 20 to 35g dietary fibers per day\textsuperscript{19}. The sources of fiber include\textsuperscript{225} soluble fibers such as pectin, gums, hemicellulose that are present in fruits. The benefits of soluble fiber are in increasing intestinal transit time, delayed gastric emptying, slow glucose absorption and lower serum cholesterol. Insoluble fibers such as cellulose and lignin that are present in vegetables and grains decrease intestinal transit time, increase faecal bulk, delay glucose absorption and slow starch hydrolysis\textsuperscript{225}. Fiber may need to be increased gradually in each patient’s
diet. A gradual increase in dietary fiber consumption helps to prevent the GI side effect. If dietary fiber is to be increased, patient should be advised to consume a greater amount of water as long as they do not have coexistent medical conditions that restrict fluid consumption.

5. Sodium

Sodium recommended for people with diabetes does not differ from those for the general population of 3000mg/day. If a patient has mild to moderate hypertension, less than or equal to 2400mg/day of sodium is recommended. If a patient has hypertension and nephropathy, less than or equal to 2000mg/day is recommended.

6. Alcohol

The recommendations for consumption of alcohol are the same for individuals with or without diabetes. The dietary guidelines recommend that men have no more than two drinks per day and women have no more than one drink per day. Alcohol inhibits the gluconeogenesis by the liver. If an individual takes insulin or oral hypoglycemic agents and drinks alcohol without eating any food, hypoglycemia can occur even at low levels of alcohol consumption. Modification of alcohol consumption is recommended in patients with a history of pancreatitis, dislipidemia, or nephropathy. The calories provided by alcohol are substitute for fat food.
exchanges or fat calories (1 alcoholic beverage=2 fat exchange or 90 calories)\textsuperscript{202}.

7. Vitamins and minerals

Supplementation of vitamins and minerals for people with diabetes generally is not necessary if a variety of foods are consumed on a daily basis\textsuperscript{202, 238}. The consumption of foods from all food groups in the food guide pyramid helps to assure a balanced intake of macronutrients and micronutrients\textsuperscript{238}. Supplementation of vitamins and minerals are based on a thorough assessment of patient's dietary practice and current health status. Zinc deficiencies can frequently occur in people with diabetes. Supplementation of zinc, however, has not been shown to make a difference in glycaemic control\textsuperscript{95}. Potassium may need to be supplemented in the presence of low serum levels of the same\textsuperscript{202}. Patient taking some types of diuretics are at risk for hypokalemia\textsuperscript{202}. In addition, hypokalemia can develop in patients using angiotensin-converting enzyme inhibitors or who have renal insufficiency\textsuperscript{202}. Potassium supplementation would be life threatening for these patients\textsuperscript{202}. A magnesium deficiency can occur in the presence of prolonged glucouria. Therefore, patients at risk for magnesium deficiency are assessed for this abnormality\textsuperscript{202}. 

38
8. Sweeteners

Low calorie and sugar-free drinks are useful for patients on low calorie diets. These drinks usually contain non-nutritive sweeteners. Many diabetic foods contain sorbitol or fructose, which have gastrointestinal side effects, are relatively high in energy, may be expensive and are therefore not particularly recommended as part of the diabetic diet. Non-nutritive sweeteners such as saccharin, aspartame and sucramate are the most widely used non-nutritive sweeteners and provide means for reducing energy intake without loss of palatability.

B. Exercise

A number of studies over the past decade have demonstrated that exercise has the ability to improve the health of individuals with diabetes. The first comprehensive review of diabetes and exercise was published slightly more than two decades ago. The first studies to examine the relationship between physical training, IGT and Type 2 diabetes were published in 1979. In the first of these studies, a group of obese subjects with Type 2 diabetes were trained for 6 weeks and a small but statistically significant increase was noted in intravenous glucose disappearance measured 6 days after the final exercise training bout.
Benefits of exercise for diabetic patients

Aerobic exercise is proven to have significant benefit for people with diabetes\(^6,7,60,94,147\).

1. Exercise improves glucose control
2. Improves circulation
3. Prevents complications such as atherosclerosis
4. Exercise is correlated with success in maintaining weight loss
5. Increased insulin sensitivity and insulin secretion
6. Exercise has been shown to reduce cholesterol, triglycerides and blood pressure\(^7\)
7. Exercise also increases the energy level, lowers tension and improves the ability to handle stress and promoting longevity

Potential risk of exercise\(^112\)

Minimizing exercise-related adverse events also is important when designing an exercise program. Whereas potential risk for individual with diabetes is relatively low, each person should be made aware of the potential risks and solution for this risk. There are, however, several risks that are associated with exercise\(^112\). The potential adverse events of exercise in patients with diabetes are detailed in Table 2.
Table 2. Potential adverse events of exercise in patients with diabetes

<table>
<thead>
<tr>
<th>Cardiovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cardiac dysfunction and arrhythmias caused by ischemic heart disease (often silent)</td>
</tr>
<tr>
<td>• Excessive increments in blood pressure during exercise</td>
</tr>
<tr>
<td>• Post exercise orthostatic hypotension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Microvascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Retinal hemorrhage</td>
</tr>
<tr>
<td>• Increased proteinuria and acceleration of microvascular lesions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Worsening of hyperglycemia and ketosis</td>
</tr>
<tr>
<td>• Hypoglycemia in patients with insulin or sulfonylurea therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal and traumatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Foot ulcers (especially in the presence of neuropathy</td>
</tr>
<tr>
<td>• Orthopedic Injury related to neuropathy</td>
</tr>
<tr>
<td>• Accelerated degenerative joint disease</td>
</tr>
<tr>
<td>• Eye injuries and retinal hemorrhage</td>
</tr>
</tbody>
</table>

Contraindications of exercise

The contraindications of exercise are detailed in Table 3.
Table 3. Absolute and relative contraindications to exercise

<table>
<thead>
<tr>
<th>A-Absolute contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A recent significant change in the resting ECG suggesting ischemia, recent myocardial infarction (2 days) or other acute cardiac event</td>
</tr>
<tr>
<td>• Unstable angina</td>
</tr>
<tr>
<td>• Uncontrolled cardiac arrhythmias causing symptoms of hemodynamic compromise</td>
</tr>
<tr>
<td>• Severe symptomatic aortic stenosis</td>
</tr>
<tr>
<td>• Uncontrolled symptomatic heart failure</td>
</tr>
<tr>
<td>• Acute pulmonary embolus of pulmonary infarction</td>
</tr>
<tr>
<td>• Acute myocarditis or pericarditis</td>
</tr>
<tr>
<td>• Suspected or known dissecting aneurysm</td>
</tr>
<tr>
<td>• Acute infections</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B-Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Left main coronary stenosis</td>
</tr>
<tr>
<td>• Moderate stenotic valvular heart failure</td>
</tr>
<tr>
<td>• Electrolyte abnormalities (e.g., hypokalemia and hypomagnesemia)</td>
</tr>
<tr>
<td>• Severe atria hypertension (i.e., systolic blood pressure if &gt;200 mm Hg or a diastolic blood pressure of &gt; 110 mm Hg)</td>
</tr>
<tr>
<td>• Tachyarrhythmias or bradyarrhythmias</td>
</tr>
<tr>
<td>• Hypertrophic cardiomyopathy and other forms outflow tract obstruction</td>
</tr>
<tr>
<td>• Neuromuscular, musculoskeletal or rheumatoid disorders that are exacerbated by exercise</td>
</tr>
<tr>
<td>• Third degree atrioventricular block</td>
</tr>
<tr>
<td>• Left ventricular aneurysm</td>
</tr>
<tr>
<td>• Uncontrolled metabolic disease (e.g., diabetes, thyrotoxicosis or myxedema)</td>
</tr>
<tr>
<td>• Chronic infectious disease (e.g., mononucleosis, hepatitis and AIDS)</td>
</tr>
</tbody>
</table>
Pre-exercise medical history and physical examination

Before starting an exercise program for individuals with diabetes, a comprehensive medical history is taken and the patient is referred to his primary health care provider for a complete physical examination\(^7\). The primary focus of the medical history and physical examination is on microvascular, macrovascular and neurological complications associated with diabetes. The general components of pre-exercise medical history and physical examination are described in Table 4 and Table 5.

Table 4. Major components of pre-exercise medical history\(^7\)

- Past or present history of cardiovascular disease
- Current diabetes history and recent history of metabolic instability (e.g., recent hospitalization for severe hyperglycemia or frequent hypoglycemia)
- Presence of diabetes related-complications
- Comorbid conditions
- General health practice (e.g., smoking)
- Psychosocial issues affecting participant in physical training programs
Table 5. Major components of the pre-exercise physical examination

- Height, weight, waist-hip ratio
- Ophthalmoscopic examination
- Pulse rate and regularity
- Blood pressure
- Chest auscultation
- Cardiac examination
- Palpitation and auscultation of carotid, abdominal and femoral arteries
- Palpitation and inspection of lower extremities for edema and presence of arterial pulses
- Foot examination
- Neurological examination
- Absence or presence of xanthoma and xanthelasma
- Orthopedic or other medical conditions that would limit exercise or require special consideration
- Laboratory tests (if not recently performed and clinically indicated) including fasting blood glucose, glycosylated hemoglobin, fasting serum lipids and lipoproteins, serum creatinine, urinalysis, thyroid function test and resting ECG

Physical training programs

There are several of physical training programs that include aerobic exercise, resistance training and stretching-flexibility. Aerobic exercise is defined as an activity that uses large muscle groups, is rhythmic in nature and can be sustained over prolonged period of time. Examples of aerobic
exercise include walking, jogging, cycling (stationary or outdoor), swimming and group exercise.

1. Duration

There are two popular methods for quantifying the desired duration of aerobic exercise. In the first method, the American Heart Association recommends burning at least 700 kcal/week for minimal improvements and up to 2000 kcal/week for maximal improvements in oxygen consumption. Frequency, intensity and duration of the exercise sessions are adjusted appropriately in order to reach the desired goal. The second method for quantifying exercise is the determination of the amount of time within targeted heart rate range (THR). The American College of Sports Medicine (ACSM) recommends that individuals exercise between 20 to 60 minutes per session at a predetermined target heart rate. The initial exercise duration should be of 10 to 15 minutes per session. After several weeks of monitoring heart rate and blood pressure the amount of physical activity can be increased to 20 minutes, with the maximum duration not to exceed 60 minutes.

2. Frequency

The American Diabetes Association recommends exercising 3-5 days per week, whereas American College of Sports Medicine recommends
exercising between 4 to 7 days per week\textsuperscript{94}. Exercising at maximum of 7 days per week only is recommended at low intensities and for those who are having trouble controlling their blood glucose level\textsuperscript{14,94}.

3. Intensity

There are two most common methods that determine exercise intensity. The first method is the determination of (1) the percent of the maximum heart rate ($HR_{\text{MAX}}$) and (2) the heart rate range (HRR). The first step in each of these calculations is the determination of maximal heart rate\textsuperscript{60}.

The general guidelines to avoid exercise-induced complications are detailed in Table 6.

Table 6. Recommendations to avoid exercise-induced complications\textsuperscript{60}

- Adequate warm-up and cool-down
- Careful selection of type of exercise and intensity
- Participant education
- Monitor blood glucose before during and after each exercise session
  - Avoid exercise when metabolic control is poor (3000 mg/dL)
- Drink plenty of water before, during and after exercise
  - Carry a carbohydrate snack and something sweet for emergency
- Proper footwear (e.g., gel or air cushioned shoes)
- Avoid exercise in extreme hot or cold
- Avoid exercise at site of insulin injection
- Inspect feet daily and after exercise
- Maintain adequate hydration
C. Pharmacological management

1. Insulin therapy

There are several types of insulin preparations that differ in pharmacological properties. The characteristics of each of those preparations are detailed in Table 7.

Table 7. Characteristics of insulin preparations and action

<table>
<thead>
<tr>
<th>Types</th>
<th>Onset</th>
<th>Peak</th>
<th>Effective duration</th>
<th>Maximal duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro</td>
<td>&lt;0.25 hrs.</td>
<td>0.5-1.5 hrs.</td>
<td>3-4 hrs.</td>
<td>4-6 hrs.</td>
</tr>
<tr>
<td>Aspart</td>
<td>&lt;0.25 hrs.</td>
<td>40-50 m.</td>
<td>?</td>
<td>4-6 hrs.</td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>&lt;0.5-1 hrs.</td>
<td>2-3 hrs.</td>
<td>3-6 hrs.</td>
<td>46-10 hrs.</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>2-4 hrs.</td>
<td>6-10 hrs.</td>
<td>10-16 hrs.</td>
<td>14-18 hrs.</td>
</tr>
<tr>
<td>Lente</td>
<td>3-4 hrs.</td>
<td>6-12 hrs.</td>
<td>12-18 hrs.</td>
<td>16-20 hrs.</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultralente</td>
<td>6-10 hrs.</td>
<td>10-16 hrs.</td>
<td>18-20 hrs.</td>
<td>20-24 hrs.</td>
</tr>
<tr>
<td>Glargine</td>
<td>2 hrs.</td>
<td>----</td>
<td>24 hrs.</td>
<td>24 hrs.</td>
</tr>
<tr>
<td><strong>Mixtures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70/30 (70% NPH/30% regular)</td>
<td>0.5-1 hrs.</td>
<td>4.4 hrs.</td>
<td>10-16 hrs.</td>
<td>14-18 hrs</td>
</tr>
<tr>
<td>50/50 (50% NPH/50% regular)</td>
<td>0.5-1 hrs.</td>
<td>3.3 hrs.</td>
<td>10-16 hrs.</td>
<td>14-18 hrs</td>
</tr>
<tr>
<td>Mix.75/25 (75% NPH/25% lispro)</td>
<td>&lt;0.25 hrs.</td>
<td>2.6 hrs</td>
<td>?</td>
<td>22 hrs.</td>
</tr>
</tbody>
</table>
Production of insulin

Human insulin is composed of 51 amino acids and consists of an α- and β-chain that is linked by two disulfide bonds. It is synthesized as a large pre-proinsulin in the cells of the pancreas. The pre-proinsulin subsequently is modified to proinsulin that is stored in secretary vesicles within the Golgi apparatus. The proinsulin undergoes enzymatic modification within the secretary vesicle and, as a result, a connecting peptide (C-peptide) is cleaved from the α- and β-chain. Thus, an additional hormone, C-peptide, is secreted from the pancreatic β-cells in equimolar amounts with insulin. Insulin was purified initially from the pancreas of pigs and cows. During the late 1970s, human insulin became available through the use of recombinant DNA technology. Initially, recombinant human insulin was produced by introducing the human insulin gene into a special strain of nonpathogenic Escherichia coli. Subsequently, human insulin was produced by other methods such as the chemical substitution of a single amino acid threonine for alanine at the terminal 30 positions in the insulin β-chain of porcine insulin.

The initial work in the development of human insulin through genetic engineering also has led to the production of insulin analogs that are produced to mimic normal physiologic insulin responses better than conventional insulin preparations such as insulin lispro (Humalog),
glargine (Lantus), aspart (Novolog) and one new analog combination (Humalog Mix 75/25).249

Indication for insulin therapy

The indications for insulin therapy include198,218

1. Patients with Type 1 diabetes
2. Patients with Type 2 diabetes who do not show response to diet and oral hypoglycemic agents to control hyperglycemia
3. Insulin is recommended during pregnancy when diet alone is inadequate to achieve therapy target
4. Other relative indications are diabetics undergoing surgery, diabetes in presence of complications such as infection, neuropathy, nephropathy or during vascular complications, when oral hypoglycemic agents are contraindicated

Insulin regimens

There are several insulin regimens that can be used in the treatment of diabetes patient. Each individual case require schedule for control of hyperglycemia. Most patients require large doses of insulin more than 80U daily4. Therefore, insulin delivery in two or more daily injections is most likely to provide better physiologic coverage than insulin required in a single injection4.
Side effects of insulin therapy

Insulin therapy is relatively safe, but associated with certain side effects, such as (1) hypoglycemia and weight gain\textsuperscript{196,218}, (2) formation of insulin resistance\textsuperscript{218} (3) lipodystrophies\textsuperscript{218}, (4) insulin anti-bodies\textsuperscript{198}, (5) insulin edema\textsuperscript{198} and (6) hyperkeratosis\textsuperscript{198}.

2. Oral hypoglycemic agents

Oral hypoglycemic agents are considered after a regimen of dietary treatment fails to achieve therapy targets in Type 2 diabetes mellitus\textsuperscript{198}. These drugs can be used alone or in combination to modify the primary physiological abnormalities of Type 2 diabetes function (i.e. decreased insulin secretion, insulin resistance and decreased suppression of hepatic glucose production)\textsuperscript{246}.

Classification of oral hypoglycemic agents

There are several classes of oral hypoglycemic agents approved for treatment of Type 2 diabetes today. These classes include Sulfonylureas, Bigunides, Meglitinides, thiazolidinediones, Alpha-glucosidase inhibitors.

Sulfonylureas

Sulfonylureas have been an important part of diabetes pharmacological therapy for decades with their relative low side effects, cost and excellent treatment efficacy. These medications continue to remain the mainstay of
diabetes therapy for many patients with Type 2 diabetes\textsuperscript{196}. Currently there are six sulfonylureas available; these include four first-generation sulfonylurea (i.e., acetohexamide, chloropropamide, tolbutamide, and tolazamide) and three second-generation sulfonylureas (i.e., glyburide, glipizide, and glimepiride)\textsuperscript{196}.

**Mechanism of action**

The primary mechanism through which sulfonylureas exert their effects is through stimulating insulin secretion from the pancreatic $\beta$-cell\textsuperscript{196}. Adenosine triphosphate (ATP)-dependent potassium channels, located in the plasma membrane of the pancreatic cell, regulate secretion of insulin\textsuperscript{196}. Each ATP-dependent potassium channel consists of two subunits, one containing a sulfonylurea receptor and the other containing the channel itself\textsuperscript{196}. Sulfonylureas bind to the sulfonylurea receptor and close ATP-dependent potassium channels\textsuperscript{18}. As the potassium accumulates within the $\beta$-cell membrane, the $\beta$-cell depolarizes leading to an influx of calcium\textsuperscript{18}. The increased concentration of calcium causes insulin granules to migrate to the cell surface\textsuperscript{158}, where the granules rupture. Insulin is released by exocytosis\textsuperscript{158}.

**Pharmacokinetics\textsuperscript{196}**

There are marked differences in the absorption, elimination and metabolism of the various oral sulfonylurea medications\textsuperscript{196}. The first-
generation oral sulfonylurea medications are highly protein bound\textsuperscript{18}. Oral sulfonylureas are metabolized in the liver to active, inactive, or weakly active metabolites that are excreted in bile or kidney\textsuperscript{196}. The first-generation sulfonylureas primarily are excreted by renal mechanisms. Chlorpromide is metabolized in the liver to active metabolites and cleared almost solely by the kidney\textsuperscript{17}. Therefore, chlorpromide is associated with significant hypoglycemia in individuals with the renal impairments. The second-generation sulfonylureas, glyburide and glipizide are metabolized in the liver to inactive or weakly active metabolites and excreted into the bile and kidney\textsuperscript{17}. All sulfonylureas are almost completely absorbed; however, the onset, peak and duration of action are determined by specific properties and formulations of each medication\textsuperscript{213}. In general, the oral sulfonylureas are absorbed rapidly from the gastrointestinal tract. With exception of glipizide, all of the sulfonylureas may be taken with food\textsuperscript{18}. It is recommended that glipizide is ingested 30 minutes before meals\textsuperscript{213}. In addition, the absorption of glyburide depends on whether it is in a micronized or nonmicronized formulation\textsuperscript{213}. The micronized formulation of glyburide is well absorbed, whereas the absorption of the nonmicronized formulation is less predictable when taken with food or in the presence of an altered hydrogen ion concentration (PH)\textsuperscript{213}. Most oral sulfonylurea medications have a half-life that range from 3 to 5 hours or 6 to 8 hours\textsuperscript{213}.\textsuperscript{52}
Chlorpromide, however, has a half-life that range from 24 to 45 hours, which partially accounts for its extended duration of action\textsuperscript{213}.

**Dosages**

The recommended dosage for sulfonylurea is shown in Table-8.

Table 8. The approved daily dosages of oral diabetes medications include\textsuperscript{17, 18}

<table>
<thead>
<tr>
<th>Medications</th>
<th>Classification</th>
<th>Dose range (mg/dL)</th>
<th>Starting daily dose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromide</td>
<td>1\textsuperscript{st}-generation oral sulfonylurea</td>
<td>100-500</td>
<td>250</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>1\textsuperscript{st}-generation oral sulfonylurea</td>
<td>500-3000</td>
<td>1000-2000</td>
</tr>
<tr>
<td>Tolazamide</td>
<td>1\textsuperscript{st}-generation oral sulfonylurea</td>
<td>100-1000</td>
<td>100-250</td>
</tr>
<tr>
<td>Acetohexamide</td>
<td>1\textsuperscript{st}-generation oral sulfonylurea</td>
<td>250-1500</td>
<td>250-500</td>
</tr>
<tr>
<td>Glyburide (unmicronized Formulation)</td>
<td>2\textsuperscript{nd}-generation oral sulfonylurea</td>
<td>1.25-20</td>
<td>1.5-5</td>
</tr>
<tr>
<td>Glyburide (micronized Formulation)</td>
<td>2\textsuperscript{nd}-generation oral sulfonylurea</td>
<td>.75-12</td>
<td>1.5-3</td>
</tr>
<tr>
<td>Glipizide</td>
<td>2\textsuperscript{nd}-generation oral sulfonylurea</td>
<td>2.5-40</td>
<td>5</td>
</tr>
<tr>
<td>Glipizide GITS</td>
<td>2\textsuperscript{nd}-generation oral sulfonylurea</td>
<td>5-20</td>
<td>2.5-10</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>2\textsuperscript{nd}-generation oral sulfonylurea</td>
<td>1-8</td>
<td>1-2</td>
</tr>
<tr>
<td>Metformin</td>
<td>Biguanide</td>
<td>500-2550</td>
<td>500 bid</td>
</tr>
<tr>
<td>Acarbose</td>
<td>$\alpha$ -glucosidase inhibitor</td>
<td>25-300</td>
<td>25 tid</td>
</tr>
<tr>
<td>Miglitol</td>
<td>$\alpha$ -glucosidase inhibitor</td>
<td>25-300</td>
<td>25 tid</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Meglitinide</td>
<td>1-16</td>
<td>1.5-6</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Thiazolidinedione</td>
<td>15-45</td>
<td>15-30</td>
</tr>
<tr>
<td>Rosiglazone</td>
<td>Thiazolidinedione</td>
<td>4-8</td>
<td>4</td>
</tr>
</tbody>
</table>
Indications

Oral sulfonylureas are indicated for the treatment of Type 2 diabetes. The patients most likely to benefit from oral sulfonylureas include those\textsuperscript{17} (1) with onset of hyperglycemia after 30 years of age, (2) patient with diagnosis of hyperglycemia for less than 5 years, (3) patient with a fasting blood glucose level less than 300mg/dL, (4) patient who have normal weight or are obese (5) patient who are not totally insulin deficient and (6) patient who are willing to comply with a reasonable nutrition and exercise program.

Contraindications

The contraindication to use oral sulfonylureas include Type 1 diabetes, diabetic ketoacidosis with or without coma, hypersensitivity to oral sulfonylureas, during pregnancy and lactation, in severe liver or kidney disease, during periods of extreme stress such as major surgery, severe infections and trauma because endogenous insulin requirements are increased, patients with acute myocardial infarction and allergy to sulphonylureas\textsuperscript{17}.

Side effects

The most common side effect of oral sulfonylureas is hypoglycemia\textsuperscript{214}. There are several adverse reactions specific to certain medications in the sulfonylurea category. For example, chlorpropamide is associated with
water retention and hyponatremia and have to be used with caution in a patient with heart failure. In addition, the administration of chlorpropamide and tolbutamide in combination with alcohol may present a cutaneous flushing of the face or trunk\textsuperscript{214}.

**Biguanides**

Biguanides which including metformin and phenoforin like sulfonylureas, also represent an old class of oral hypoglycemic agents in the treatment of Type 2 diabetes\textsuperscript{196}.

**Mechanisms of action**

Metformin has several effects on carbohydrate and lipid metabolism, but the exact biochemical mechanisms through which these effects are mediated are unknown. In particular, metformin enhances the sensitivity of peripheral and hepatic tissues to insulin\textsuperscript{196}. The enhancement of muscle sensitivity is related to several factors that include an increase in GLUT4 transporter number and activity\textsuperscript{135}. In addition, this compound has multiple effects on the liver, reducing hepatic glycogenolysis\textsuperscript{135} and gluconeogenesis\textsuperscript{229} and increased glycogen synthesis\textsuperscript{135}. Specific to Type 2 diabetes, this reduction in hepatic glycogenolysis and gluconeogenesis results in a reduction of hepatic glucose production and fasting blood glucose levels\textsuperscript{135,229}.
Pharmacokinetics

Metformin mainly is absorbed from the small intestine. Metformin at doses of 0.5 to 1.5 g has an absolute bioavailability of 50% to 60%. Gastrointestinal absorption is complete within six hours of ingestion. Metformin is distributed rapidly in most tissues following absorption and does not seem to bind plasma proteins as with the sulfonylurea medications. There have been no metabolites or conjugates of metformin identified, which suggest that metformin does not undergo metabolism in the liver or is not secreted into the bile. Approximately 90% of the compound is excreted unchanged in the urine within 12 hours after administration of the dose. The elimination of the drug is by renal glomerular filtration and renal tubular secretion, therefore, the half-life of metformin is increased in renal insufficiency.

Indications

Metformin monotherapy is considered to be a first-line treatment for obese individuals with Type 2 diabetes who have not been satisfactorily managed through diet and exercise control alone. Metformin may be used as monotherapy or concomitantly with sulfonylureas, the meglitinide repaglinide, and the thiazolidinediones, pioglitazone and rosiglitazone. The recommended dosage for metformin is shown in Table-8.
Contraindications

Metformin is contraindicated in patients with (1) acute or chronic metabolic acidosis, (2) who have a known hypersensitivity to metformin, (3) who has congestive heart failure, (4) patient with renal disease or dysfunction as evidenced by serum creatinine levels of more than or equal to 1.5mg/dL (men) and more than or equal to 1.4mg/dL (women) or who are more than 80 years old with an abnormal creatinine clearance, (5) with chronic obstructive lung disease with associated hypoxia which may precipitate acidosis, (6) patient with hepatic impairment, (7) during pregnancy and (8) alcoholism\textsuperscript{18,196}.

Side effects

The primary side effect associated with metformin include (1) gastrointestinal symptoms such as diarrhea, abdominal bloating, nausea and vomiting. (2) B\textsubscript{12} malabsorption has been noted in patient on 200 mg or more in metformin therapy and (3) Metformin is excreted primarily by kidney, therefore, in the presence of renal insufficiency, the drug accumulates and the risk for lactic acidosis increases\textsuperscript{65,196}.

Meglitinides

Meglitinides comprise a new class of insulin secretagogues derived from benzoic acid that are structurally and pharmacologically distinct from oral hypoglycemic agents\textsuperscript{18}. 
Mechanisms of action

Meglitinides stimulate insulin secretion through mechanism of action that are similar to those of sulfonylureas\textsuperscript{196}. There are distinct differences, however, between the onset and duration of action of sulfonylureas and miglitinides\textsuperscript{196}. Whereas sulfonylureas cause insulin to be released in a sustained fashion and are associated with a longer duration of action, miglitinides cause insulin to be released rapidly and are associated with a much shorter duration of action. Meglitinides bind with pancreatic $\beta$-cell receptors including the sulfonylurea receptors, which result in the closure of ATP-dependent potassium channels\textsuperscript{196}. The closure of these channels inhibits potassium efflux from the cell and cause membrane depolarization and calcium influx\textsuperscript{196}. This influx of calcium stimulates the secretion of insulin from the $\beta$-cell as described previously with response to sulfonylureas\textsuperscript{196}.

Pharmacokinetics

Repaglinide is absorbed rapidly from the gastrointestinal tract following oral administration. Plasma blood levels begin to rise within 15 minutes following oral administration with peak plasma concentrations occurring within 40 to 60 minutes\textsuperscript{196}. The drug is metabolized by the cytochrome P450 3A4 isoenzymes of the liver to inactivate metabolites\textsuperscript{18}. 
Approximately 90% to 92% of the inactive metabolites are excreted in feces and the remaining 8% are excreted in the urine\textsuperscript{196}.

**Indications**

Repaglitnide is indicated as an adjunct to nutrition and exercise in patients with Type 2 diabetes to reduce hyperglycemia\textsuperscript{196}. Unlike other existing insulin secretagogues (i.e., sulfonylureas), the primary action of repaglinide is a reduction in post-prandial hyperglycemia\textsuperscript{196}. The recommended dosage for repaglinide is shown in Table-8.

**Contraindications**

Repagilitnide is contraindicated in (1) pregnancy, (2) breast-feeding, (3) Type 1 diabetes, (4) diabetic ketoacidosis and (4) liver disease\textsuperscript{194}.

**Side effects**

Repagilitnide is metabolized by cytochrome P450 3A4 isoenzymes of the liver to inactivate metabolites\textsuperscript{18}. These enzymes can be inhibited by several drugs such as ketoconazole, miconazole and erythromycin. The coadministration of repaglinide with cytochrome p450 3A4 isozyme inhibitors can result in higher serum repaglinide levels thus increasing the risk for hypoglycemia. Conversely, barbiturates, carbamazepine and rifampin can induce P450 3A4 isozyme activity and reduce the effectiveness of repaglinide\textsuperscript{13}. 
Thiazolidinediones

Thiazolidione compounds are another group of drugs used in the treatment of Type 2 diabetes.

Mechanisms of action

The complete mechanism of thiazolidinediones is not understood completely. They seem to improve blood glucose control in individuals with Type 2 diabetes by enhancing hepatic and peripheral insulin sensitivity. The effects of thiazolidinediones are mediated through a family of nuclear receptors called the peroxisome proliferator-activated (PPAR) receptors. The PPAR family of receptors is responsible for modulation of lipid homeostasis, adipocyte differentiation and insulin action. In particular, thiazolidinediones bind and activate the PPAR isoform, improving glucose tolerance, decreasing hepatic glucose production and increasing insulin stimulated glucose disposal. The thiazolidinediose also show some cross-reactivity with other isoforms in the FPAR family such as PPAR-α, which account for their potential roles in a variety of cellular processes such as regulation of lipid metabolism.

Pharmacokinetics

When pioglitazone is administered in the fasting state, peak concentrations of pioglitazone are noted within two hours. When pioglitazone is ingested
with food, however, there is a delay in the time to peak serum concentrations of 3 to 4 hours. This delayed effect does not seem to affect the clinical efficacy of the medication, and pioglitazone may be taken without meals. Peak concentrations of rosiglitazone are observed approximately 1 hour after dosing. As with pioglitazone, there is a slight delay in the absorption of pioglitazone at the time the medication is taken with food, however, this does not seem to have any effect on the clinical efficacy of the medication. Pioglitazone is metabolized extensively by hydroxylation and oxidation and several metabolites are formed and converted to glucuronide on sulfate conjugates. In addition to pioglitazone, M-IV is the principal metabolites found in human serum after multiple dosing. Several metabolites, M-II, M-III and M-IV, have been noted to be pharmacologically active in animal models of Type 2 diabetes. Approximately 99% of pioglitazone and 98% of M-III and M-IV are bound to protein, primarily, albumin. In addition, approximately 99.8% rosiglitazone is bound to albumin extensively. Rosiglitazone is extensively metabolized by N-demethylation and hydroxylation extensively followed by conjugation with sulfate and glucuronic acid. All of the circulating metabolites of rosiglitazone are less potent than the parent compound and are less likely to contribute to the insulin sensitized effects of the drug.
Indications

Rosiglizone and pioglitazone are approved as monotherapy in the treatment of Type 2 diabetes\textsuperscript{221}. In addition, pioglitazone is approved as combination therapy with metformin, sulfonylureas, or insulin. Rosiglizone is approved in combination with metformin\textsuperscript{221}. The recommended dosage for thiazolidinediones is shown in Table-8.

Contraindications

Thiazolidinediones are contraindicated in patients with (1) severe Liver disease, (2) diabetes complicated by acidosis, ketosis or coma, (3) pregnancy and lactation, (4) sensitivity to thiazolidiones, (5) severe congestive heart failure and (6) Type 1 diabetes\textsuperscript{221, 230}.

Side effects

The side effects of thiazolidinediones therapy include the following. (1) The first thiazolidinediose, troglitazone was associated with hepatic failure (hepatotoxicity)\textsuperscript{213, 221, 230}, (2) patients who are treated with thiazolidinediones in combination with insulin or other hypoglycemic medication are at increased risk for developing hypoglycemia\textsuperscript{18}, (3) the thiazolidinediones may cause resumption of ovulation in premenopausal women with an ovulation secondary to insulin resistance such as those with polycystic ovary syndrome (PCOS)\textsuperscript{18} and (4) the thiazolidinediones also are associated with weight gain, edema and anemia\textsuperscript{17}. 

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Alpha-glucosidase inhibitors

A relatively new group of oral hypoglycemic agents, α-glucosidase inhibitors is now available to modulate carbohydrate absorption. The compounds of α-glucosidase include acarbose and miglitol.

Mechanism of action

α-glucoside inhibitors are named for their ability to bind reversibly to α-glucosidase enzymes (i.e., sucrase, maltase, isomaltase and glucoamylase) in the brush border of the small intestine. The α-glucosidase inhibitors break down disaccharides and oligosaccharides into glucose and other monosaccharides that can be absorbed in the small intestine. The competitive reversible binding by the α-glucosidase inhibitors to these enzymes delay the absorption of carbohydrate from the gastrointestinal tract, which leads to a more even absorption of sugars through the gut. As a result, there is a blunting of the normally sharp rise in postprandial blood glucose levels associated following a meal. More specifically, these medications block α-glucosidase enzymes in the proximal small bowel, which delays the absorption of carbohydrates. During the first few weeks of therapy, the unabsorbed carbohydrate passes further down the small intestine, where it cause somatic fluid attraction and fermentation that result in the production of softer stools, diarrhea, flatulence and bloating. After 4 to 6 weeks, however, this repetitive
presentation of undigested carbohydrate to the distal small bowel results in the induction of new locally acting carbohydrate–metabolizing enzymes\textsuperscript{196}. The overall result of \( \alpha \)-glucosidase inhibitor therapy is the absorption of a small amount of carbohydrates in the small bowel with the remainder absorbed in the distal small bowel\textsuperscript{149}.

**Pharmacokinetics**

There are some differential effects in the pharmacokinetics of the two available \( \alpha \)-glucosidase inhibitors, acrobase and miglitol. Following oral administration, a small amount of acrobose is absorbed by the small intestine (bioavailability of 1\% to 2\%), whereas miglitol is absorbed from the gastrointestinal tract. Miglitol, which possesses an elimination half-life of 2 hours, is not metabolized and is excreted in urine\textsuperscript{18}.

**Indications**

The \( \alpha \)-glucosidase inhibitors are used as mono-therapy for mild Type 2 diabetes but also can be used in combination with insulin or other oral hypoglycemic medications in more severe Type 2 diabetes\textsuperscript{18}. The recommended dosage for alpha-glucosidase inhibitors is shown in Table-8.

**Contraindications**

\( \alpha \)-glucosidase inhibitors are contraindicated in several gastrointestinal problems including inflammatory bowel disease, colonic ulceration and
partial intestinal obstruction\textsuperscript{18}. It is also contraindicated in the presence of any chronic intestinal disease associated with marked disorder of digestion or absorption and any gastrointestinal conditions that may deteriorate as a result of increased intestinal gas formation and in patients with ketoacidosis or hypersensitivity to acrobose or miglitol or any of its components\textsuperscript{196}.

**Side effects**

Initially there may be gastrointestinal side effects such as bloating and flatulence\textsuperscript{18}.

**D. Self-Monitoring of Blood Glucose**

Monitored of glycaemic control is recognized as an essential component of management of diabetes\textsuperscript{198}. Self-monitoring of blood glucose (SMBG) depends on type of treatment, the facilities available and therapy target set\textsuperscript{198}. Regular home blood glucose monitoring has the potential to increase the patient’s involvement in self-care and enter into a partnership with the health care provider.

**Glucose monitoring systems**

- **Visual test strips**

Visual strips provide a semi-quantitative measure of glycaemic control with which patients discriminate between low, near normal and elevated blood glucose values, but can not be used for patients who use test results to
adjust insulin\textsuperscript{163}. In the visual testing method, a blood sample is applied to a
reagent strip that develops a color change proportion to amount of glucose
in the blood. The reacted strip is compared with a color chart to obtain an
estimate of the blood glucose value. Differences in visual acuity, color
discrimination, sample size and timing affect the accuracy of the test
results\textsuperscript{163}.

- **Glucose monitor devices**

Glucose monitors employ one of two types of technology\textsuperscript{163}: (1) enzyme
photometric principles or (2) electrochemical methods, both use an
enzyme, glucose oxidase or hexokinase that catalyzes a glucose reaction\textsuperscript{92}.  
First generation monitors use reflectance photometry in which the monitor
analyzes the amount of color (light) reflected from the test strip after the
blood is placed. The monitor displays a numerical value that represents the
blood glucose value\textsuperscript{92}. Second generation monitors use biosensor
technology in which an electric current passes though the blood sample as
the enzyme-glucose reaction is occurring. The monitor quantifies the
electrical charge and produces a digital readout of the blood glucose
value\textsuperscript{92}.

- **Accuracy of glucose monitors**

Accuracy of glucose monitors depend on the analytic performance of the
instrument and on factors related to patient use including the proficiency of

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the patient in using the instrument, maintenance of the instrument, quality of reagent strip and the use of recommended quality control measures, glucose control solution and the check strip testing. SMBG results will be approximately 15% lower than a laboratory reference.

- **Setting target glycaemic goals**

Glycaemic goal setting should take into consideration the capacity and motivation of the patient to achieve the glycaemic goals, the age of the patient, coexisting illness and the potential danger that hypoglycemia would cause for the patient. According to Eurodiab, the targets of glycaemic control as follows.

Table 9. Target glycaemic control for diabetic patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Good</th>
<th>Moderate</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting/pre-prandial</td>
<td>80-110</td>
<td>111-140</td>
<td>&gt;140</td>
</tr>
<tr>
<td>mg/dL mmol/L</td>
<td>4.4-6.1</td>
<td>6.2-7.8</td>
<td>&gt;7.8</td>
</tr>
<tr>
<td>Post-prandial</td>
<td>100-145</td>
<td>146-180</td>
<td>&gt;180</td>
</tr>
<tr>
<td>mg/dL mmol/L</td>
<td>5.5-8.0</td>
<td>8.1-10.0</td>
<td>&gt;10.0</td>
</tr>
</tbody>
</table>

- **Frequency and timing of self-monitoring**

Patients who control blood glucose through diet and exercise only should monitor glucose two to three times weekly. In patients with well-controlled diabetes treated with oral hypoglycemic agents, a good indicator
of overall glycaemic status is one test daily, alternative pre-meal, hour-of-sleep and postprandial tests. Patient with uncontrolled diabetes and those who take insulin or a combination of insulin and oral hypoglycemic agents should test two to four times daily, including the time of greatest insulin action.

2.1.7 Complications of diabetes mellitus

A. Acute Complications: The three major acute complications of diabetes include: hypoglycemia, diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic nonketotic syndrome (HHNKS).

1. Hypoglycemia
   • Definition
   Hypoglycemia defined as blood glucose level below (60 mg/dL) result from an imbalance between glucose production and glucose use that occur when glucose use exceeds glucose production.

   • Precipitating factors
   The precipitating factors of hypoglycemia include excess exogenous insulin, excess oral hypoglycemic agents, omission of meals or decreased caloric intake in patient using insulin or oral hypoglycemic agents, increased exercise or physical activity in patients using insulin or oral
hypoglycemic agents, time between insulin injection and meal too long or too much alcohol intake\textsuperscript{195,257}.

- **Symptoms and signs of hypoglycemia**

The symptoms of hypoglycemia may be divided into two groups\textsuperscript{120,218}.

1. **Sympathetic symptoms:** This results from stimulation of the adrenergic system in response to a fall in the level of glycemia\textsuperscript{218}. The symptoms including hunger, faintness, weakness, pallor, nervousness, anxiety, irritability, sweating, palpitation, tachycardia, diaphoresis and occasional nausea and vomiting\textsuperscript{120,218}.

2. **Neuroglycopenic symptoms:** This arises from a decrease in the blood glucose level in the cerebral circulation\textsuperscript{218}. The symptoms including headache, abdominal pain, blurred vision, abnormal behavior, diplopia, lethargy, aggressiveness, confusion, drowsiness, difficult speech, papillary dilatation, loss of memory and sensory dysfunction\textsuperscript{120,218}. In severe neuroglycopenic disorientation, seizure, coma and death may result\textsuperscript{120}.

- **Laboratory diagnosis**

Common laboratory value for hypoglycemia is random plasma glucose of (less than 60mg/dL)\textsuperscript{195}.
• **Prevention of hypoglycemia**

An example of protocol for the prevention of hypoglycemia is as follows:

1. adequate education of patients as part of a structured program
2. intermittent review of understanding of hypoglycemia
3. meal planning
4. regular review of blood glucose profiles, insulin dose distribution
5. reporting of unrecognized/not-remembered events by family/friends
6. avoidance of excess alcohol

• **Management of hypoglycemia**

An example of protocol for the treatment of hypoglycemia is as follows:

1. Minor episodes: these are managed by rest and ingesting 10-20 g of carbohydrate (e.g., a glass of orange juice and two biscuits or 2 teaspoons of sugar in water) following this the patient should feel better within 10-15 minutes, if not repeat the dose, and then the patient should eat a snack or meal to maintain blood glucose control.

2. Hypoglycemic coma: most cases recover spontaneously or with the help of family/friends. If possible, the patient should be given glucose orally, which is made easier by the use of currently available gels or glucagons injection.
2. Diabetic Ketoacidosis (KDA) and Hyperosmolar Hyperglycemic Nonketotic Syndrome (HHNKS)

DKA and HHNKS have been considered the major acute complications of Type 1 and Type 2 diabetes respectively\textsuperscript{195}.

- Precipitating factors of DKA and HHNKS

There are several precipitating factors in the development of DKA and HHNKS in patients with diagnosed or undiagnosed Type 2 diabetes\textsuperscript{195}. In general these patients have an underlying impaired glucose metabolism and, when challenged by physiologic stress, require an increase in endogenous insulin requirement\textsuperscript{195}. Patient at greater risk for developing HHNKS include individuals who are most likely to become dehydrated, such as the elderly and those unable to meet fluid needs, those with renal insufficiency or extensive burn and those treated with peritoneal dialysis or receiving total parenteral nutrition\textsuperscript{195}. The most common physiologic stresses associated with an increase in counter-regulatory hormones include infectious processes (e.g., pneumonia, urinary tract infection and acute pancreatitis), endocrine disorders (e.g., Cushing's disease), concurrent medications (e.g., phenytoin, corticosteroids and thiazide diuretics) and vascular disorders (e.g., myocardial infarction or cerebral vascular accident). A recent study of DKA in Chinese adults with Type 2 diabetes
reported that the development of DKA was correlated with older age and severe coexisting illness\textsuperscript{258}. In addition, reports have shown that drugs such as cocaine may be precipitating factors in the development of DKA in Type 1 diabetes\textsuperscript{243} and HHNKS in Type 2 diabetes\textsuperscript{3}. In patients with Type 1 diabetes omission of insulin\textsuperscript{248} is the most common cause of DKA, whereas in patients with Type 2 diabetes, the most common cause of DKA is infections\textsuperscript{248}.

- **Signs and symptoms of DKA and HHNKS**

In general, these clinical signs and symptoms predominantly result from one or more of the following underlying pathophysiologic causes: hyperglycemia, dehydration, hyperosmolality, metabolic acidosis and electrolyte disturbances\textsuperscript{87}. HHNKS is not associated with metabolic acidosis and the degree of hyperglycemia, dehydration and hyperosmolality is much more severe in HHNKS than DKA\textsuperscript{87}. Diabetic ketoacidosis is associated with polyuria, polyphagia, polydipsia, weight loss, fatigue, blurred vision, tachycardia, hypotension, orthostatic hypertension, decreased skin turgor, kussmaul respiration (deep rapid respiration), cardiac arrhythmia, acetone odor to breath, anorexia, red flushed face, nausea and vomiting, decreasing mental status, coma, hypothermia and leg cramps\textsuperscript{87,195}. HHNKS is associated with polyuria, polyphagia, polydipsia, weight loss, fatigue, blurred vision, tachycardia, hypotension, orthostatic
hypotension, decreased skin turgor, cardiac arrhythmia and decreased mental status, seizures, thrombosis, hypothermia and leg cramps.

- **Laboratory diagnosis**

Laboratory values in DKA and HHNKS are shown in Table-10

| Table 10. Common laboratory values in DKA and HHNKS
<table>
<thead>
<tr>
<th>Diabetic Ketoacidosis</th>
<th>Hyperosmololar, Hyperglycemic, Nonketotic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random plasma glucose: (&gt;250 mg/dL)</td>
<td>Random plasma glucose: (&gt;600 mg/dL)</td>
</tr>
<tr>
<td>Arterial pH: &gt;7.3</td>
<td>Arterial pH: normal</td>
</tr>
<tr>
<td>Plasma bicarbonate: (&lt;15mEq/L)</td>
<td>Plasma bicarbonate: normal</td>
</tr>
<tr>
<td>Anion gap: increased</td>
<td>Anion gap: normal</td>
</tr>
<tr>
<td>Serum ketones: present</td>
<td>Serum ketones: absent</td>
</tr>
<tr>
<td>Urinary ketones: absent</td>
<td>Urinary ketones: absent</td>
</tr>
<tr>
<td></td>
<td>Serum osmolality (&gt;340 mOsm/kg)</td>
</tr>
</tbody>
</table>

- **Management of DKA and HHNKS**

DKA and HHNKS are medical emergencies, which should be treated in the hospital. Treatment should be checked against the plasma concentration of 73
glucose, potassium and bicarbonate\textsuperscript{87}. The overall treatment of DKA and HHNKs revolves around general measures, insulin administration, fluids and electrolytes replacement and bicarbonate\textsuperscript{87}.

**B. Long-term complications of diabetes**

The results of the Diabetes Control and Complications Trial (DCCT)\textsuperscript{233} and the United Kingdom Prospective Diabetes Study (UKPDS)\textsuperscript{237} clearly demonstrated that chronic hyperglycemia is associated with the development and progression of microvascular complications such as nephropathy, neuropathy and retinopathy. Neither the DCCT\textsuperscript{233} nor the UKPDS\textsuperscript{237} however show strong association between hyperglycemia and macrovascular disease, suggesting that the development of CVD in Type 2 diabetes is multifactorial.

**1. Cardiovascular diseases**

More than 80\% of deaths from diabetes are from cardiovascular disease (CVD) of which 75\% are a result of coronary heart disease (CHD)\textsuperscript{244}. Several studies have documented that diabetes mellitus is a major risk factor for cardiovascular disease in men and women\textsuperscript{168,254}. The risk for developing coronary artery disease and stroke is two to fourfold greater in individuals with diabetes compared with the patients without diabetes and the risk for myocardial infarction and death from coronary artery disease is
the same as the risks for people without diabetes who have previous diagnosis of myocardial infarction\textsuperscript{69,121}. Peripheral vascular diseases, or atherosclerosis of the peripheral arteries, are four times more likely to develop in people with diabetes than in the general population. Atherosclerosis is the most significant complication of diabetes mellitus accounting for approximately 80% of mortality in these patients\textsuperscript{175}. The incidence of atherosclerosis increases with age and duration of diabetes\textsuperscript{12}.

2. Neuropathy

Neuropathy is the most common long-term complication of diabetes, some form of which affects 60% to 70% of all people with diabetes\textsuperscript{99}. Neuropathy can affect any region of the body but is most commonly seen in the legs, feet and hands (peripheral neuropathy)\textsuperscript{12}. Diabetes can lead to neuropathy, which is decreased or distorted function in the nerve, particularly affecting those responsible for sensation. Peripheral neuropathy is the most significant factor in the pathway leading to lower extremity ulceration and is found in approximately 80% of all cases\textsuperscript{12}. Early and aggressive treatment of people who are at a particular risk for foot and legs problem can prevent 50% of amputations\textsuperscript{99}. If diabetes affects the nerve in the autonomic nervous system, abnormalities of blood pressure control, bowel and bladder function and male sexual function can occur. In some
cases, neuropathy may block angina, the warning chest pain for heart disease and heart attack\textsuperscript{12}.

3. Retinopathy

Diabetes accounts for 12,000 to 24,000 new cases of blindness annually and is the leading cause of new cases of blindness in adults aged 20 to 74 with long duration of the disease and low control of insulin administration. Nearly all Type I diabetes will develop retinopathy\textsuperscript{12}, although only a minority of cases cause severe vision loss or blindness\textsuperscript{12}. By the seventh year, retinal damage has occurred in 50\% of Type 1 diabetes patients and after 14 years, more than 60\% develop retinopathic changes\textsuperscript{233}. About 20\% of Type 2 diabetic patients have some eye damage in diagnosis and blurred vision is common\textsuperscript{233}. People with diabetes are also at high risk of development of cataracts and certain types of glaucoma\textsuperscript{218}.

4. Nephropathy

Kidney disease is a very serious complication of diabetes. It is a primary cause of disability and death in the diabetes patients\textsuperscript{8,15}. The risk for this complication increases with coronary artery disease, hypertension and problems in the urinary tract\textsuperscript{13,22}. Diabetes is responsible for approximately 35\% of new cases of early stage of renal disease\textsuperscript{8}. Data from the DCCT\textsuperscript{233} and UKPDS\textsuperscript{237} demonstrated that near-normalization of blood glucose
levels result in a significant reduction in the development progression of diabetic nephropathy. The UKPDS\textsuperscript{237} however, clearly demonstrated that tight control of blood pressure in patient with diabetes is associated with reductions in macrovascular disease. Hypertension is also a major contributor to the development of diabetic renal disease.

C. Skin manifestations

Diabetes can affect every part of the body, including the skin\textsuperscript{114}. As many as one-third of people with diabetes develop a skin disorder caused or affected by diabetes at some time in their lives\textsuperscript{114}. There are a number of skin manifestations of diabetes, such as diabetic dermopathy, necrobiosis lipoidica diabeticorum, bullosis diabeticorum, eruptive xanthomatosis, acanthosis nigricans and disseminated granuloma annulare\textsuperscript{114}. 
SECTION TWO:

2.2 DIABETES SELF-MANAGEMENT EDUCATION
2.2.1. Benefits of Diabetes Self-Management Education

Diabetes mellitus is a chronic disease which requires long-term medical treatment and extensive life-style adjustment of the patients. Diabetes Self-Management Education (DSME) is the cornerstone of care for all individuals with diabetes who want to achieve successful health-related outcomes\textsuperscript{170}. Diabetes education is the process of teaching individuals to manage their diabetes\textsuperscript{23}. It constitutes an important part of the clinical management of individuals with diabetes since the 1930s\textsuperscript{36}. The goals of DSME are to optimize metabolic control, prevent acute and chronic complications, maintain ideal body weight and optimize quality of life, while keeping costs acceptable\textsuperscript{72}. The term patient education has conventionally been employed to define the knowledge and skills taught to people with diabetes to become self-sufficient in taking day-to-day care of themselves\textsuperscript{198}. In 1993 the Diabetes Control and Complication Trial (DCCT)\textsuperscript{77} showed the value of diabetes education program to reach desirable metabolic control. In 1988 Germany incorporated diabetes education as an essential part of diabetes care. The American Diabetes Association recommended assessment of self-management skills and knowledge of diabetes at least annually and the provision or encouragement of continuing diabetes education\textsuperscript{23}. One of the diabetes related-objectives of the US Department of Health and Human Services
"Healthy people 2010" document is to increase the proportion of individuals with diabetes who receive formal diabetes education from the 1998 baseline level of 40% to 60%, since Clement estimated that there is significant knowledge and skill deficits in 50-80% of patients with diabetes and ideal glycaemic control (HbA1c less than 7.0%) is achieved in less than half of individuals with Type 2 diabetes.

The effects of diabetes self-management education no longer need to be debated. Several studies have examined the impact of a variety of diabetes education over the world. Available data suggest that patient education have yielded consistent results. In reviewing the literature, it is clear that diabetes-self-management education has evolved from the primarily didactic interventions of the 1970s and 1980s into the collaborative, more theoretically based "empowerment" models of the 1990s. Didactic interventions focusing on the acquisition of knowledge and information demonstrate positive effects on knowledge but mixed results on glycemic control, weight, serum lipids levels and blood pressure. Collaborative interventions focusing on knowledge tend to demonstrate positive effects on glycemic control in the short-term and mixed results with follow-up of more than 1 year. Effects of collaborative interventions on lipids, body weight and blood pressure were mixed. Brown's meta-analyses support the effectiveness of diabetes education,
with positive effect sizes (from largest to smallest) for the outcomes of knowledge, dietary compliance, skill performance, metabolic control, psychological outcomes and weight loss. Padgett et al.\textsuperscript{186} reviewed the effectiveness of diabetes education in 1988 and found that dietary instruction to be the most effective on physical outcomes and knowledge. Most studies measuring changes in diabetes knowledge demonstrate improvement with diabetes education\textsuperscript{40,47,89,146,166,217,250}, including those with follow-up of 6–12 months. A number of studies demonstrated that regular reinforcement or repetition of the intervention seemed to improve knowledge levels at variable lengths of follow-up. Bloomgarden et al.\textsuperscript{40} (nine visits in 18 months), Korhonen et al.\textsuperscript{146} (one visit every 3 months for 12 months), Campbell et al.\textsuperscript{47} (regular reinforcement with visits and telephone calls over 12 months) and Fernando et al.\textsuperscript{89} (12 visits in 12 months). A large case–control study of avoidability of long-term complications of diabetes by Nicolucci et al.\textsuperscript{178} found that diabetes education to be related significantly to the likelihood of microvascular and macrovascular complications. Patients who did not receive diabetes education had a fourfold greater risk for major complications. Litzelman et al.\textsuperscript{155} noted a decrease in serious foot lesions at 1 year after an intervention consisting of group education, with three follow-up visits, provider guidelines and chart reminders. Malone et al.\textsuperscript{160} found a significant
decrease in foot ulcer and amputation rates. A systematic review of the effectiveness of DSME in Type 2 diabetes conducted by Norris et al\textsuperscript{179} reported that in a total of 27 studies described in 48 articles, positive effects of self-management education on knowledge, frequency and accuracy of self-monitoring of blood glucose, self-reported dietary habits and glycaemic control were observed. Effect of interventions on lipids, physical activity, weight and blood pressure were variable. However, several studies\textsuperscript{63,89,136,166,199,217,247} reported that an improvement was noted in glycemic control in the intervention group compared with the control group. Percentage change in glycated hemoglobin ranged from -26 to +4% in the intervention groups and from -33 to +15% in the control groups. However, many studies reviewed by Brown\textsuperscript{43} demonstrated modest improvements in hemoglobin HbA\textsubscript{lc} levels, confirming that knowledge is not necessarily translated to behavior. As a result, studies conducted in the late 1980s and into the 1990s expanded to include providing knowledge along with behavioral strategies aimed at empowerment and problem\textsuperscript{43}. These interventions focused on outcomes indicators such as weight loss and compliance with regimens involving blood glucose testing, medications or appointment keeping. Various studies\textsuperscript{48,71,97} examined the effects of self-management education on lipid levels. These studies showed improvement in total cholesterol in intervention group (range -0.9 to -0.07
mmol/dL), LDL (-0.4mmol/dL) and HDL (+0.1mmol/dL). Several studies examined the effect of DSME on dietary changes. The results showed a positive outcome for self-reported changes, including improvements in dietary carbohydrate or fat intake, a decrease in caloric intake and an increase in consumption of lower glycemic index foods. As a result, many studies demonstrating improved dietary changes found corresponding improvements in weight and glycemic control. Other many studies, examined effect of diabetes self-management education on psychological outcomes. Improvements were noted in problem solving, anxiety levels and quality of life.

2.2.2 Components of Diabetes Self-Management Education

Certain aspects have to be taken into consideration whilst providing DSME.

1. Educational Setting

It is accepted that diabetes education is provided best in the outpatient setting. Patients with diabetes who are hospitalized generally have comorbid conditions, are ill and have shortened lengths of stay. Furthermore, they are not in their usual setting in which behavior modification strategies can be practiced. The setting where diabetes education is provided is defined best by practicality and health care provider.
2. Diabetes educators

DSME involves the interaction of the individual with diabetes with a multifaceted education instructional team, which may include a nurse, dietitian, pharmacist, exercise specialist, physician, podiatrist or behaviorist. DSME instructors are collectively qualified to teach the content areas. DSME has been shown to be most effective when delivered by a multidisciplinary team with a comprehensive plan of care. The multidisciplinary team utilized in DSME is one in which the different team members retain their individual disciplinary identity, work interdependently, consult with one another and have shared goals. The team should have a collective combination of expertise in medical treatment, medical nutrition therapy, teaching skills and behavioral psychology. It is essential in this collaborative and integrated team approach that individuals with diabetes assume an active role in their care. Nurses have been utilized most often as instructors in the delivery of formal DSME. Since the emergence of medical nutrition therapy, registered dietitians have become an integral part of the diabetes education team. In recent years, the role of the diabetes educator has also expanded to other disciplines. Although there is no evidence demonstrating that one discipline is more effective than another, the literature review favors current practice that utilizes the registered nurse.
and registered dietitian as key members of the multidisciplinary team preparing and assisting in the delivery of DSME\textsuperscript{75,96,154}. In addition to the registered nurse and registered dietitian, a number of articles reflect the ever changing and evolving health care environment to include other health professionals (e.g., physicians, behaviorists, pharmacists, exercise physiologists, ophthalmologists, optometrists and podiatrists) and paraprofessionals as members of the educational team\textsuperscript{54,59,131,209,240}. However, the literature reflects that additional research is needed to demonstrate that these professionals may play a major role on the diabetes education team\textsuperscript{27,61,90,183}.

### 3. Curriculum of Diabetes Self-Management Education

The literature supports a strong core group of topics in the design of the curriculum\textsuperscript{32,49,89,64,115,127,144,157,171,211,220}. The curriculum is defined as a coordinated set of courses and educational experiences to accomplish a set of outcomes\textsuperscript{138}. The individual with diabetes needs the knowledge and skills to make informed choices, to facilitate self-directed behavior change\textsuperscript{183} and ultimately to reduce the risk of complications\textsuperscript{190}. Ten content areas have been identified as the core topics that need to be provided as a part of comprehensive education to the person with diabetes\textsuperscript{9,170}.

1. Describing the diabetes disease process and treatment options
2. Incorporating appropriate nutritional management

3. Incorporating physical activity into lifestyle

4. Utilizing medications (if applicable) for therapeutic effectiveness

5. Monitoring blood glucose, urine ketones (when appropriate) and using the results to improve control

6. Preventing, detecting and treating acute complications

7. Preventing (through risk reduction behavior), detecting and treating chronic complications

8. Goal setting to promote health and problem solving for daily living

9. Integrating psychosocial adjustment to daily life

10. Promoting preconception care, management during pregnancy and gestational diabetes management (if applicable)

Inclusion of particular topics should be based on the individual's needs assessment. Principles of adult learning suggest that the patients will learn only what he or she perceives is necessary to know at that time. In addition to enhancing patient knowledge in specific content areas, diabetes education involves learning to change behaviors. Behavior change strategies and problem-solving skills are imperative components of patient-centered empowerment approach to diabetes education. The content areas above provide instructors with an outline for developing this content. These content areas are presented in behavioral terms and thereby guide the
instructor toward creative delivery methods that promote behavior change rather than simply acquisition of knowledge. The above-listed content areas are designed to be applicable in all settings.  

4. Education of Health Care Providers  

It is necessary to obtain regular continuing education in the areas of diabetes management, behavioral interventions, teaching and learning skills and counseling skills. Studies indicate that instructors without specialized training in diabetes, behavioral interventions, teaching and learning skills, and counseling skills may not focus on patient behavior change and therefore, clinical outcomes may not improve. Quality diabetes care and education require that professional staff have continuing education in diabetes educational strategies and behavioral interventions beyond their basic preparation. Behavior and lifestyle changes are the keys to successful self-management of diabetes. Selected studies of health care professionals have shown a need for increased knowledge and ability to utilize behavioral interventions with individuals living with diabetes and other chronic diseases. Therefore, the instructors delivering quality DSME must remain current in therapeutic modalities and medical nutrition therapy, as well as teaching skills and behavioral interventions.
7. Phases of Diabetes Self-Management Education

Diabetes Self-management Education should be available at diagnosis and changed when management plan is required\textsuperscript{37}. Traditional models of education that many clinicians are familiar with dictate that patients should be provided with everything they need to know in the beginning because it is not known when they may need it or when they might be seen by their clinician again\textsuperscript{37}. The educational program needs to be phased especially in the context of the patient's clinical status. There are three phases\textsuperscript{56}:

**Phase one:** At and shortly after diagnosis. In this phase the aim is to provide the minimum skills to enable the diabetes patient to obtain control over their new situation. The contents of this phase includes on education the nature and outcomes of diabetes, self-injection technique, self-monitoring of blood glucose, urine test for ketones, preventing, recognizing and treatment of hypoglycemia and hyperglycemia and dietary planning.

**Phase two:** In the months following diagnosis. This is best given on one to one basis. In this phase the content includes specific topics including those covered previously but additionally:- coping with illness, target of insulin therapy, healthy eating, complications of diabetes, associated risk factors, self-care (skin, foot, eye and teeth care), employment or schooling, insurance, driving, travel, pregnancy, genetic counseling and contraception.
**Phase three:** In the long-term, Periodic reinforcement of one and two is best achieved after annual evaluation of patient education.

6. Educational Methods

The type of learning/teaching strategies will be determined by local circumstances. There are two educational approaches.

A. Individual Counseling

Individual counseling by the physician is not always possible and is often insufficient. However, every effort should be made during the consultation to discuss aspects of self-care and other issues raised by the patients.

B. Group Discussion

Group discussion is recommended. It has the advantages allowing useful interaction among individuals with diabetes. Encouraging interaction and exchange of experiences between diabetic patients in the setting of education has been found to induce favorable change of attitudes.

7. Educational Materials

Computer programs, videos and reading materials such as posters, pamphlets and other materials are useful can supplement education sessions.
2.2.3 Implementing Diabetes Self-Management Education

Generally successful implementation of diabetes self-management education involves a four-step-process:

1. Assessment

In this phase information should be collected in order to help define goals and direct the intervention\(^{37}\). An individualized assessment, development of an educational plan and periodic reassessment between participant and instructors will direct the selection of appropriate educational materials and interventions\(^{170}\). Each participant brings unique life experiences and preferences to an encounter that help determine the intervention. The assessment includes relevant medical history, cultural influences, health beliefs and attitudes, diabetes knowledge, self-management skills and behaviors, readiness to learn, cognitive ability, physical limitations, family support and financial status\(^{49,68,70}\). Multiple studies evaluating attitudes and beliefs toward diabetes indicate the importance of individualizing education plans based on the assessment\(^{28,58,84,108,109,255}\). The bulk of the literature supports the importance of attitudes and health beliefs in diabetes care outcomes\(^{80,150,151,259}\). Periodic individualized reassessment determines attainment of the educational objectives or the need for additional and creative interventions and future reassessment\(^{84,165}\).
2. Goal Setting

Goal setting involves prioritizing problem areas and selecting behavioral tactics to improve outcomes in those areas\(^\text{37}\). The health care provider and the patient should determine what their medical goals and which one to work on first. Likewise, the patients decide what specific behavior he or she can change or do to achieve their goals\(^\text{37}\). This decision involves setting specific behavior-oriented goals\(^\text{37}\). Diet and physical activity are the cornerstone of the management of diabetes. Studies clearly have shown that, diet and physical activity together are more effective in the long-term weight loss, maintenance and improved glycemic control than either alone\(^\text{125}\). Self-monitoring of blood glucose also has been shown to be important to achieving desired medical outcomes and it is a third important behavior required in goal setting\(^\text{23}\). Goal setting should be individualized to the patient's age and cultural background\(^\text{37}\).

3. Intervention

Intervention refers to the health professional deciding how best to provide and facilitate the education of the patient and family or caregivers to achieve the agreed on goals\(^\text{37}\). This choice involves deciding the format, teaching materials and learning/teaching strategies that work best with the patients. Learning styles also differ between individuals and are influenced by issues such as literacy and cultural learning styles. Various studies have
shown that for older adults, group programs using socialization and group interaction and support may provide slightly better results particularly in the area of weight loss and physical activity. In Brown's meta-analysis, she identified that as age increases there is a diminishing effect of education itself on patient knowledge. Perhaps the socialization effect may be stronger in this age group. Not every person will do well in a group setting nor will their real life schedules allow for attending a program with times that may be inconvenient. Individual education sessions are especially helpful in educating younger individuals who do not feel comfortable in a group with individuals who do not share the same lifestyles or of vastly different ages. Some clinicians speculate that the best approach is a combination of group and individual education. Some things such as insulin therapy or management of nutrition therapy are practiced better individually because of the needs for demonstration. Other topics such as foot care can be easily covered in a group setting.

2. Evaluation

The success of patient education should be formally evaluation at a minimum 1 to 2 years. Such evaluation should include:

1. Traditional biomedical measures such as change in body weight, blood glucose and serum triglyceride concentration

2. Evidence of appropriate behaviors such as membership of diabetes
associations, appropriate footwear and injection sites in good condition

3. Assessment of life-style, emotion adjustment and perceptions of barriers to activities and self-care from diabetes

4. Perceptions of desired short-term goals (weight control) and long-term vulnerability

5. Review of diabetes skills (monitoring, injection, hypoglycemia and hyperglycemia management and food identification)

6. Well-being and health profile assessments especially for diabetes are becoming available.