CHAPTER 1

INTRODUCTION

1.1 DIABETES DEFINED

Diabetes Mellitus is a metabolic disorder in which the cells of the body are unable to absorb glucose from the bloodstream and convert it to energy required for biological work and daily activities. To understand diabetes it is necessary to understand the normal physiological process, which occurs, during and after a meal. As food passes through the digestive system, nutrients, including proteins, fat and carbohydrates are absorbed into the bloodstream. Sugar is a type of carbohydrate, and its presence in the bloodstream is a signal to the endocrine pancreas to secrete the hormone insulin. When secreted, insulin causes an uptake and storage of sugar by almost all the tissues in the body, especially the liver, musculature and fat tissue (Roussel, 1998).

1.2 CLASSIFICATION, PATHOGENESIS AND MORBIDITY OF DIABETES

There are two distinct forms of diabetes, termed type-I or insulin-dependent diabetes (IDDM) and type-II or non-insulin dependent diabetes mellitus (NIDDM). Type-I or IDDM, formerly labeled as "juvenile–onset diabetes", generally occurs in younger individuals and is associated with an absolute deficiency of insulin. When the pancreas produces little or no insulin, the body cannot absorb sugar from the blood, the cells begin to 'starve' and the blood sugar level is constantly elevated. The immediate remedy is to supply insulin by injection or insulin pump. IDDM appears to be an autoimmune disease in which the body attacks and ultimately destroys insulin producing pancreatic beta cells in an inflammatory reaction. In addition to a genetic component, evidence indicates that a viral infection may trigger the autoimmune process either due to similarities with beta-cell protein or sensitization to destroyed beta cells (Hasson, 1994).

NIDDM, formerly labeled as "adult–onset diabetes", generally occurs in older individuals and is not associated with an absolute deficiency of insulin. The pathogenesis in this case is that the pancreas produces insulin but the body does not utilize the insulin correctly. This is primarily due to peripheral tissue insulin resistance where the insulin-receptors within body cells are insensitive to insulin and consequently glucose does not readily enter the tissues (primarily muscle and adipose tissue) leading to hyperglycemia or elevated blood glucose concentrations (Albright, 1997). This increase in blood glucose in turn causes the beta cells of the pancreas to secrete more insulin in an attempt to maintain a normal blood glucose concentration. Insulin resistance is often associated with hypertension, lipid disturbances and obesity. Apart from genetic dispositions, diet and obesity, animal experiments as well as epidemiological data suggest that a lack of physical activity may contribute to insulin resistance (Hamar, 1999; Pickup & Williams, 1991). Occasionally, oral medication or insulin injections are indicated for individuals with NIDDM to counteract insulin resistance.

When insulin was discovered in 1921, and the first children with IDDM were treated successfully it was thought that a cure had eventually been found for this fatal disease. Long-term prognosis for both IDDM and NIDDM is darkened by the manifestation, in some patients of potentially serious complications, which contribute to the mortality and morbidity of diabetes (Pickup & Williams, 1991; Horton, 1995). These complications include the specific diabetic problems of retinopathy, nephropathy and neuropathy, which are often termed diabetic micro-angiopathic or 'microvascular' disease and the non-specific macrovascular problems of occlusive atherosclerotic disease affecting heart, brain, and legs. Although both types of diabetes are affected by these complications, the IDDM suffers of early onset are particularly susceptible to microvascular problems. Although the insulin dependent diabetics risk for developing diabetic complications as time progresses is high, the risk is not only related to the duration of the disease, but also to the degree of glycemic control (Oakley *et al.*, 1974). The ultimate index of disease severity is the risk of premature death. For diabetic patients overall, the mortality risk is about twice that in the age-matched,

non-diabetic population (Gatling *et al.*, 1987). For IDDM patients in particular, the risk is considerably greater, being about four to five times normal (Goodkin, 1975), and up to seven times normal for those whose disease presents in childhood (Dorman *et al.*, 1984). Overall life expectancy is reduced by about 25%. Nephropathy and heart disease account for 70% of deaths in IDDM whereas in NIDDM, 70% of deaths are due to cardiac and cerebral arteriosclerosis. Interestingly mortality rates peak at about fifteen to twenty years duration of IDDM, and decrease thereafter (Green *et al.*, 1985). It is thus deduced that diabetes mellitus is associated with significantly increased morbidity and mortality due to long-term complications of the disease (Horton, 1995; Pickup & Williams, 1991).

The individual with NIDDM is more likely to be troubled by large-vessel disease, partly because NIDDM generally appears at a lifetime when arteriosclerotic problems are frequent even in the non-diabetic population. NIDDM patients frequently have many other adverse arteriosclerotic risk factors such as obesity, hypertension, hyperlipidaemia (Barret-Connor *et al.*, 1981), and smoking-which makes large-vessel disease more prevalent amongst diabetic as opposed to non-diabetic subjects, (Kyne & Gill, 1987). Peripheral vascular disease may cause intermittent claudication and gangrene, sometimes requiring amputation. Together with neuropathy, it is a major cause of the diabetic foot syndrome, a source of considerable morbidity and cost to the health services. Coronary artery disease is the main scourge of NIDDM. Angina afflicts 17% or more of patients (Gill, 1986), nearly 60% die from ischaemic heart disease as compared with 15% of patients with IDDM (Marks & Krall, 1971). The specific micro-vascular complications of diabetes are less prominent in NIDDM than in IDDM. Retinopathy and cataracts affect about 15% of patients, but maculopathy is an especially common form of retinopathy in NIDDM and may threaten vision (Watkins *et al.*, 1987). Nephropathy is also likely to develop in NIDDM (Watkins et al., 1987), although its prevalence is lower in NIDDM than in IDDM subjects and they usually have a shorter exposure to diabetes and less opportunity to progress to end stage nephropathy with renal failure. Neuropathy is a common

complication and causes serious morbidity in a substantial proportion of NIDDM subjects, about 8% of whom have painful (rather than a symptomatic) neuropathy (Gill, 1986), and at least one-third of male NIDDM patients, when directly questioned, have some degree of impotence (McCulloch *et al.*, 1980).

1.3 PREVALENCE OF DIABETES MELLITUS

Diabetes mellitus is a universal health problem and is prevalent in all countries and affects all ethnic groups (Betteridge, 1997; Helmrich *et al.*, 1994). There is some data on the prevalence of diabetes in Africa, but that available indicate a considerable variation in different groups in the same and different countries. In South Africa a number of studies have been conducted and it is estimated that there are at least one million known diabetics and possibly up to an equal number who are currently undiagnosed. The prevalence of diabetes in South Africa is high, and is estimated to be 10% in the Indian community and 5-6% in the black community (Society of Endocrinology, Metabolism and Diabetes in South Africa, 2001). An earlier study undertaken in South Africa by Seedat (1989) comparing different ethnic groups, however the highest prevalence of diabetes, estimated at greater than 45%, to occur in the Indian population and labeled this condition as the "Challenge of the 1990's", thus indicating predominance of diabetes in the Indian population.

Most studies on the prevalence of IDDM have been conducted in children, adolescents and young adults. This is so, because older subjects presenting with diabetes are unlikely to have IDDM and so are often omitted from such studies (Pickup & Williams, 1991). In recent years an increasing number of diabetes registries have been established in different countries and many of these are co-coordinated within the group designated as Diabetes Epidemiology Research International (1987). Their work has clearly demonstrated an enormous range of incidence rates between populations, with lesser degrees of variation within populations. There are considerable geographic variations in the incidence of IDDM. Scandinavia has the highest incidence (in Finland, incidence

is 35 per 100, 000 per year). Pacific Rim has a much lower rate (in Japan and China, incidence is 2 to 3 per 100, 000 per year); Northern Europe and the United States of America (USA) share an intermediate rate (8 to 17 per 100,000 per year). Much of the increased risk of IDDM is believed to reflect the frequency of high-risk HLA alleles among ethnic groups in different geographic variations (Braunwald *et al.*, 2001; Pickup & Williams, 1991). These differences in incidence lead additional support to the proposed role of environmental factors in the genesis of IDDM (Diabetes Epidemiology Research International, (1987).

A number of problems complicate attempts to compare the prevalence of NIDDM between and within populations over different periods of time, or between different geographical locations during the same periods (Pickup & Williams, 1991). In 1974, West compared the prevalence rates of abnormal glucose tolerance between 12 different populations. West's data indicates large difference in the prevalence of NIDDM between populations studied, with the North Carolina Cherokee Indians being the highest. Several North American Indian populations have been observed to have very high rates of NIDDM, much higher than those observed in the descendants of European immigrants to the USA (West, 1974). Pima Indians have the highest incidence of diabetes in the world (30% of adults are affected). Zimmet *et al*, (1979) documented that the second highest rate of diabetes in the world was observed in the Asian Indian population of Fiji. Similarly high rates have also been noted in migrant Indian populations in South Africa (Marine *et al.*, 1969), Trinidad (Poon *et al.*, 1968), Singapore (Cheah *et al.*, 1975) and the United Kingdom (Mather & Keen, 1985). This high prevalence in the Indian population can be attributed to external migration and even migration within the country i.e. from rural to urban environments (Verma *et al.*, 1986).

1.4 SOCIO-ECONOMIC IMPACT OF DIABETES

Economic analyses of the impact of diabetes add an additional dimension to our appreciation of the magnitude of the problem (Williams, 1986). The impact of

diabetes on personal and public health is already considerable, and is increasing in several areas of the world (Keen, 1986). In most countries for which data is available, the disease is sufficiently common and its adverse effects on morbidity, employment, productivity and premature mortality sufficiently great to rank as one of the most important burdens on world health (Pickup & Williams, 1991). Overall mortality is 14.9 per 1000 person-years of diabetes. Differences observed in patients with different ethnic origins are fundamentally linked to unfavorable social and economic conditions that worsen the risk of poor blood glucose control.

A study done by Hodgson & Cohen (1999) on the medical expenditure for diabetes in the USA indicated total expenditures of $47.9 billion in 1995, including $18.8 billion for first listed diabetes, $18.7 billion for chronic complications, $8.5 billion for unrelated conditions, and $1.9 billion for co-morbidities. Studies done by Herman & Eastman (1998) and Philips (1998), compared the effects of treatment on the direct costs of diabetes. In this study intensive therapy was shown by the Diabetes Control and Complications Trial to avert complications. Economic analyses show the cost-effectiveness of intensive therapy to be two to three times greater than that of conventional therapy. Intensive therapy comprises a group receiving multiple administration of insulin each day along with intense educational, psychological, and medical support, whereas in conventional therapy a group receives twice-daily insulin injections and quarterly nutritional, educational and clinical evaluation. The goal of the intensive therapy is normoglycemia; the goal of conventional therapy is prevention of symptoms of diabetes. Intensive therapy as compared to conventional therapy reduces the risk of major complications, and produces major benefits in years of life, years of sight and years free from end-renal disease and amputation.

In Africa, a rise in complications of diabetes mellitus has gone in hand with the growing disease prevalence, clearly demonstrating the importance of assessing complications (Sidibe, 2000). Diabetes mellitus constitutes a major financial

burden in developing countries in Africa with relatively limited resources. Infection is particularly frequent and is often fatal in tropical Africa.

1.5 EXERCISE AND DIABETES

The fundamental management of diabetes is to normalize the storage and utilization of metabolic fuels by attempting to maintain blood glucose as close to normal as feasible. Generally management programs for diabetics involve dietary modification in conjunction with the use of various forms of insulin medication for IDDM that act at different time periods throughout the day. Many insulin-dependent diabetics may take multiple insulin injections, the most common being the split dose i.e. a combination of quick acting-insulin and intermediate-acting insulin (Cantu, 1987).

Exercise has also been recognized as a possible yet underutilized tool in the management of diabetes. In developed countries a sedentary life-style has become more apparent and the incidence of diseases related to inactivity is increasing. Inactivity is associated with unfavorable serum lipoprotein profiles and peripheral insulin resistance. These alterations are known aetiological risk factors for NIDDM and co-morbidity's such as obesity and cardiovascular disease. Thus, in a global health perspective, it is desirable to encourage daily physical activity in order to prevent increases in the incidence of hypokinetic diseases and to promote well being (Wallberg-Hendriksson, 1992).

Ironically before the discovery of insulin, physical activity was already an established part of the treatment of the disease and including exercise in diabetic management makes good sense for both IDDM and NIDDM subjects (Hornsby, 1994). Research has shown (Coram & Magnum, 1986; Hanson, 1993; Albright, 1997) that regular exercise whether it be housework, walking or jogging benefits diabetic patients in various ways in the treatment or prevention of diabetes. These mechanisms include reductions in insulin dose in IDDM diabetics due to exercise-induced lowering of blood glucose levels, improving the body's

sensitivity and response to insulin and reducing the risk of cardiovascular disease and co-morbidity's such as hypertension and obesity among NIDDM.

The role of exercise in the management of IDDM has been widely researched internationally (McCargar *et al*, 1991; Hamar, 1999; Roussel, 1998). For instance, a study conducted by McCargar *et al.* (1991) in the USA on the benefits of exercise training on IDDM men, indicated that healthy male subjects with IDDM could benefit from regular exercise with a redistribution of body fat and improved exercise capacity. It is thus evident that people with IDDM diabetes should be encouraged to control their blood sugar levels with insulin injection in conjunction with dietary modification and regular exercise (Hamar, 1999).

In the South African context a few diabetic institutions and information center offer help to diabetic patients. The South African Diabetes Association publishes a journal entitled "Diabetic Focus" which enlightens diabetic patients and people involved in diabetes on recent findings and general information on this chronic disease. South African pharmacological institutes for diabetes such as Nova Nordisk, Novacare, Roche and Lilly publish manuals on practical guidelines to assist in the management of diabetes. However, research on the specific application of exercise in the management of IDDM is virtually unexplored in the South African context with the majority of the literature focusing primarily on subject's abroad.

1.6 STATEMENT OF THE PROBLEM

Research has shown (Albright, 1997; Hanson, 1993) that regular exercise helps in the treatment or prevention of diabetes. Although IDDM patients generally have an obvious abnormal glucose homeostasis and the impact of exercise on the metabolic state would be more pronounced, the control of IDDM appears to be aided by regular exercise (Hamar, 1999). People with this condition should thus control their blood sugar levels with insulin injection in conjunction with dietary modification and exercise. There has been intensive research undertaken

in other countries (Hamar, 1999), pertaining to IDDM and exercise. A similar survey on diabetes and exercise was undertaken in 1995 in which the researcher investigated the attitudes and beliefs about exercise among persons with NIDDM. This study examined a smaller sample group of 83 diabetics with non-insulin dependent diabetes who had completed outpatient counseling. The study yielded that a significant majority (52%) exercised three and more days a week. Positive and negative attitudes towards exercise characterized the group, however only negative attitudes were related to exercise. Both exercisers and non-exercisers perceived barriers to exercise. The results of this study indicated that providing assistance in identifying support for exercise and overcoming perceived barriers to exercise may increase compliance to exercise (Swift *et al.*, 1995).

In South Africa some research has been conducted on NIDDM and exercise (Heilbrunn, 1999). The problems associated with NIDDM have little or no similarity to IDDM, and most of the IDDM research primarily focuses on drug therapy (Nemchik, 1998), related diseases (Nova Nordisk Handbook) and mortality rate (Lipton *et al.*, 1999). Hence the area of exercise in the management of IDDM among the South African population is in need of research. Such information would be of definite value to institutions involved with diabetics.

1.7 PURPOSE AND AIMS OF THE STUDY

In cognizance of the foregoing, the purpose of this study was to gain insight into the:

i) knowledge;
ii) attitudes;
iii) beliefs and
iv) practices

of insulin dependent diabetics with respect to exercise/physical activity, in conjunction with diet and medication, in the management of IDDM.

1.8 DELIMITATION

Considering the high prevalence of IDDM in the Indian population of South Africa, data were sampled from various hospitals in Kwa-Zulu Natal, which service diabetic patients. This study was delimited to a descriptive analytical survey of the exercise practices, dietary habits and medication usage among insulin dependent diabetics between the ages of ten to fifty years. There were no restrictions placed on the gender, race or physical activity status of the study group.

CHAPTER 2

LITERATURE REVIEW

1. PREVALENCE OF DIABETES

As described in the opening chapter, diabetes can be categorized into two major variants that differ in their patterns of inheritance, insulin response and origins. The first is type-I diabetes also called insulin dependent diabetes mellitus (IDDM) and/or juvenile-onset diabetes. This variant accounts for 10-20% of all cases of primary diabetes. The remaining 80-90% have type-II diabetes, also called non-insulin dependent diabetes mellitus (NIDDM) and/or adult-onset diabetes (Bach, 1994). Although the two major types of diabetes have different pathogenic mechanisms and metabolic characteristics, associated long term complications to blood vessels, kidneys, eyes, and nerves occur as a result of both types and are major causes of morbidity and death from diabetes (Atkinson & Maclaren, 1994).

Diabetes and its complications claims more lives each year than acquired immune deficiency syndrome, breast cancer and lupus combined (Mahan *et al.*, 2000). In 1995, an estimated 135 million people worldwide had diabetes (Canadian Diabetes Association, 2001). The World Health Organization (WHO) estimates the number of people with diabetes in the world will reach an alarming 300 million by 2025. The prevalence of diabetes increases with age. As the general population ages, the number of people with diabetes is expected to grow substantially (Canadian Diabetes Association, 2001).

A similar survey on diabetes and exercise was undertaken in 1995 in which the researcher investigated the attitudes and beliefs about exercise among persons with NIDDM. This study examined a smaller sample group of 83 diabetics with

non-insulin dependent diabetes who had completed outpatient counseling. The study yielded that a significant majority (52%) exercised three and more days a week. Positive and negative attitudes towards exercise characterized the group, however only negative attitudes were related to exercise. Both exercisers and non-exercisers perceived barriers to exercise. The results of this study indicated that providing assistance in identifying support for exercise and overcoming perceived barriers to exercise may increase compliance to exercise (Swift *et al.*, 1995).

IDDM occurs most frequently in persons of European descent. The disease is much less common among other racial groups, including blacks, Native Americans, and Asians. Diabetes can aggregate in families; the mode of inheritance of susceptible genes remains unknown. About 6% of children of first-order relatives with IDDM develop the disease. Among identical twins, the concordance rate (i.e. both twins affected) is only 40%, indicting that both genetic and environmental factors play an important role (Atkinson *et al.*, 1994).

Information derived from the American Diabetes Association and the National Institute of Health suggests that diabetes affects an estimated 16 million persons in the USA and is the fourth leading cause of death by disease in the USA (Amos *et al.*, 1997). Annually 625 000 new cases of diabetes are diagnosed in the USA and each year about 29 700 develop IDDM. The diagnosis, epidemiology, and clinical management of IDDM and NIDDM has undergone substantive changes. More than 16 million Americans live with the disease, and many are affected but undiagnosed (Amos *et al.*, 1997). An estimated 11% of the USA population aged 65-74 years has diabetes. Women have a higher prevalence of diabetes (20%). NIDDM occurs more frequently in some population groups at higher risk including African Americans, Mexican Americans and Native Americans. The Pima Indians of Arizona in the USA are known to have the highest prevalence of diabetes in the world. Nearly 50% of

the Indian populations in Arizona between the ages 30-40 years old have diabetes (Life Scan, 2001).

Since European settlement in Australia over 200 years ago, many diseases became an issue, one of which being diabetes mellitus. Nearly one million Australians suffer from diabetes and 100 000 have IDDM. This incidence of juvenile diabetes has doubled in the last 5 years and Australia has one of the highest incidences of juvenile diabetes in the world (Juvenile Diabetes Foundation Australia, 2001). In the 25-45 year old age group, indigenous Australians are seven-eight times more likely to contract diabetes than non-Aborigines and twice as likely to do so in the 45-54 year old age group (Australian Bureau of Statistics, 1996). As a result of many Aborigines being forced into accepting a European lifestyle, they are more likely to suffer from diabetes than other Australians (Issues for the Nineties, 1997). This has also resulted in native Australians having much higher rates of eye and heart disease and stroke than other Australians (International Diabetes Institute, 2000).

In Canada diabetes is the seventh leading cause of death by disease, amounting to at least 5 500 deaths each year (Mahan *et al.*, 2000). Some researchers believe that immigrant Aboriginal populations in many countries are able to survive on less food than other people. This is termed a "conservatory gene". Such individuals are susceptible to diabetes because their bodies are used to an environment where they have to work very hard for very little food. The Aboriginal people in Canada are displaced native Australians who have only been introduced to European lifestyle in the past 100-150 years. Their genetic make-up has not yet had time to adapt to this new way of life so they are more susceptible to diabetes (Herbert, 2001). A scientific theory of an Aboriginal "thrifty gene" suggests natives store body fat more aggressively than other people as protection against the historical experience of food scarcity (Canadian Diabetes Association, 2000).

India has a population of more than a billion. Its citizens appear prone to developing diabetes later in life, and are more vulnerable to diabetes complications. The prevalence of NIDDM in Indian cities is high. Part of the aetiology falls on the adoption of a Western lifestyle, involving more fatty foods and a sedentary lifestyle (BBC News, 2001). According to research at the Appollo hospital in Chenal (India) it has been stated that by the year 2005 there will be 30-35 million diabetics in India and every fifth diabetic in the world would be an Indian (BBC News, 2001). Indians appear to be more prone to diabetes than any other populations in the world. Indians in India or living abroad develop diabetes 10 years earlier than other population groups, and their life expectancy is shorter (Rao, 2001).

There are a few data on the prevalence of diabetes in Africa, but those available indicate considerable variations in different ethnic groups in the same and in different countries. Diabetes mellitus is rapidly emerging as a major public health problem in South Africa (SA). Diabetes is one of the nation's most prevalent and serious health problems. Many public health experts consider this chronic and potentially disabling disease to be epidemic in proportion (Capriotti & McLauglin, 1998). In SA a number of studies save been conducted and it is estimated that there are at least 1 million known diabetics and an equal number who are undiagnosed (Society of Endocrinology, Metabolism, and Diabetes of South Africa, 2001). In a study undertaken on diabetes in South Africa comparing the different ethnic groups (Seedat, 1989), has also shown a predominance of diabetes in the Indian population. The prevalence of diabetes in the Indian community is estimated to be 10% and 5-6% in the Black community. The latter prevalence is far higher than for black Africans elsewhere and has increased over the last two decades. The effects of urbanization and an unhealthy lifestyle are important contributors to this rising prevalence (Society of Endocrinology, Metabolism, and Diabetes of South Africa, 2001).

2. DISEASE CONDITION

Diabetes mellitus is not a single disease but represents a heterogeneous group of disorders of varying etiology and pathogenesis. These are disorders characterized by increased fasting and postprandial blood glucose concentration, insulin insufficiency resulting in impaired ability to transport glucose across the cell membrane for its subsequent oxidation, decreased insulin action, abnormalities of glucose, lipid and protein metabolism and the development of both acute and long-term complications (Horton, 1995; Wallberg-Hendriksson, 1992).

Diabetes often leads to serious pathological complications of various organ systems, which may subsequently impair quality of life and reduce life expectancy. The pancreas is both an endocrine gland that produces the peptide hormone insulin, glucagon and somatostatin, and an exocrine gland that produces digestive enzymes (Mycek *et al.*, 2000). The peptide hormones are secreted from cells located in the islets of Langerhans (B-cells produce insulin, D-cells produce somatostatin, A-cells produce glucagon). These hormones play an important role in regulating the metabolic activities of the body and by doing so; help maintain the homeostasis of blood glucose (Mycek *et al.*, 2000). Diabetes may arise secondarily from any disease causing extensive destruction of pancreatic islets, however the most common and important forms of diabetes mellitus arise from the primary disorders of the islet cells – insulin system (Kumar *et al.*, 1997).

2.1 INSULIN PHYSIOLOGY

Diabetes mellitus is a complex disorder caused by pathologic mechanisms in the secretion and metabolism of the hormone insulin, leading to alterations in the

metabolism of carbohydrate, protein and fats, which result in elevated blood sugar levels (Kumar *et al.*, 1997). There are two distinct forms of diabetes, termed type-I or insulin-dependent diabetes (IDDM) and type-II or non-insulin dependent diabetes mellitus (NIDDM). IDDM, formerly labeled as "juvenile–onset diabetes", generally occurs in younger individuals and is associated with an absolute deficiency of insulin. When the pancreas produces little or no insulin the body cannot absorb sugar from the blood, the cells begin to 'starve' and the blood sugar level is constantly elevated. The immediate remedy is to supply insulin by injection or insulin pump. NIDDM, formerly labeled as "adult–onset diabetes", generally occurs in older individuals and is not associated with an absolute deficiency of insulin. The pathogenesis in this case is that the pancreas produces insulin but the body does not utilize the insulin correctly. Occasionally, oral medication or insulin injections are indicated for individuals with NIDDM to counteract insulin resistance. The insulin gene is expressed in the beta-cells of the pancreatic islets, where insulin is sensitized and stored in granules before secretion. Release from beta-cells occurs as a biphasic process involving two pools of insulin. A rise in the blood glucose levels calls forth an immediate release of insulin, presumably that stored in the beta-cell granules. If the secretory stimulus persists, a delayed and protracted response follows, which involves active synthesis of insulin (Bach, 1994).

The principle metabolic function of insulin is to increase the rate of glucose transport into certain cells in the body (Kahn, 1994). Insulin is a major anabolic hormone. It is therefore necessary for:

1. Trans-membrane transport of glucose and amino acids;
2. Conversion of glucose to triglycerides;
3. Nucleic acid synthesis; and
4. Protein synthesis.

2.2 DIAGNOSIS

Currently the following criteria are utilized for the laboratory diagnosis of diabetes mellitus (Mahan *et al.*, 2000; Kumar *et al.*, 1997; Braunwald *et al.*, 2001; American Diabetes Association, 2001).

1) Fasting (overnight) venous plasma glucose concentration ≥ 125.5 mg/dl (6.9 mmol/l) on more than one occasion indicates a diagnosis of diabetes.
2) In the presence of symptoms of diabetes, a confirmed non-fasting plasma glucose (casual) value of ≥ 200mg/dL (11 mmol/l) is indicative of diabetes.
3) An oral glucose tolerance test, involving ingestion of 75 gm of glucose and measurement of the plasma glucose 2 hours later, with values of ≥ 200mg/dL (11 mmol/l) indicating a diagnosis of diabetes.

In asymptomatic, undiagnosed individuals, testing or screening for diabetes should be considered in all individuals aged 45 years and older. If test results are normal, screening should be repeated at 3-year intervals. According to the Expert Committee on the Diagnosis and Classification of Diabetes (1997), testing should be considered at a younger age, or be carried out more frequently in individuals who:

- Are obese;
- Have a 1st degree relative with diabetes;
- Are members of a high risk ethnic group;
- Are women who have babies weighing more than 4 kg at birth or having gestational diabetes mellitus;
- Are hypertensive (blood pressure ≥140/90 mmHg);

- Have an HDL cholesterol level $\leq$ 35 mg/dl (1.9 mmol/l) and or a triglyceride level exceeding 250 mg/dl (13.5 mmol/l);
- Had impaired glucose tolerance or impaired fasting glucose on previous testing.

2.3 PATHOGENISIS AND ETIOLOGY OF INSULIN DEPENDENT DIABETES MELLITUS

This form of diabetes (IDDM) results from a lack of insulin caused by a reduction in the beta cell mass. IDDM usually develops in childhood, becoming manifest and severe in puberty. Patients depend on insulin for survival, hence the term insulin dependent diabetes mellitus. Without insulin, they develop serious metabolic complications such as acute ketoacidosis and coma. Three interlocking mechanisms are responsible for the islet cell destruction; viz. genetic susceptibility, auto-immunity, and environmental insult. A postulated sequence of events involving these three mechanisms is shown in Figure 2.1 (Kumar *et al.*, 1997).

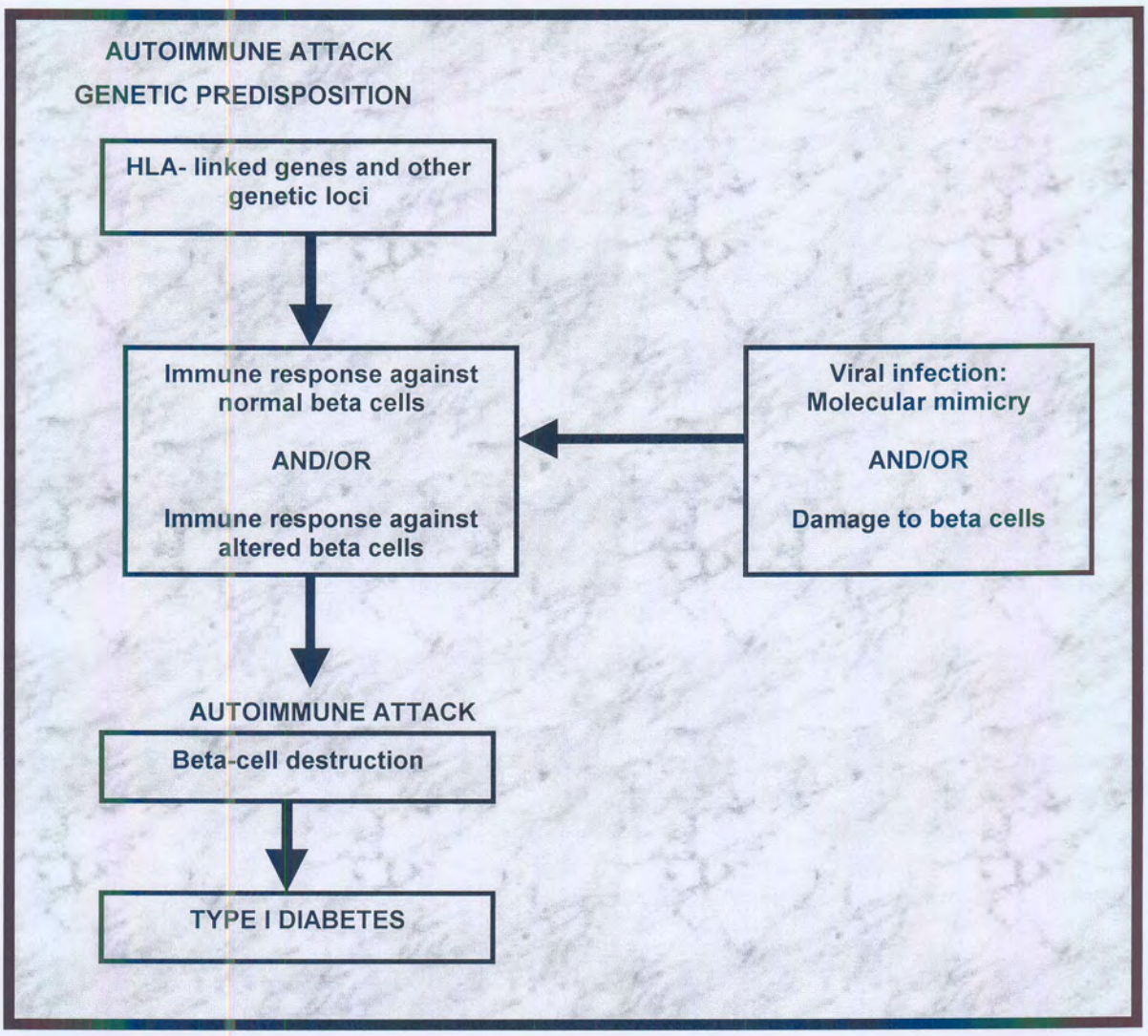


Figure 2.1: Pathways to Beta-Cell destruction

2.4 PATHOGENESIS AND ETIOLOGY OF NON-INSULIN DEPENDENT DIABETES MELLITUS

Less is known about the pathogenesis of NIDDM despite being the most common. There is no evidence that autoimmune mechanisms are involved (Polonsksy, 1996). Lifestyle plays a major role, where obesity is considered. Genetic factors are more important in NIDDM than IDDM. Epidemiological studies indicate that NIDDM appears to result from a collection of multiple genetic defects, each contributing its own predisposition risk and each modified

by environmental factors (Ghosh & Schork, 1996). Figure 2.2 exemplifies two metabolic defects that characterize NIDDM, that is, a derangement in the beta-cell secretion of insulin and an inability of peripheral tissue to respond to insulin (insulin resistance), (Kahn, 1994). Genetic predisposition and environmental influences converge to cause hyperglycemia and overt diabetes. The primary cause of deranged beta-cell insulin secretion and peripheral insulin resistance is not established; in patients with clinical disease, both defects are demonstrated (Kumar *et al.*, 1997).

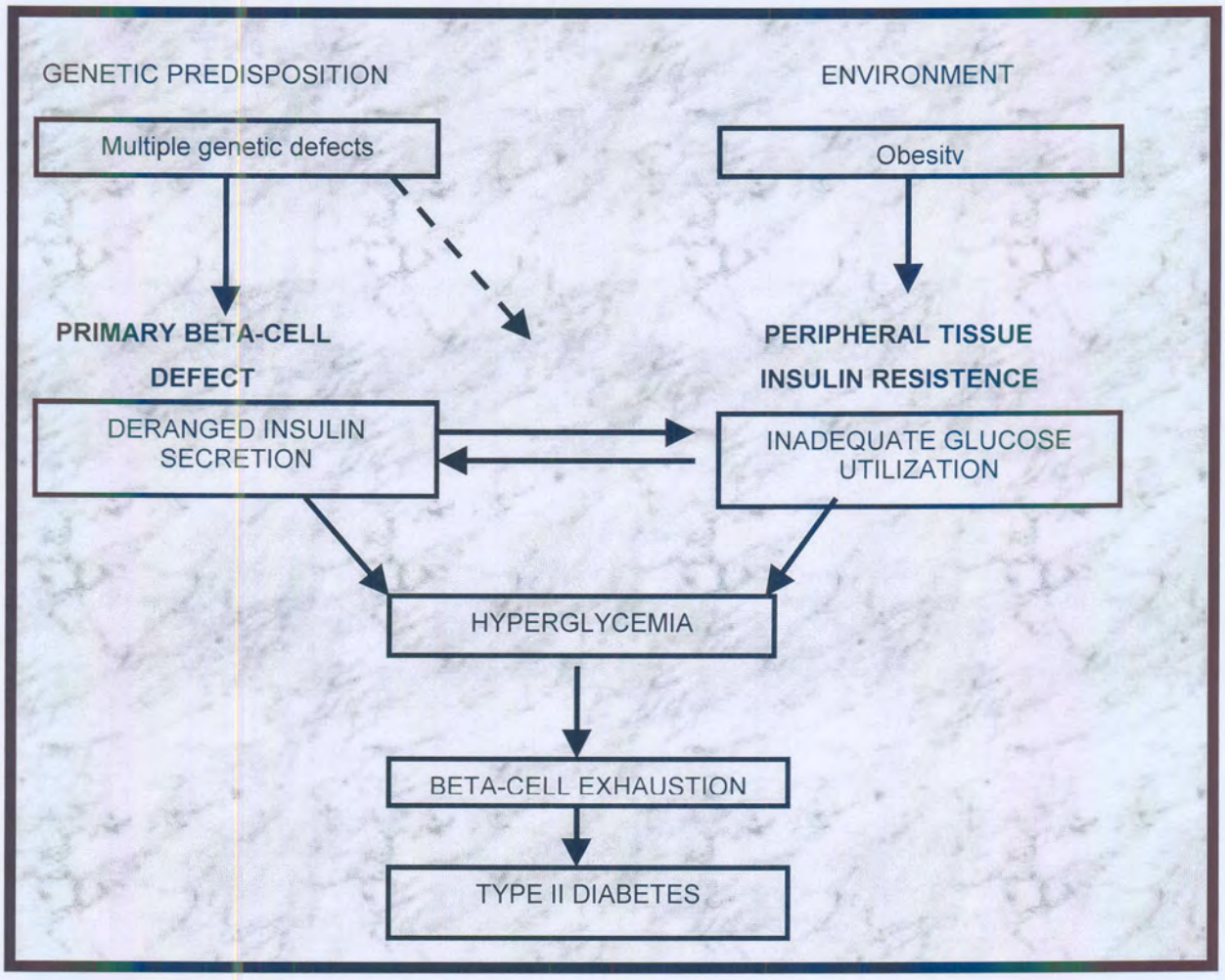


Figure 2.2: Pathogenesis of NIDDM

2.5 NORMAL METABOLIC PROCESSES

During aerobic glycolysis acetyl coenzyme A molecule enters the citric acid cycle (Krebs Cycle) by combining with a molecule of oxaloacetic acid to form citric acid. The citric acid is then changed by a series of reactions (decarboxylation and dehydrogenation) back into oxaloacetic acid, and the cycle is completed. As citric acid is produced, coenzyme A is released and this can be used again in the formation of acetyl coenzyme A from pyruvic acid molecules (Hole, 1993). During various steps of the citric acid cycle, carbon dioxide and hydrogen atoms ate released. For each glucose molecule metabolized in the presence of oxygen, two molecule of acetyl coenzyme A enters the citric acid cycle. As the result of the four carbon dioxide molecules and sixteen hydrogen atoms being released, two molecules of ATP are formed via substrate phosphorylation. The released carbon dioxide dissolves in the cellular fluid and is transported away via the blood to the lungs. Most of the hydrogen atoms released from the citric acid cycle, and those released during glycolysis and the formation of acetyl coenzyme A, supply electrons to the respiratory chain with the production of ATP via oxidative phosphorylation (Hole, 1993).

CARBOHYDRATE PATHWAY

When excess glucose is present, it enters anabolic carbohydrate pathways and is converted into storage form such as glycogen. Although most cells can produce glycogen, the liver and muscle cells store the greatest amounts following a meal when blood glucose concentration is high, liver cells obtain glucose from the blood and convert it to glycogen, when blood glucose concentration is lower, the reaction is reversed, and glucose is released into the blood. Glucose can also be converted into fat molecules, which are later deposited in fat tissue, this happens when a person takes in more carbohydrates than can be stored as glycogen, or are needed for normal activities. The body has an almost unlimited

capacity to perform this type of anabolic metabolism, this an excessive intake of nutrients can result in becoming overweight (obese) (Hole, 1993).

LIPID PATHWAY

Foods contain lipid in the form of phospholipids or cholesterol, the most common dietary lipids are fats called triglyceride. Triglycerides consist of glycerol portion and three fatty acids. The metabolism of lipids is controlled mainly by the liver, which can remove them from the circulating blood and alter their molecular structures. Lipids provide for a variety of physiological functions, however fats are used mainly to supply energy. Before energy can be released from triglycerides molecules, the molecule must undergo hydrolysis. As shown in figure 2.3 some of the fatty acid portion can be converted into molecules of acetyl coenzyme A by a series called beta-oxidation. In the first phase of beta-oxidation reaction, the fatty acids are converted into activated forms. This change requires a supply of energy form ATP molecule and the presence of a special group of enzyme (thiokinases). Each of the enzymes in this group can act upon a fatty acid with a particular carbon chain length. Once the fatty acid molecule has been activated, other enzymes called acid oxidases that are located within mitochondria break them down. In this phase of the reaction, segments of fatty acid chains (containing two carbon atom each) are removed. Some of these segments are converted into compound called ketone bodies, such as acetone, which later may bee changed to acetyl coenzyme A. Lipids are oxidized in a "carbohydrate flame" as glycolysis provides the kreb cycle with oxaloacetate via pyruvate, unless glycolysis provides sufficient oxaloacetate to "pick-up" acetyl coenzyme A fragments prior to conversion to citric acid, acetyl coenzyme A fragments are converted to ketone bodies. In diabetes the insulin deficiency (IDDM) or insulin resistance (NIDDM) leads to less carbohydrate being utilized in the cells, with accompanying decrease in the formation of oxaloacetate, via pyruvate, thus exacerbate the formation of ketones leading to diabetic

ketoacidosis. In other case, the resulting acetyl coenzyme A can be oxidized by means of the citric acid cycle (Hole, 1993). When ketone bodies are formed more rapidly than they can be decomposed, some of them are eliminated though the lungs and kidney. The breath and urine may develop a fruity odour due to the presence of ketone acetone. This occurs when a person fasts, forcing the body cells to metabolize fat, in order to lose weight. Persons suffering form diabetes mellitus are likely to metabolize excessive amounts of fats, at the same time they may develop a serious imbalance in pH called acidosis, which is due to an over-accumulation of acidic ketone bodies (Hole, 1993).

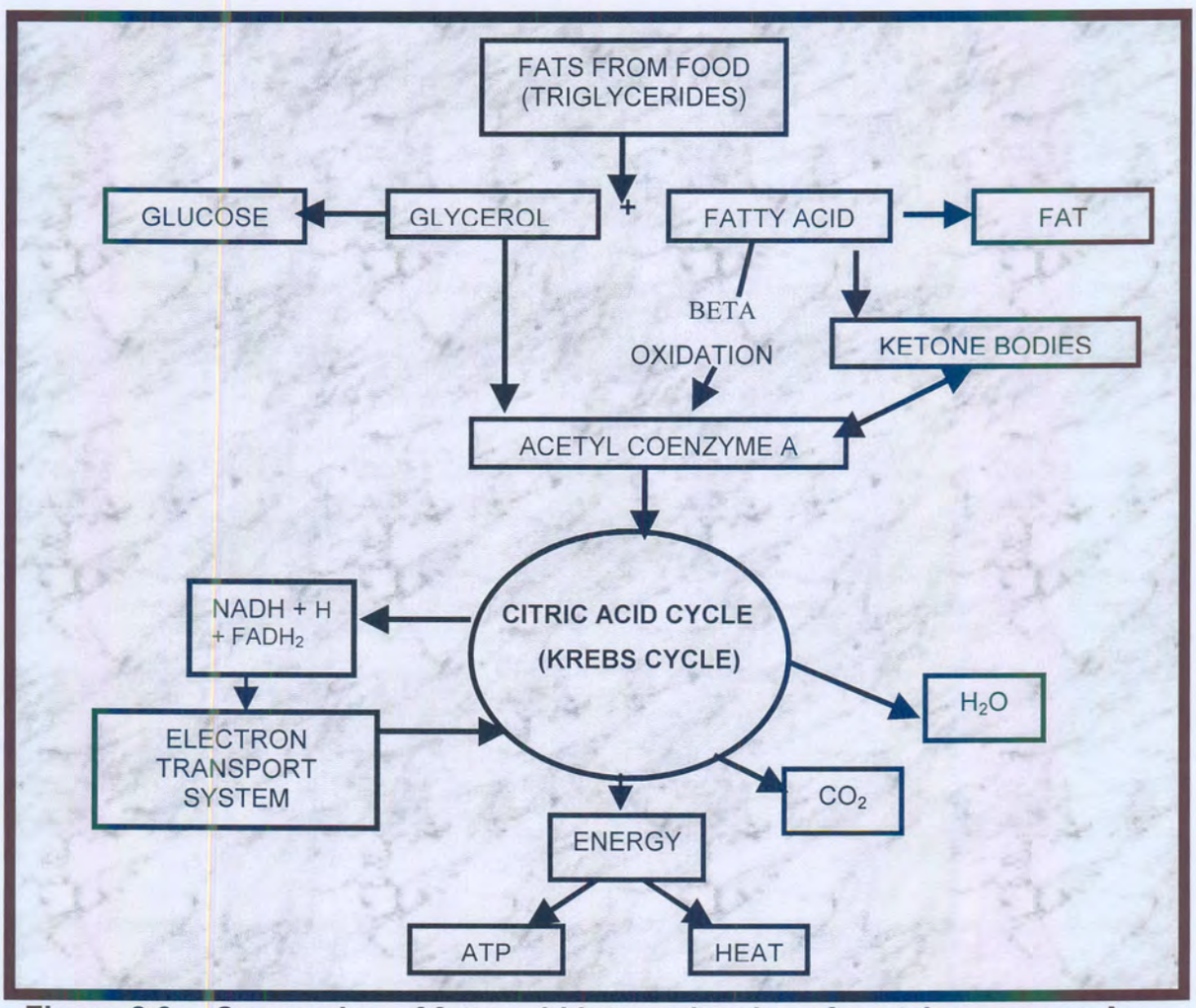


Figure 2.3: Conversion of fatty acid into molecules of acetyl coenzyme A (Hole, 1993).

When dietary proteins are digested the resulting amino acids are absorbed and transported by the blood to various blood cells. Many of these amino acids are reunited to form new protein molecules, as specified by DNA, which then may be incorporated into cell parts or serve as enzymes, others may first be broken down into amino acids. The amino acids undergo deamination, a process that occurs in the liver and involves removing the nitrogen-containing portion ($-NH_2$ groups) from amino acids. These $-NH_2$ is later converted into waste substance called urea. Depending upon the amino acids involved, the remaining deaminated portion of the amino acid molecules are decomposed by one of several pathways. Some of these pathways lead to the formation of acetyl coenzyme A, and other lead more directly to various steps of the citric acid cycle. As energy is released from the cycle, some of it is captured in molecules of ATP (figure 2.4). If not needed immediately, the deaminated portions of the amino acids may be changed into glucose or fat molecules. Glucose can be changed back into some amino acids if certain nitrogen-containing molecule are available, eight necessary amino acids cannot be synthesized in adequate amounts in human cells and so must be provided in diet. For this reason these are called essential amino acids (Hole, 1993).

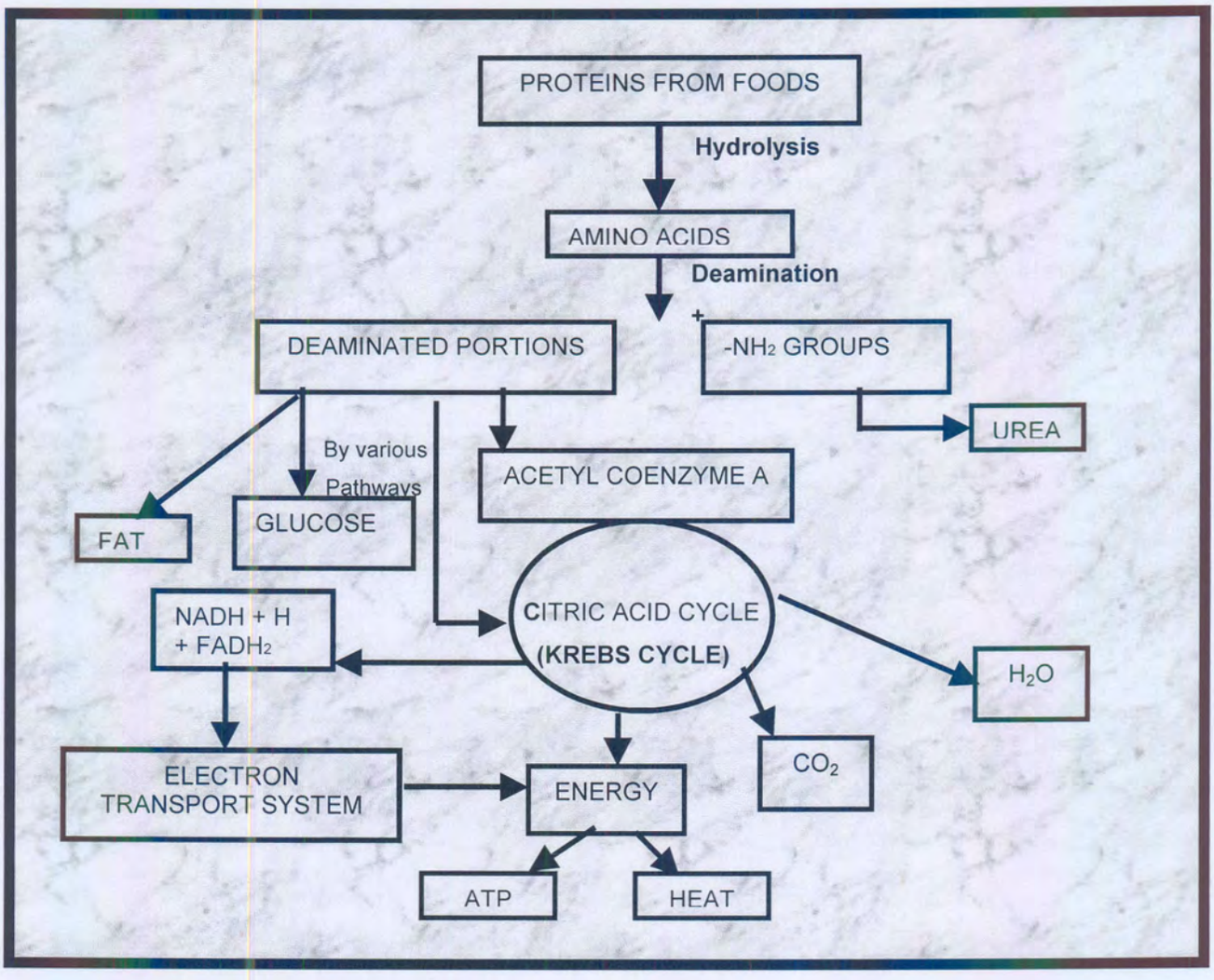


Figure 2.4: Deamination of amino acid before it is used as energy (Hole, 1993).

2.6 ACUTE METABOLIC DISTURBANCES

IDDM is associated with acutely lowered blood sugar (hypoglycemia), hyperglycemia and ketoacidosis (Molitch, 1988; Kumar *et al.*, 1997; Mahan & Escott-Stump, 2000). These complications occur exclusively to IDDM and are the result of severe insulin deficiency coupled with absolute or relative increases of glucagons (Kumar *et al.*, 1997). An absolute insulin deficiency leads to a catabolic state (figure 2.5), eventuating in ketoacidosis and severe volume depletion. These cause sufficient central nervous system compromise to lead to coma, and eventual death if left untreated (Kumar *et al.*, 1997).

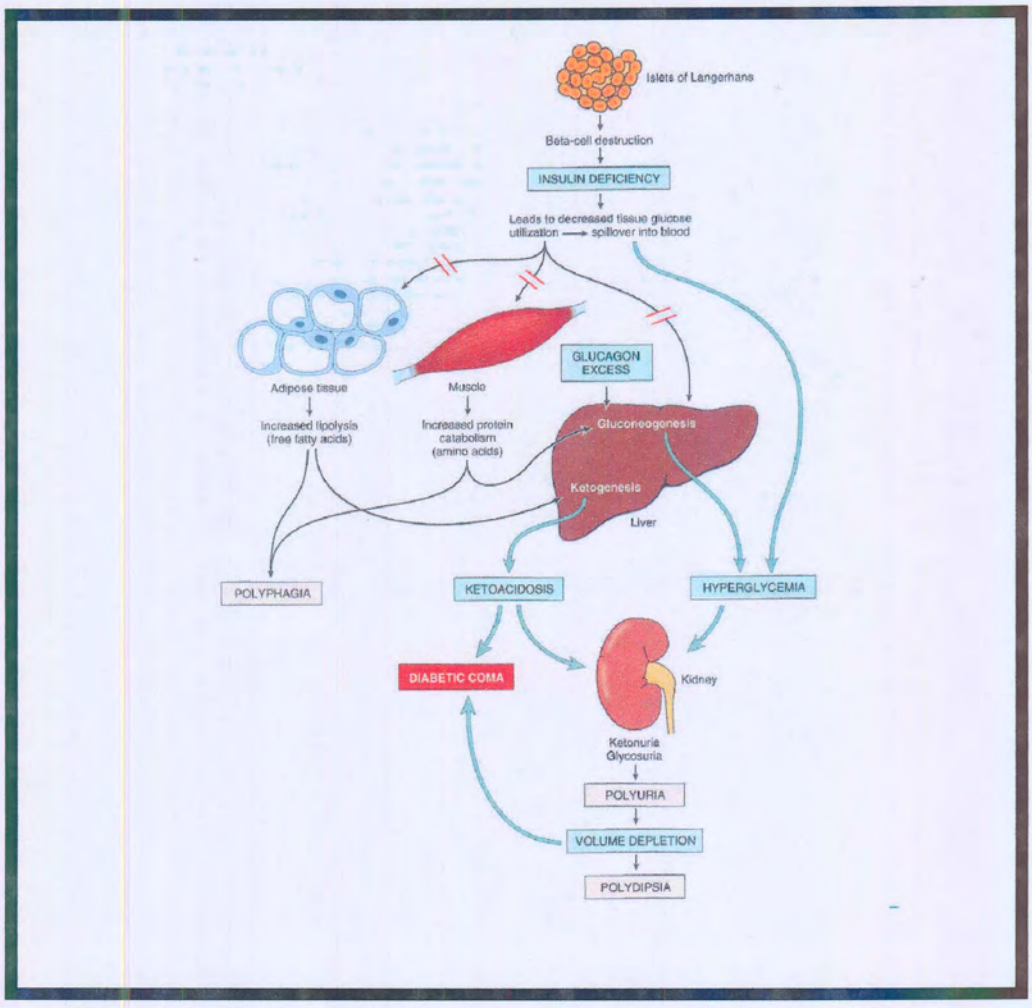


Figure 2.5: Sequence of disturbances in IDDM

2.6.1 HYPOGLYCEMIA

Hypoglycemia is defined as an abnormally, low level of glucose in the blood circulation (≤2.0 mmol/l), and is not a disease but a laboratory finding that is often associated with characteristics signs and symptoms. Hypoglycemia occurs when normal homeostatic mechanisms fail to maintain the circulating glucose level within the normal range 4-7 mmol/l. This disorder has common signs and

symptoms that reflect inadequate glucose delivery to the brain and compensatory activation of the sympathetic nervous system (Kahn, 1994).

Hypoglycemia is the most frequent acute complication in IDDM and represents the major limiting factor in the management of diabetes aiming for near-normoglycemia (Solte'sz, 1998). Hypoglycemia may be symptomatic or asymptomatic. Symptomatic hypoglycemia can be divided into three grades, viz. grade 1 (mild), grade 2 (moderate), and grade 3 (severe) (Chiarelli *et al.*, 1999; Davis & Jones, 1998). Mild refers to self administration of food or glucose being possible, moderate requires some form of external assistance such as help to eat, and a severe grade requires glucagons or intravenous glucose to be given and/or severe symptoms such as coma or seizures occurring (Edge & Matyka, 1997; Capriotti & McLaughlin, 1998). Hypoglycemia occurring in children under the age of 5 years cannot be classified as mild because young children are not able to help themselves (Silink, 1996). Severe hypoglycemia is the most anxiety promoting feature of diabetes in children, but is rarely a direct cause of death (Ispad, 1995). Hypoglycemia is a common side effect of insulin therapy (Mahan & McLaughlin, 2000; Beaufort, 1998, Capriotti & McLaughlin, 1998). Autonomic symptoms occur which are general signs of hypoglycemia including shaking, sweating, palpitation and hunger (Sherman, 1990; Mahan & McLaughlin, 2000; Clarke, 1997). Moderate and advanced hypoglycemic symptoms are related to neuroglycopenia and include headaches, confusion, lack of co-ordination, blurred vision, anger, seizures and comas (American Diabetes Association, 1998., Caprotti & McLaughlin, 1998). There are several causes of hypoglycemia, which lie in the disruption of the balance between insulin dosage, activity and food intake. A skipped or partly eaten meal, strenuous exercise or too much insulin injection will cause this insulin relaxation or insulin shock (Betteridge, 1987).

Diabetics must be able to recognize the signs of hypoglycemia and understand how to treat them. The failure of patients to identify symptoms of developing

hypoglycemia is a determinant of the development of severe hypoglycemia (Chiarelli *et al.*, 1999; Cryer, 1994; Davis *et al.*, 1997). According to Niskanen (1996) and Dorchy (1998), subjects with IDDM experience triple the risk of severe hypoglycemia as compared to NIDDM. Accordingly a diabetic should be taught that the appropriate treatment for hypoglycemia is 15 grams of carbohydrate every 15 minutes until hypoglycemia resolves (Bodzin, 1997; Mahan & Escott-Stump, 2000; Davis & Jones, 1998). Diabetics, however, need to judge the carbohydrate content accurately, because the tendency is to over-treat hypoglycemia and cause unnecessary hyperglycemia (Capriotti & McLaughlin, 1998).

The Diabetes Control and Complications Trial (DCCT), demonstrated that the level of metabolic control achieved in adolescence and adulthood with insulin dependent diabetes mellitus is an important determinant of the development and progression of the macrovascular complications of the disease (DCCT, 1991). Improved glycemic control and reduced rates of development and progression of complications, decreased rates of hypoglycemia (DCCT, 1991; Nordfelst & Ludigsson, 1997; Davis & Jones, 1998). Good control of hypoglycemia in younger patients is a substantial long-term benefit that reduces the morbidity and mortality of IDDM (Davis & Jones, 1998). A hypoglycemic event may have a detrimental effect on brain functioning (Dammaco *et al.*, 1998; Kahn & Weir, 1994). Brain functioning depends on glucose to fuel metabolism and a reduction in circulatory glucose induces central nervous system dysfunction (Davis *et al.*, 1998; Soltész, 1998), thus a major danger of hypoglycemia is associated impairment of the brain. Hypoglycemia can cause neuropsychological abnormalities as well as reduction in mental efficiency (attention, memory) and motor performance (Soltész, 1998). Permanent electro-encephalographic (EEG) abnormalities and irreversible intellectual deficit have been related to prolonged severe and recurrent hypoglycemia in diabetic children (Bolt & Bolt, 1997).

In the non-diabetic, the aim of glucose homeostasis is to prevent hypoglycemia (Bolli, 1998). To do this insulin levels between meals must be kept low. Hypoglycemia is a consequence of imperfect insulin substitution together with a defective counter-regulatory response impairing hormonal responses that counteract insulin-induced hypoglycemia (Cryer *et al.*, 1994; Davis *et al.*, 1998).

The diabetics feeling of impeding hypoglycemia is the most important defense against hypoglycemia. In diabetes, alpha cell function is lost, so glucagons secretion (the normal physical counter-regulation mechanism) cannot counteract hypoglycemia, this leaves adrenaline as the primary defense mechanism, other hormones such as growth hormone and cortisol also plays a role in increasing blood glucose levels (Bolli, 1998; Mycek *et al.*, 2000). When hypoglycemia occurs frequently, the adrenaline response is impaired and the patient loses symptoms that provide awareness of hypoglycemia. The two factors combined (adrenalin response and loss of awareness) increase the risk of severe hypoglycemia with potential to cause irreversible brain damage (figure 2.6). However if recurrent hypoglycemia is avoided by changing insulin regime, the adrenaline response recovers and so does hypoglycemia awareness (Amiel *et al.*, 1987).

Research has shown that hypoglycemia is more frequent at night (Davis & Jones, 1998), and asymptomatic hypoglycemia is also common during sleep (Porter *et al.*, 1997). Nocturnal hypoglycemia needs to be estimated, because a significant number of nocturnal episodes go unnoticed (Dammoco *et al.*, 1998; Pickup & Williams, 1991), and their frequency is increased in diabetic children younger than 5-7 years with lower HBA_1C levels (hemoglobin A_1C test or glycosylated hemoglobin test) revealing average blood glucose over a period of 2-3 months (Dammaco *et al.*, 1998; Chiarelli *et al.*, 1999).

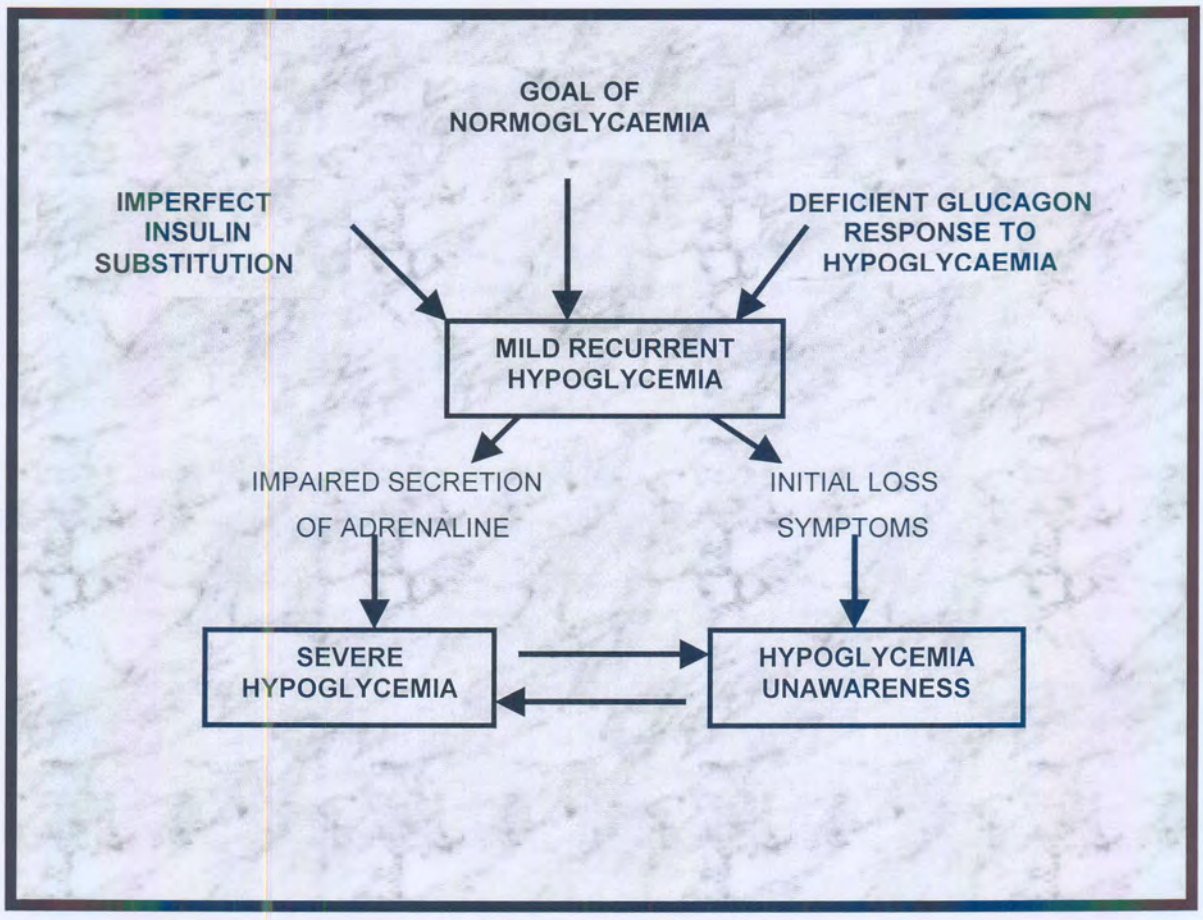


Figure 2.6: Hypoglycemic events in IDDM (Soltész, 1998).

In studies examining the effects of hypoglycemia on sleep in a group of children with diabetes (Davis & Jones, 1998; Soltész, 1998), it was noted that moderate and often prolonged hypoglycemia did not awaken the patients or disturb their sleep patterns (Davis & Jones, 1998; Soltész, 1998). According to Soltész (1998), clinicians should be suspicious of nocturnal hypoglycemia if fasting blood sugar levels before breakfast are less than 4.4 mmol/l. According to Dammaco *et al.* (1998), the most frequently perceived causes of hypoglycemia are exercise, delayed or reduced food intake and inappropriate insulin administration and states that a significant number of hypoglycemic episodes could be prevented if diabetics are better informed.

2.6.2 HYPERGLYCEMIA

Insulin deficiency and elevated plasma levels of catabolic hormones (particularly glucagons and catecholemines) cause increased rates of hepatic glycogenolysis and gluconeogenesis (figure 2.5). Renal gluconeogenesis is also enhanced in the presence of acidosis. Glucose disposal by peripheral tissue is reduced by insulin deficiency while elevated plasma levels of catabolic hormones and fatty acids induce relative insulin resistance (Ginsberg, 1977). The blood glucose concentration falls more slowly during insulin treatment of patients with higher levels of catabolic hormones due to infection, although this degree of insulin resistance is overcome by 'low-dose' intravenous regimes (Page *et al.*, 1974). Hyperglycemia in most instances can lead to diabetic ketoacidosis (DKA); a life threatening but reversible complication characterized by severe disturbances in CHO, protein, and fat metabolism (Coram & Mangum, 1986).

2.6.3 DIABETIC KETOACIDOSIS (DKA)

Glucose, fatty acids, and ketone bodies are all inter-related as sources of energy utilized by the various cells types. All involve eventual production of acetyl coenzyme A (acetyl CoA), which the eventual outcome of ultimate breakdown to carbon dioxide and water through the citric acid cycle in energy production.
Acetyl CoA, can also be diverted (figure 2.7) to production of ketone bodies in hepatocytes, depending upon the environment of hormonal influences and dynamic energy requirements. Metabolism of ketone bodies is under hormonal control, where ketogenesis is stimulated by the catabolic hormones glucagons, epinephrine, norepinephrine, secretin, vasopressin, adrenocorticotrophic hormone (ACTH-all rapid stimulators), growth hormone, and glucocorticoids (slow stimulator) and ketolysis (breakdown of ketone bodies) is stimulated

primarily by insulin, which is an anabolic hormone (Power Pak, 2000; Alberti *et al.*, 1978).

This hormonal regulation of ketone body production is a function of regulating release of lipid from adipose tissue stores and of utilization rate In other tissue. It occurs at three sites: adipose tissue, liver, and peripheral tissue (Alberti *et al.*, 1978).

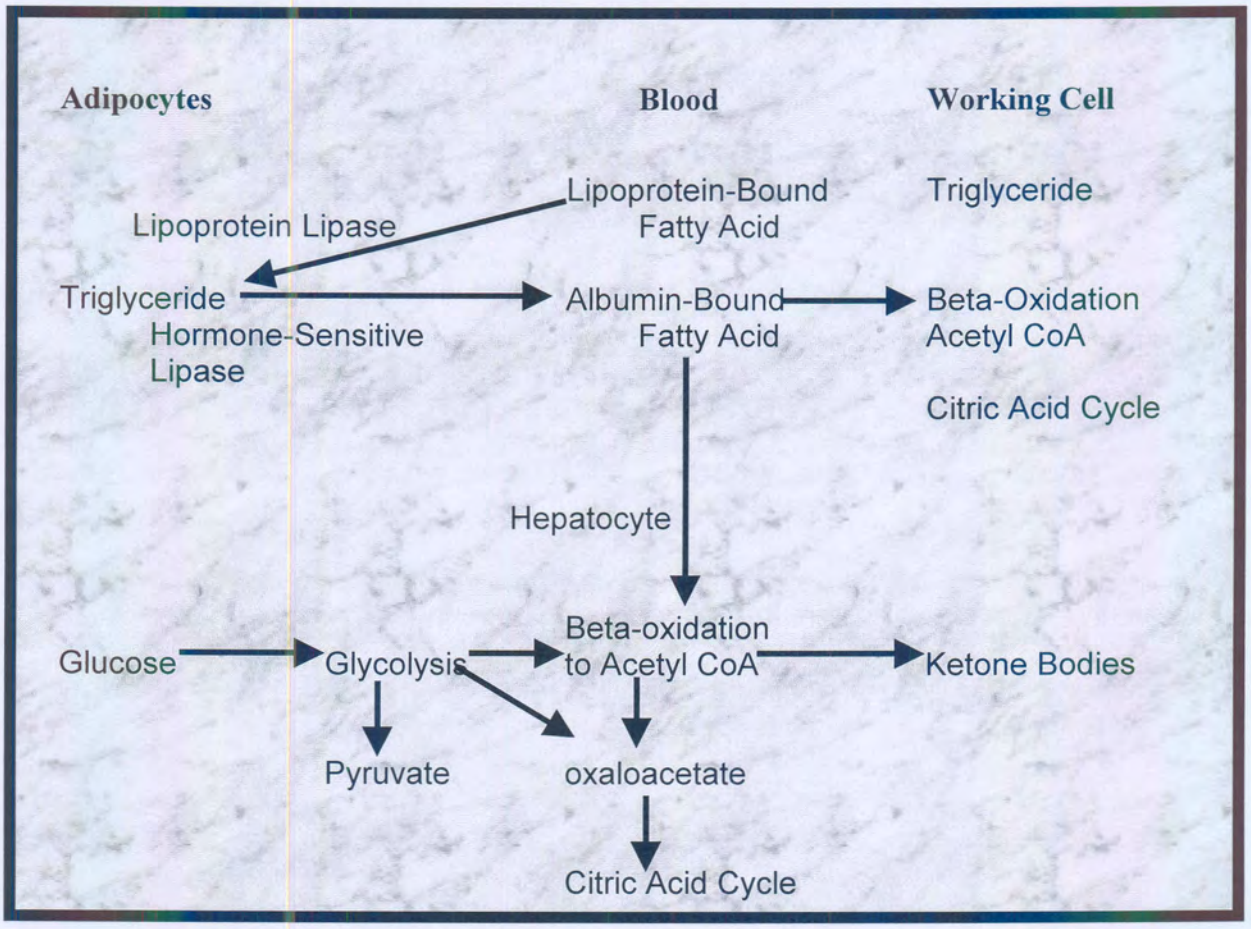


Figure 2.7: Acetyl Coenzyme A diverted to produce ketone bodies (Power Pak, 2000).

DKA results from insulin deficiency combined with counter-regulatory hormone excess (glucagon, catecholamines, cortisol, and growth hormones). Both insulin

deficiency and glucagon excess, is necessary for DKA to develop. The decreased ratio of insulin to glucagon promotes gluconeogenesis, glycogenolysis and ketone body formation in the liver, as well as increased substrate delivery from fat and muscle (free fatty acids, amino acids) to the liver (Umpierrez, 1996).

Reduced insulin levels, in combination with elevation in catecholamines and growth hormones, leads to an increase in lypolysis and the release of free fatty acids. Normally these free fatty acids are converted to triglycerides or very low density lipoproteins in the liver, but in DKA, hyperglucagonemia alters hepatic metabolism to favour ketone body formation (Braunwald *et al.*, 2001). DKA is precipitated when insulin requirements increased but insufficient insulin is available, as might occur during concurrent illnesses. Failure to augment insulin therapy appropriately compounds the problem. Diabetics using an insulin infusion device with short acting insulin have a greater potential for DKA, because an interruption of insulin delivery (e.g. mechanical malfunction) leads to insulin deficiency (Braunwald *et al.*, 2001). Studies have shown that the development of ketosis in insulin-deprived individuals is a defect in peripheral clearance of ketones rather than marked increases in ketogenesis during exercise (Fèry *et al.*, 1987).

2.7 CHRONIC CO-MORBIDITIES

The co-morbidities associated with long-standing diabetes of either types result in complications. Complications can either be microvascular or macrovascular in origin. Microvascular complications include microangiopathy, retinopathy, nephropathy, and neuropathy (peripheral and autonomic). Macrovascular concerns may involve the heart or peripheral vascular disease and hypertension. Most of the available evidence suggests that the complications of diabetes result

from metabolic derangement, mainly hyperglycemia (Solimena & DeCamililli, 1995; American Diabetes Association, 2000).

The most important physiological disturbances in diabetes are related to its many related systematic complications, because they are the major cause of morbidity and mortality. There is extreme variability among patients in the time of onset of these complications, their severity, and the particular organ or organs involved. Pathological changes are likely to be found in arteries (atherosclerosis), the kidneys (diabetic nephropathy), retina (retinopathy), nerves (neuropathy) and other tissues. These changes are seen in both types of diabetes, as illustrated in figure 2.8 (Kumar *et al*, 1997).

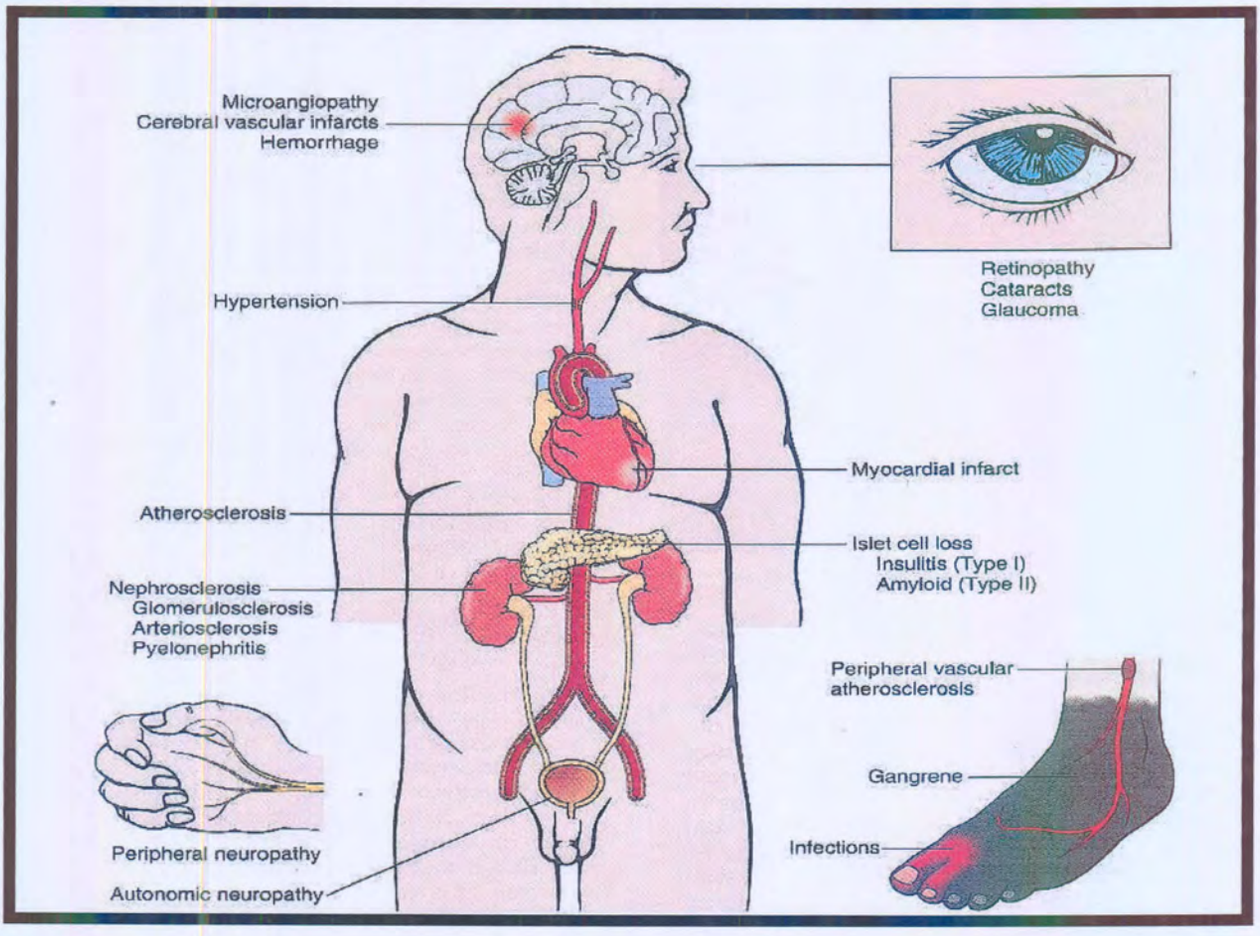


Figure 2.8: Long-term complications of diabetes

2.7.1 MACROVASCULAR DISEASES

Diabetes has a major impact on the vascular system. Vessels of all sizes are affected from the aorta down to the smallest arteries and capillaries. Macrovascular diseases such as coronary heart disease (CHD), peripheral vascular disease (PVD), and cerebrovascular disease (CVD) are more common, tend to occur at an earlier age and are more severe in people with diabetes than those without diabetes (American Diabetes Association, 1999c). The aorta and large and medium sized arteries suffer from accelerated severe atherosclerosis. Lipid abnormalities are one of the risk factors contributing to acceleration of atherosclerotic vascular disease (Polonsky, 1996; American Diabetes Association, 1999c).

Solomon (1996), concluded that individuals with diabetes have two to four fold greater risk of developing CVD than do non-diabetics with females being more susceptible than males. Diabetics also often have elevated blood concentration of low-density lipoprotein (LDL), which are strongly related to an increase in atherosclerotic plaque formation (Molitch, 1988). Myocardial infarction, caused by atherosclerosis of the coronary arteries is the most common cause of death in diabetes (Polonsky, 1996). Elevated serum cholesterol, triglycerides, low density lipoprotein (LDL), decreased high density lipoprotein (HDL) levels in conjunction with hypertension, carbohydrate intolerance, elevated fibrinogen, hyperinsulinema, abnormalities in mineral metabolism and a sedentary lifestyle, all contribute to increase cardiovascular mortality and morbidity (Goldberg *et al.*, 1979; Valdorf-Hansen *et al.*, 1987).

Hyaline arteriosclerosis, the vascular lesion associated with hypertension is more severe in diabetes than in non-diabetes. It takes the form of an amorphous, hyaline thickening of the wall of the arterioles, which causes narrowing of the lumen (Kumar *et al.*, 1997). The vascular endothelium in the IDDM subject is

often rough, this promotes increased platelet adhesion to the arterial lining. The platelets release substances that stimulate smooth muscle cell proliferation, which causes vessel narrowing. Gangrene of the lower extremities, as a result of advanced vascular disease, is about one hundred times more common in diabetics than in the general population (Kumar *et al.*, 1997).

There has been little research undertaken on the factors that may reduce macrovascular risks associated with diabetes. Any intervention that might reduce the risk of developing diabetes may also reduce the absolute rates of CVD. It has been proven that regular activity has been associated with a reduced risk of developing diabetes (Manson *et al.*, 1991).

HYPERTENSION

The Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (1993) defines high blood pressure exceeding 160/95 mmHg and borderline hypertension as that lying below these limits but above 140/90 mmHg. The goal for blood pressure control is less than 130/85 mmHg (American Diabetes Association, 1993). Besides sodium restrictions (<2400 mg/day), other beneficial nutrition interventions to reduce blood pressure include weight reduction and restricted alcohol intake.

Arterial hypertension is more common in diabetic than in non-diabetic subjects (Mogensen *et al.*, 1992). Both IDDM and NIDDM are frequently associated with hypertension. Recent data have shed new light on interrelationships involving glucose, insulin, sodium homeostasis, renal function and the systemic vasculature in blood pressure regulation. The National High Blood Pressure Education Program Working Group Report on Hypertension in Diabetes has emphasized that hypertension and diabetes are interrelated diseases that, if left

untreated, can predispose to atherosclerotic cardiovascular and renal disease (Mathiesen *et al.*, 1986).

There are major differences in the causes of hypertension in IDDM and NIDDM. Diabetic nephropathy is the most common cause of hypertension in IDDM. Although an equal number of people with NIDDM develop renal disease, hypertension often occurs with normal renal function and is better associated with older age and obesity. An increased total body sodium and enhanced vascular inactivity are common to both IDDM and NIDDM and indicate a common underlying determinant related to the metabolic abnormality. Evidence of insulin resistance in hypertension has advanced the understanding of the role of insulin in both diabetic hypertension and essential hypertension (Laragh & Brenner, 1995).

Studies done by Pablos-Velasco (1997) on the prevalence of hypertension in patients with IDDM, stated that the presence of hypertension and of microalbuminuria and macroalbuminuria was associated with a negative lipid profile, which drastically increased the prevalence of hypertension in young IDDM adults. In these patients the rise of blood pressure was related to the development of diabetic nephropathy. Treatment of hypertension in persons with diabetes should also be vigorous to reduce the risks of macrovascular and microvascular diseases. Early and aggressive anti-hypertensive treatment benefits at least those patients with incipient nephropathy (Parving, 1991).

2.7.2 MICROVASCULAR DISEASES

MICROANGIOPATHY

Microangiopathy is the most consistent feature of diabetes and is defined as the diffuse thickening of basement membranes. The thickening is evident in the capillaries of the skin, skeletal muscle, retinas, renal glomeruli and renal medullae (Atkinson & Maclaren, 1994). It is also seen in non-vascular structures such as renal tubules, Bowman's capsule, peripheral nerves and placenta. Despite the increase in the thickness of the basement membranes, diabetic capillaries are more porous than normal to plasma proteins. The microangiopathy underlies the development of diabetes nephropathy and some forms of neuropathy (Bach, 1994).

DIABETIC NEPHROPATHY

The kidneys are prime targets of diabetes, and renal failure is second to myocardial infarction as a cause of death from this disease. Diabetes is the leading cause of end stage renal failure (Kahn & Weir, 1994). Nephropathy develops in a higher percentage of persons with IDDM, but nephropathy is more commonly attributed to NIDDM because of the greater prevalence of NIDDM. The clinical evidence of nephropathy is confirmed by the appearance of low but abnormal urine albumin levels (>30mg/day) referred to as microalbuminuria, or incipient nephropathy (American Diabetes Association, 1999d). More than 20% of persons with both types of diabetes have overt nephropathy after 15-20 years of having diabetes, which may progress to end stage renal disease (ESRD), requiring dialysis or renal transplantation (Morgenson *et al.*, 1983; Friedman, 1989; Mahan *et al.*, 2000). The mechanisms and etiology of renal dysfunction is related to metabolic (glycemic control), hemodynamic (hyperfilteration, increased glomerular pressure), or rheologic (increased blood viscosity) factors. The

option for delaying renal disease involves blood pressure reduction, metabolic control and dietary protein restriction (Graham & McCarthey, 1990; Krolewski *et al.*, 1998).

Although diabetic nephropathy cannot be cured there are persuasive data that the clinical course of the disease can be modified. The most important factor that can influence progression of nephropathy is the optimization of metabolic control. Frequency of nephropathy may decrease with the use of more effective anti-hypertensive therapy. Angiotensin converting enzyme (ACE) inhibitors can reduce the amount of proteinuria and slow the progression of nephropathy (Lewis *et al.*, 1993; Ravid & Savin, 1993; Hoofwerf, 1999). ACE inhibitors are recommended as a primary treatment for all hypertensive patients with diabetes and microalbuminuria or overt nephropathy (American Diabetes Association, 1999b; Hoofwerf, 1999), but ACE inhibitors are particularly beneficial to a specific group of diabetic patients with microalbuminuria or frank proteinuria (Hoofwerf, 1999; Parving, 1998). ACE inhibitors exert a renoprotective effect which appears to be additional to changes in systemic blood pressure (Jerums, 1998; Parving, 1998).

Although the primary goal in protecting the kidney is to reduce the blood pressure, the current evidence indicates that ACE inhibitors protect the kidneys better than other blood pressure lowering medication, because ACE inhibitors specifically lowers the intra-renal pressure (Hoofwerf, 1999). Studies done by Lewis *et al.* (1993) on NIDDM patients with albuminuria, and mildly impaired creatinine clearance (i.e. patients who were just beginning to develop renal failure), suggested that ACE inhibition better reduced the risk for decline in renal function compared with other antihypertensive regimes (not excluding calcium channel blockers). ACE inhibitors may slow the progression of microalbuminuria to macroalbuminuria even in normotensive patients (Ravid & Savin, 1993). Enthusiasm for ACE inhibitors may be tempered by the finding of the United

Kingdom Prospective Diabetes Study (UKPDS) in which atenolol (beta-blockers) and ACE inhibitors (captopril) were equally effective in reducing the risk of albuminuria in hypertensive NIDDM subjects (UKPDS, 1998).

Valdorf-Hansen and Associates (1987) discussed the possible increased mortality in patients with proteinuria. Patients with increased urinary albumin excretion demonstrated an increased extra renal transcapillary escape rate of albumin. Its possible that patients with increased transglomerular passage of albumin are characterized by increased permeability of the vascular walls of the larger arteries, which leads to increased influx of cholesterol to sub-endothelial layers and that a moderate increase in blood pressure and the serum cholesterol, together with increased fibrinogen and platelet adhesion may accelerate the process of atherosclerosis and contribute to an increased death rate of patients.

NEUROPATHY

Diabetic neuropathy typically involves the symmetrical degeneration predominantly sensory nerves. It is often associated with autonomic dysfunction, acute mono-neuropathies, affecting single nerves such as the femoral or occu-motor nerves and pressure palsies, particularly of the median and ulnar nerves.

Diabetic neuropathy is especially common among diabetics who have had the disease for more than 15 years. Neuropathy is a major contribution to amputation, "silent" myocardial infarction and hypoglycemia (Sherman & Albright, 1990) and can be present in both IDDM and NIDDM (Mahan & Escott-Stump, 2000). Different forms of neuropathy may be present, including peripheral neuropathy, autonomic neuropathy and mononeuropathy (Yoon, 1995; Mahan & Escott-Stump, 2000; Broadstone *et al.*, 1987).

PERIPHERAL (SENSORIMOTOR) NEUROPATHY

The most frequent pattern of involvement is a peripheral, symmetric neuropathy of the lower extremities that affect both motor and sensory function but more particularly the sensory function (Capella, 1995; Broadstone *et al.*, 1987). Peripheral neuropathy usually affects the nerves controlling sensation in the feet and hands (Mahan & Escott-Stump, 2000). Signs and symptoms of sensorimotor neuropathy include losses that may result in superficial or deep pain (paresthesial, numbness, impaired balance, and loss of touch) (Broadstone *et al.*, 1987). A frequent complication of sensorimotor neuropathy includes neuropathic foot ulcers and diabetic neuroarthropathy. Neuroarthropathy (Charcot's foot) can lead to multiple fractures and disarticulation of the tarsals, metatarsals and ankle, with continued weight-bearing contributing to traumatization (Graham & McCarthey, 1990). Plantar-ulceration and infection may keep the individual bedridden to allow for normal healing, but such inactivity promotes disuse syndromes.

AUTONOMIC NEUROPATHY

Autonomic neuropathy can affect both the sympathetic and parasympathetic nervous systems (Steffes *et al.*, 1986). Autonomic neuropathy affects organ systems (Mahan & Escott-Stump, 2000; Sherman & Albright, 1990), and nerves innervating them such as the genitourinary tract, gastrointestinal tract, cardiovascular and adrenergic nervous systems with the last mechanism resulting in insulin counter-regulation (Cyrus *et al.*, 1987).

Often diabetic autonomic neuropathy produces difficulties with bladder responses and digestion, sexual function, gastro-paresis, postural hypotension, cardiac denervation syndrome, unawareness and hypoglycemia (Ewing, 1985). A well-validated test using the cardiovascular reflexes has been used to assess

autonomic nerve damage (Bernbaum *et al.*, 1989). Cardiovascular tests of autonomic neuropathy have been conducted by various researchers (Ewing, 1985; Bernbaum, 1989; Graham & McCarthey, 1990), to test the response of the heart rate and blood pressure to various stimulus, thus assessing cardiac parasympathetic and sympathetic nerve damage.

MONONEUROPATHY

Acute mononeuropathy, for example of the femoral nerve (amyothropy) or third/ sixth cranial nerves, may be due to ischaemia of the nerve or its roots. Pressure palsies occur more frequently in diabetics, possibly because the nerves are more vulnerable to compression causing localized disruption of myelin. Mononeuropathy may also be the result of an infarction of a single nerve, and the effect depends on the nerve that is afflicted (Steffes *et al.*, 1986). Mononeuropathy may occur as sudden footdrop, wristdrop or isolated cranial nerve palsies. The neurological changes may be caused by microangiopathy and increased permeability of the capillaries that supply nerves as well as by direct axonal damage due to alterations in sorbital metabolism (Sacks, 1986).

OCCULAR COMPLICATIONS

Visual impairment, sometimes even total blindness, is one of the most feared consequences of long-standing diabetes (Kumar *et al.*, 1997; Greenlee, 1987; Grand, 1989). The occular involvement may take the form of retinopathy, cataract formation or glaucoma (Kumar *et al*, 1997). Diabetic retinopathy is the major cause of vision disability among young and middle aged people (Kohner & Porta, 1990). About 60-80% of patients with IDDM show some evidence of retinopathy after 10 years of the disease (Kohner & Porta, 1990; Cerrutti *et al.*,

1989). The retinal neurosensorial losses may precede the onset of clinically detectable retinopathy, but early retinal changes in diabetes are poorly defined (Kurtenbach *et al.*, 1994; Bresnick, 1986). Retinopathy is the fourth leading disease in America (Santiago, 1986; Kumar *et al.*, 1987), and approximately five thousand new cases of blindness related to diabetes is estimated to occur each year (Zimmerman, 1998).

There are three classifications of retinopathy (Mahan & Escott-Stump, 2000). Early stage non-proliferated diabetic retinopathy (NPDR), also termed background disease, is characterized by disturbances within the retina such as microaneurysms (a pouch-like dilation of the terminal capillaries and hemorrhages, retinal exudates or cotton-like spots), venous dilation, edema and microangiopatic thickening of retinal capillaries (Aiello, 1998; Grand, 1989; Kumar *et al.*, 1997), which are frequently seen after 5 years of IDDM (Steffes, 1986). Pre-proliferated retinopathy is a more advanced pathology and is characterized by infarcts of the inner retina and by areas of capillary non-profusion (Sherman *et al.*, 1990). As the disease progresses to the middle stages gradual loss of the retinal microvasculature occurs, resulting in retinal ischemia. Extensive intra-retinal hemorrhages and microaneuryms are common reflections of increasing retinal non-perfusion (Mahan & Escott-Stump, 2000).

Positive findings for preproliferative retinopathy includes microangiopathic alterations within the retina which signal the probable onset of proliferative retinopathy (Grand, 1989). This proliferative diabetic retinopathy (PDR), is the most advance stage and most vision threatening stage of retinopathy (Aiello, 1998; Santiago, 1989). The lesion can lead to serious consequences including blindness, especially if it involves the macula. Vitreous hemorrhage can result from ruptures of the newly formed capillary and the resultant organization of the hemorrhage can pull the retina off its retinal detachment (Polonsky, 1996; Aiello,

1998). More than 80% of diabetics have some form of retinopathy 15 years after diagnosis. However, laser photocoagulation can reduce the loss of vision associated with proliferative retinopathy and occular edema by 50% if the conditions are identified in time (Zimmerman, 1998). In both types of diabetes, the development and progression of retinopathy is duration-dependent and is associated with increased glycemic control (Mahan & Escott-Stump, 2000). Figure 2.9 shows the presence of scattered microaneurysms and intraretinal hemorrhages (dots and blots) with hard exudates that do not involve the macula. This stage does not threaten vision, but signals the need to exclude more sinister lesions and follow up the diabetic in the future (Pickup & Williams, 1991).

Figure 2.10 shows ischaemic macular oedema, showing the rather featureless appearance of the center. This condition contributes to poor visual acuity (Pickup & Williams, 1991). Diabetic macular oedema is due to the breakdown of the blood-retinal barrier, which leads to the accumulation of extracelluar (retinal oedema) and/or the deposition of extravasated proteins and lipids (hard exudates). Macular oedema threatens thigh-resolution central vision (e.g. for reading) that is served by the macular.

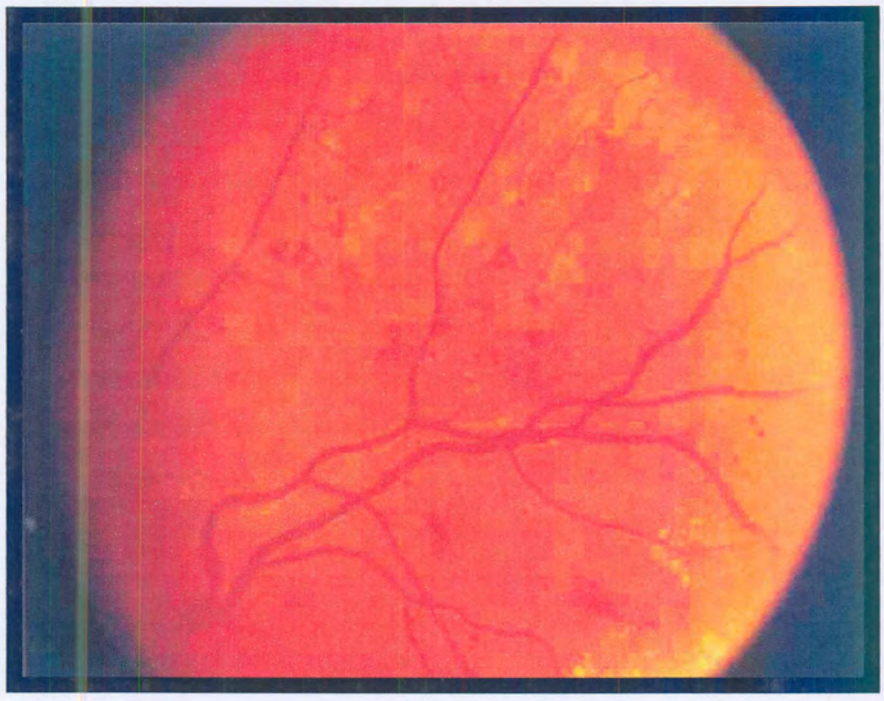


Figure 2.9: Ischaemic macular oedema, showing the rather featureless appearance of the center.

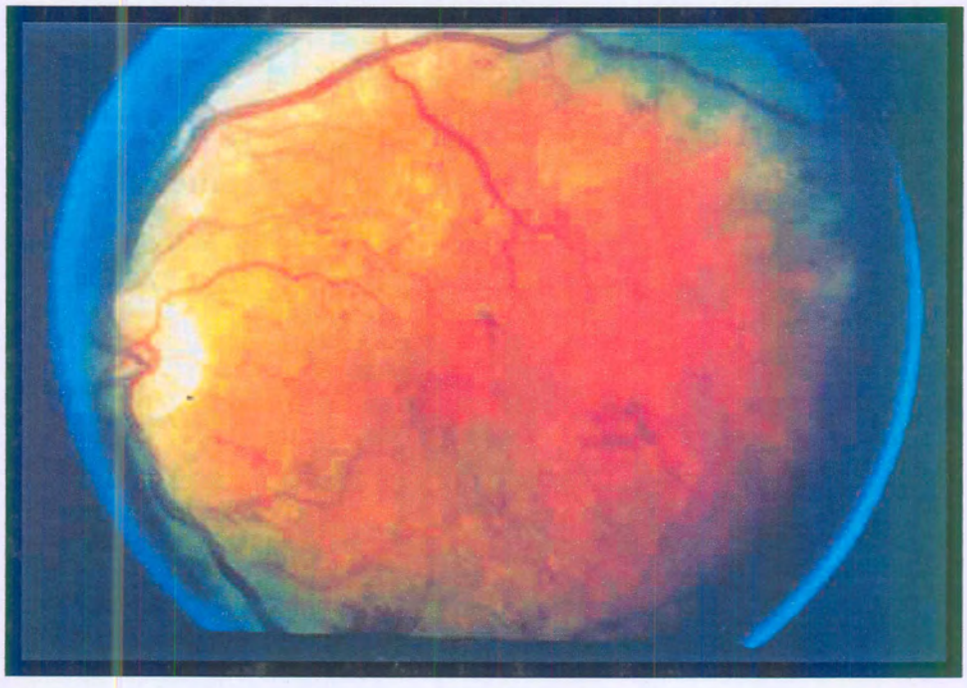


Figure 2.10: Background diabetic retinopathy showing scattered red "dots and blots' (microaneurysms and hemorrhages).

3. MANAGEMENT OF DIABETES

3.1 GLYCEMIC CONTROL

The chronic debilitating disease, if detected early and adequately managed, may allow patients a normal life span and higher quality of life (Society of Endocrinology, Metabolism, and Diabetes of South Africa, 2001). Optimal diabetic monitoring of glycemic control involves self-monitoring of plasma glucose measurements by diabetics and an assessment of long-term control by the physician (measurement of HBA_1C levels and review of the diabetics self-monitoring). The diabetics measurements provide a picture of short-term glycemic control, whereas the HBA_1C reflects the average glycemic control over the previous two to three months. Integration of both provides an accurate assessment of the glycemic control achieved (Avery, 1998; Braunwald *et al.*, 2001; Cradock, 1996).

MONITORING OF BLOOD GLUCOSE

Two devices for continuous blood glucose monitoring in a clinical setting have recently been approved by the USA food and drug administration. The glucowatch uses iontophoresis (ionization into tissues via direct current) to assess glucose in interstitial fluid whereas the other device uses an indwelling subcutaneous catheter to monitor interstitial fluid glucose. Both these devices provide useful short-term information about the pattern of glucose changes as well as the ability to detect hypoglycemic episodes (Braunwald *et al.*, 2001). Testing urine for glucose (glucosuria) does not provide an accurate assessment of glycemic control (Betteridge, 1987; Braunwald *et al.*, 2001). Urine ketones (ketonuria) are a sensitive indicator of early diabetic ketoacidosis and should be measured in individuals with IDDM when plasma glucose is consistently >16.7

mmol/l (300mg/dl), during a concurrent illness or with symptoms such as nausea vomiting or abdominal pains (Braunwald *et al.*, 2001; Ward, 1998). The glucosylated hemoglobin or HbA_1C is a standard method for assessing long-term glycemic control. The HbA_1C test gives an approximate ninety-day (two to three months) indication of blood glucose control. The blood test measures how much glucose is attached to hemoglobin (Ward, 1998; Baunwald *et al.*, 2001). The most important aspect of interpreting HbA_1C is to know your laboratory normal (children=1,8-4,0%; adults=2,2-4.8%) or "nondiabetic" range (Ward, 1998). The (DCCT) demonstrated that intensive diabetic treatment designed to achieve near-normal glycemic control substantially reduced the risk of the development and progression of microvascular and neurological complications in IDDM patients when controlled with a conventional treatment approach (DDCT, 1993).

Self-monitoring of blood glucose (SMBG) is a procedure in glycemic control as part of diabetes management and allows the diabetic to monitor their blood glucose at any time. In SMBG, a small drop of blood and an easily detectable enzymatic reaction allows measurement of the capillary plasma glucose (Braunwald *et al.*, 2001). The frequency of SMBG measurements must be individualized and adapted to address the goals of diabetes care as defined by the patient and health care provider (Cradock, 1996). Individuals with IDDM should routinely measure their plasma glucose four to eight times per day to estimate and select mealtime boluses of short-acting insulin and to modify long-acting insulin doses (Braunwald *et al.*, 2001; Avery, 1998). Most individuals with NIDDM require less frequent monitoring, but individuals with NIDDM diabetes who are on oral medication should use SMBG as a means of assessing the efficiency of their medication and diet. One to two measurements per day may be sufficient since plasma glucose levels fluctuate less in these individuals. However individuals with NIDDM who are on insulin should utilize SMBG more frequently than those on oral medication (Braunwald *et al.*, 2001; Avery, 1998).

An integral component of intensive diabetic treatment is self-monitoring of blood glucose (American Diabetes Association, 1996; DCCT, 1995). The importance of blood glucose monitoring in achieving improved glycemic control has been previously reported (Schiffrin & Belmonte, 1982; Peterson *et al.*, 1984). Strowig & Raskin (1998) undertook a study for 12 months determining the effects on glycemic control in intensively treated insulin dependent diabetics using a blood glucose meter with storage capabilities and computer assisted analysis, and found that improved blood glucose levels. The HbA_1C levels were significantly different before and after the use of the memory meter and the trend of rising blood glucose levels during the 12 months before use of the meter was reversed, resulting in a decline in HbA_1C levels. This study also showed that lower HbA_1C levels reduced the risk of retinopathy progression, neuropathy and nephropathy (American Diabetes Association, 1997; American Diabetes Association, 1996). Thus the improvement in glycemic control that occurred with the use of the memory meter was clinically meaningful in that it represents a reduction for the progression of long term complications. Studies suggest that blood glucose meters with storage capabilities used in conjunction with computer assisted analyses can be an effective tool in improving blood glucose levels. The effectiveness of monitoring glucose by a memory meter is that frequent follow-up and feedback is possible so that self-monitoring is used to make self-management decisions that lead to appropriate regulations of insulin, diet and other aspects of the treatment plan (Strowig & Raskin, 1998).

3.2 MEDICATION

Insulin therapy is a cornerstone of the treatment of individuals with IDDM, but it cannot be used as the only therapeutic strategy to maintain glycemic goals (Becker, 1998). Intensive insulin therapy consists of the delivery of multiple daily

injections mixing short and longer duration insulin preparations and is a key component of intensive diabetes therapy (Becker, 1998).

Insulin's discovery and production started in 1922. The source of insulin is important because it affects the speed of absorption, peak and duration of action. Since 1984, human insulin has been produced synthetically. Human synthesized insulin has a shorter duration than animal synthesized insulin. A major advantage of human insulin is that it produces fewer antibodies and, as a result, can also be used for intermittent periods of insulin treatment, such as during pregnancy and surgery (Mahan & Escott-Stump, 2000).

The type and timing of insulin regimes should be individualized, based on eating and exercise habits and blood glucose levels (Mahan & Escott-Stump, 2000; Colberg, 2001; Braunwald *et al.*, 2001). Insulin requirements increase with both the duration of diabetes, the age and pubertal status of the diabetic. Insulin requirements have been shown to increase during puberty owing to its associated insulin resistance (Caprio *et al.*, 1989). Studies undertaken by Komulainer *et al.* (1998) showed that prepubertal girls with IDDM have higher exogenous insulin requirements than boys. This study was conducted two years after the diagnosis of diabetes of the patient. Girls had an insulin does 13.6% higher than that of boys. The study concluded that prepubertal girls with IDDM have poorer insulin sensitivity than boys (Komulainer *et al.*, 1998).

Persons who have IDDM depend on insulin to survive, whereas in persons who have NIDDM, insulin may be needed to restore glycemic control to near normal (Mahan & Escott-Stump, 2000; Avery, 1998). Circumstances that require the use of insulin in NIDDM include failure to achieve adequate control with administration of oral glucose-lowering medication (Mahan & Escott-Stump, 2000; Avery, 1998).

Different types of insulin can affect the circulation levels of insulin during an activity and the ensuing blood sugar (figure 2.11). Predicting the response to a given exercise session requires one to take into account the types of insulin used (short-acting and long-acting insulin have different peak action time and duration), when to inject it, and how much circulating insulin is available before and during and exercise. Therefore insulin has four properties: action, concentration, purity and source and these properties determine its onset, peak, and duration.

SHORT ACTING INSULIN (CLEAR)			
INSULIN	ONSET	PEAK	DURATION
LISPRO (HUMALOG)	5-15 MIN	30-75 MIN	2-3 HOURS
REGULAR (R)	30-45 MIN	2-3 HOURS	4-6 HOURS
BACKGROUND INSULN (CLOUDY)			
INSULIN	ONSET	PEAK	DURATION
NPH (N)	2-4 HOURS	4-10 HOURS	10-18 HOURS
LENTE (L)	2-4 HOURS	4-10 HOURS	10-18 HOURS
ULTRALENTE (U)	3-5 HOURS	8-14 HOURS	18 HOURS
PRE-MIXED INSULIN (SHORT ACTING AND BACKGOUND TOGETHER)			
70/30 OR 50/50	30-60 MIN	2-12 HOURS	UP TO 18 HOURS

Figure 2.11: Comparative Actions of Different Insulin (Mahan & Escott-Stump, 2000).

Regular insulin and Lispro are short-acting insulins, and provide a burst of insulin to cover the meal that is just about to be eaten. Regular insulin needs to be taken 30-40 minutes before eating. Humalog has been shown to closely match physiological insulin production, thereby improving blood glucose levels after meals. Although its not suitable for all patients, studies indicate it does have clinical advantages (Anderson *et al.*, 1997).

Studies undertaken (Schernthander *et al.*, 1998; and Puttangunta & Toth, 1998) indicated that Lispro insulin injected immediately after a standard meal provided background postprandial blood glucose control at least as good as a regular insulin injected before a meal. Puttangunta & Toth (1998), tested insulin Lispro (Humalog) on healthy volunteers and showed a much faster, higher and longer-lasting peak serum levels compared with regular insulin. Significantly fewer hypoglycemic episodes were seen with insulin Lispro than with regular insulin, while insulin Lispro also improved hemoglobin (HbA_1C) levels without increasing the risk of hypoglycemia (Puttangunta & Toth, 1998; Braunwald et al., 2001). Both Lispo insulin and regular insulin may be used in combination with a background or intermediate-acting insulin, and may also be used independently during acute illness, in insulin pumps and in multiple daily injection regimes. According to Puttangunta & Toth (1998), the use of insulin Lispro has been shown to improve HbA_1C levels in diabetics using insulin pumps. Background and intermediate acting insulin's include NPH and Lente. Their appearance is cloudy and their onset, peak, and duration are similar. Ultralente is slightly longer-acting insulin than intermediate-acting insulin. Premixed insulin's are also available, viz. 70/30 which is 70% NPH and 30% regular; and 50/50, which is 50% NPH and 50% regular (Mahan & Escott-Stump, 2000).

Hypoglycemia is the most common effect of intensive insulin therapy and severe hypoglycemia is the most feared complication of insulin therapy (McCrimmon &

Frier, 1994). Research (Rovert & Alvarez, 1997; Chiarelli *et al.*, 1999) indicates that long-term exposure to low blood glucose values may cause cognitive impairment in diabetic subjects, and can be associated with severe mobidity, including death (McCrimmon & Frier, 1994).

It has been proposed that insulin Lispro may be a new therapeutic option for adolescent insulin dependent diabetics (Schernthaner *et al.*, 1998; Howey *et al.*, 1994; Zinman *et al.*, 1997). Insulin Lispro (Humalog) is a rapid acting analogue of human insulin that is absorbed more rapidly than regular human insulin from subcutaneous injection sites. The use of insulin analogue Lispro has been associated with reduced risk of late hypoglycemia because of the faster onset of action, a shorter time of activation compared to peak activity, and a shorter time of action compared with regular human insulin (Howey *et al.*, 1994; Holleman *et al.*, 1997; Wilde & McTavish, 1997). This activity profile decreases the postprandial rise in blood glucose in both IDDM (Howey *et al.*, 1994; Anderson, 1997), and NIDDM patients (Anderson *et al.*, 1997; Anderson *et al.*, 1997), when compared with equivalent dosages of regular human insulin. Studies with insulin Lispro thus indicate a reduction in the frequency of symptomatic and biochemical hypoglycemia (Anderson, 1997) and the frequency of nocturnal hypoglycemia (Anderson, 1997; Pfützner *et al.*, 1996).

As documented in Brunelle *et al.* (1998), a meta-analysis was undertaken in various countries including South Africa to compare insulin Lispro, and regular human insulin with respect to postprandial glucose level, frequency of hypoglycemic episodes, metabolic control and safety in patients with type I diabetes. The meta-analysis revealed a significant reduction in severe hypoglycemia during Lispro therapy. The reduction accounted for a more precise time action profile at mealtime of insulin Lispro and lesser overlapping with basal insulin due to shorter duration of action with insulin Lispro compared with regular human insulin.

The observation that insulin Lispro may reduce hypoglycemia has a number of clinical implications (Brunnelle *et al*, 1998). Firstly, risk during intensive insulin therapy will be reduced, thus aiming to achieve better glycemic control to reduce long-term complications (Fanelli *et al.*, 1993; Cryer, 1993; Wredling *et al.*, 1992; Morris *et al*, 1997). Secondly, reduction of hypoglycemia can restore the counter-regulation response to hypoglycemia, and improve hypoglycemic awareness among insulin dependent diabetics (Fanelli *et al.*, 1993). Thirdly, both somatic morbidity and psychological anxiety associated with hypoglycemia can be reduced (Cryer, 1993; Wredling *et al.*, 1992). A smaller risk of hypoglycemia can improve the quality of life, compliance with insulin therapy and long term prognosis of people with IDDM (Morris *et al.*, 1997).

ABSORPTION AND ACTION OF INJECTED INSULIN

The anatomical region of insulin injection is important as absorption is fastest from the abdominal compared to the arm or leg and slowest from the gluteal region (Koivisto & Felig, 1980). Absorption is faster in lean persons (Jørgenson, 1999). There is increased absorption from exercising limbs. A potentially important mechanism contributing to the increased risk of hypoglycemia during exercise is the possible effects of exercise in the absorption of insulin injected under the skin. If the speed at which insulin reaches the bloodstream from the injected sites increases, this in turn increases the risk of hypoglycemia (Betterridge, 1987). Studies have shown that insulin levels rise during exercise if insulin has been administered subcutaneously, whereas no rise occurred when administered intravenously.

Koivisto (1980) and Bergman (1985) found that leg exercises occurring five minutes after an insulin injection resulted in increased insulin absorption from leg injection sites but not from arm or abdominal sites. Kemmer and associates

(1979) cited in Bergman & Auerhahn (1985), found no difference in absorption between leg and arm sites during exercise, but did note a small post exercise enhancement of absorption with leg injection. Insulin absorption from sites in the abdominal is significantly more rapid than from sites in the thigh (Burr & Nagi, 1999; Betterridge, 1987). Experimental data (Koivisto & Felig, 1978) showed that muscular activity speeds insulin absorption form exercising limbs.

Factors other than injection sites and peak activity that may have relevance include the timing of meals before exercise (pre/exercise snack) and variation in individual absorption rate. Therefore an individual's response to changes in injection sites, meal patterns and timing of exercise need to be assessed (Bergman & Auerhahn, 1985).

3.3 DIET

Dietary modification is the oldest of the three treatment modalities (diet, insulin therapy and exercise) recommended for diabetes. As early as 1550 BC, as described in the Ebers papyrus, the use or avoidance of particular foods has been recommended for those with diabetes (Kahn, 1994). Diet plays an important role in human health. Nutritional habits affect glycometabolic control that directly regulates physical growth and body maturation (Pinelli *et al.*, 1998). Good nutrition appears to be essential in the prevention of diabetes–associated chronic degenerative disorders including atherosclerosis, cardiovascular disease, hypertension, glomerular hyperfilteration and obesity. Close links have been demonstrated between these condition and the immoderate diets of Western industrialized countries, exhibiting an excess of protein, animal fat, simple sugars and sodium (Pinelli *et al.*, 1998). Ironically the afore mentioned diet closely reflects the nutritional pattern generally prescribed for IDDM patients, which is aimed at controlling post-prandial blood glucose peaks by reducing carbohydrate

dietary amounts and increasing protein and fat intake. Coronary artery disease is the leading cause of death in diabetics which provides a severe risk factor (Valsania *et al.*, 1991), therefore IDDM patients must be educated as to a healthy diet to prevent damage from long-term unbalanced diets (Mahan & Escott-Stump, 2000).

To integrate nutrition effectively into the overall management of diabetes requires a coordinated team effort including a dietician who is knowledgeable and skilled in implementing current principles and recommendations for diabetics (Kalkarni, 1998). Medical nutrition therapy requires an individualized approach and effective nutrition self-management education. Dieticians must also take responsibilities for evaluating outcomes. Monitoring glucose and glycosylated hemoglobin levels, lipid values, blood pressure, weight and quality of life issues are essential in evaluating the success of nutrition related recommendations. If desired outcomes from medical nutrition therapy are not met, changes for overall diabetes care and management should be recommended (Avery, 1998).

The main role of dietary therapy for all forms of diabetes as stated by research (McGill, 1997; Avery, 1998), is to:

1. Optimize glycemic control
2. Reduce the incidence of hyperglycemia and hypoglycemia;
3. Reduce the incidence of macro vascular disease, particularly cardiovascular disease; and
4. Optimize nutritional status.

Studies (Zinman *et al.*, 1984; Wallberg-Henriksson, 1992) have shown that even when patients with IDDM exercise regularly, overall blood glucose control does not improve. The primary reason is that athletes with diabetes tend to overeat in

anticipation of exercise, thus diet is an important concern in achieving the desired blood glucose levels in athletes with IDDM.

Diet has always been recognized as the cornerstone of therapy for diabetes mellitus ever since the disease was first identified. Two major concepts stimulated interest in the nutritional approach to control postprandial glycemic rise in diabetes; viz. the glycemic index (GI) and dietary fibre (Lafrance *et al.*, 1998). Crapo *et al.* (1976; 1977) were the first to report that different forms of carbohydrate have different effects on postprandial blood glucose. In 1991, the concept of the GI describing the properties for various foods was developed (Jenkins *et al.*, 1981; Wolever *et al.*, 1992). It was envisaged that the index provided a means of predicting the impact of individual carbohydrate containing foods on the postprandial glucose, which helped in the selection of foods for diets.

NUTRITION THERAPY AND INSULIN DEPENDENT DIABETES MELLITUS

A meal plan based on the individuals usual food intake should be used as a basis for integrating insulin therapy into the usual eating and exercise pattern (American Dietetics Association, 1994; Braunwald *et al.*, 2001). Medical nutrition therapy (MNT) is a term used by the American Diabetes Association to describe optimal co-ordination of caloric intake with other aspects of diabetes therapy (insulin, exercise and weight loss) (Braunwald *et al.,* 2001).

A study done by Lafrance *et al. (*1998) assessed the effect of a low GI diet and a high-fibre diet on glycemic control and on pre-meal insulin requirement in well-controlled IDDM subjects undergoing intensive insulin therapy. An increase in dietary fibre decreased the post-prandial rise in plasma glucose, and a low GI diet reduced fasting glucose, but this was not sufficient to allow adjustments of

insulin dose. The study thus concluded that IDDM subjects on intensive therapy can therefore incorporate low dietary fibre in their diet without any modification of insulin adjustment to maintain normoglycemia without increased risks of hypoglycemia. Diabetics thus can safely use the carbohydrate content of the meals alone to calculate their insulin requirements and maintain good glycemic control.

It is recommended that individuals using insulin therapy eat at consistent times synchronized with the time-action of the insulin preparation used (American Dietetics Association, 1994; Kahn & Weir, 1994). The primary goal of therapy for persons with IDDM is the maintenance of appropriate body weight and the prevention of hypoglycemia and hypoglycemia. Individuals with IDDM are usually young and lean, and their caloric intake should be adequate to support normal growth and development (Kahn & Weir, 1994). Individuals with IDDM should co-ordinate and match the caloric intake, both temporally and qualitatively with the appropriate amount of insulin. MNT must be flexible to allow for exercise, and the insulin regime must also allow for deviations in caloric intake. An important component of MNT in IDDM is to minimize the weight gain often associated with intensive diabetes management (Braunwald *et al.*, 2001).

The goals and emphasis of MNT in NIDDM addresses the increased prevalence of cardiovascular risk factors (hypertension, dyslipedemia, and obesity) and other disease in this population (Braunwald *et al.*, 2001, American Dietetics Association, 1994). Eighty to ninety percent of individuals with NIDDM are overweight, and the first goal of dietary therapy is weight loss (Joslin, 1994). Hypocaloric diets and modest weight-loss often result in rapid and dramatic glucose lowering in individuals with recent onset of NIDDM (Kahn & Weir, 1994). Studies have proven that long-term weight-loss is uncommon; therefore current MNT for NIDDM should emphasis modest caloric reduction, increased physical

activity, reduction of hyperlipidemia and hypertension (Braunwald *et al.*, 2001, American Dietetic Association, 1994).

Increased consumption of soluble, dietary fibre may improve glycemic control in individuals with NIDDM (Braunwald *et al.*, 2001). For persons with IDDM and NIDDM, dietary therapy is concerned with:

1) The maintenance of proper nutrition;

2) The total number of calories ingested;

3) The distribution of calories throughout the day; and

4) The individual food sources that contribute those calories.

(American Diabetes Association, 1987; National Institute of Health, 1987).

Eating is one of the greatest pleasures of life and a cornerstone of treatment for people with diabetes. It is crucial that people with diabetes are referred to a dietician to provide healthy attitudes towards foods and with appropriate education it is clear they may enjoy a non-restrictive eating plan while achieving good glycemic control (Braunwald *et al.*, 2001). As the ideal eating plan for people with diabetes is not known, unnecessary dietary restrictions should not be imposed, unless good evidence is available for any recommended changes (Ridley, 1999). Just as no single insulin regime works for everyone with diabetes, nutritional interventions including the nutritional prescription and educational tools, should be based on an assessment of each individual's usual and customary intake and nutritional status (Mahan & Escott-Stump, 2000). Intervention is ongoing throughout the lifespan and should be outcome-driven. Of major concern is what the individual with diabetes is able and willing to do, therefore to facilitate adherence, cultural, ethnic and financial considerations are of prime importance (American Diabetes Association, 1999c).

3.4 EXERCISE

Physical exercise has traditionally been recommended as an important and integral component of diabetic treatment. These recommendations were based on the blood glucose lowering effect of exercise (Ford & Herman, 1995). Exercise is an integral part of the treatment plan for persons in diabetes care (Braunwald *et al.,* 2001; Mahan & Escott-Stump, 2000), which brings about a healthier mental outlook and has multiple positive outcomes such as cardiovascular benefits, reduced blood pressure, maintenance of muscle mass and reduction in body fat (Braunwald *et al.,* 2001; Rowland *et al*, 1985). Participation in physical activity may also have psychological benefits in improving self-esteem and a feeling of wellbeing, which are especially important in patients with chronic diseases (Riley & Rosenbloom, 1980). Furthermore exercise programs help all diabetic patients to lead normal and healthier lives. Self-monitoring and a thorough understanding of the metabolic and endocrine responses and adaptations during exercise, along with the adjustment the diabetic has to make in order to prevent hypoglycemia during exercise, are mandatory to integrate exercise in the daily life of diabetics. In subjects with an impaired glucose tolerance the main goal of any exercise program is the prevention of diabetes (Vandistel & Muls, 1998). When the non-diabetic person exercises, insulin levels decline while counter-regulatory hormones (primarily glucagons) rise. In this way increased glucose utilization by the exercising muscle is matched precisely with increased glucose production (Mahan *et al.*, 2000). The metabolic and hormonal response to exercise in IDDM patients is determined by several factors, such as the intensity and duration of the exercise, the patient's level of metabolic control, the type and dose of injection, and the timing of the previous insulin injection and meal relative to the exercise (Mahan *et al.*, 2000; Colberg, 2001). Blood glucose concentration can decline, which is the most common response, increase or remain unchanged.

In persons with NIDDM diabetes, blood glucose control can improve with exercise, largely because of decreased insulin resistance and increased insulin sensitivity, which results in increased peripheral use of glucose not only during but also after the activity. Because enhanced insulin sensitivity is lost within 48 hours after exercising, repeated periods of exercise at regular intervals are needed to reduce the glucose intolerance associated with NIDDM. This exercise induced enhanced insulin sensitivity occurs without changes in body weight. Exercise also decreases the effects of counter-regulatory hormones, reducing the hepatic glucose output contributing to impaired glucose control (Mahan *et al.*, 2001; DeFonso *et al.*, 1983; Horton, 1983; Sherman & Albright, 1992). Timing the exercise session for persons with NIDDM may be advantageous. For example, exercise performed later in the day has shown to reduce overnight hepatic glucose output and fasting glycemia. Exercise after eating can also be beneficial in reducing postprandial hyperglycemia, which is common in NIDDM (Mahan & Escott-Stump, 2000).

Studies undertaken by Campaign & Gunnarsson (1988), concluded that regular exercise alone, without alteration in insulin treatment and/or diet has no effect on long-term blood glucose control in IDDM patients. However with NIDDM, appropriate exercise programmes should be an adjunct to diet and/ or drug therapy to improve glycemic control, reduce certain cardiovascular risk factors and increase psychological wellbeing in individuals with NIDDM. Exercise may also improve glucose control in NIDDM patients and may assist in body fat reduction (Sherman & Albright, 1992).

An important variable is the level of plasma insulin during and after exercise. Excessive insulin levels can potentiate hypoglycemia because of insulin-enhanced muscle glucose uptake by the exercising muscle (Mahan & Escott-Stump, 2000; Braunwald *et al.*, 2001). In contrast, because insulin levels are too low in poorly controlled (under insulinized) exercisers, production of glucose and

free fatty acids continue with minimal uptake. This results in large increases in plasma glucose and ketone levels (Wasserman & Zinman, 1994).

In insulin dependent diabetics receiving multiple injections, the dosage of short-acting insulin before exercise can be reduced by 30%-50%, instead of dietary adjustment (Wallberg-Hendriksson, 1986). If exercise lasts for several hours, the insulin dosage can be reduced by 40% and extra carbohydrates taken during exercise (Sane *et al.*, 1988). The insulin formulation (short- or intermediate-acting) to be reduced is that which has its maximal action at the time of exercise. If blood glucose increases during exercise and this is not due to overeating, the insulin dosage should be slightly increased or the injection schedule changed in order to achieve higher plasma insulin concentrations during exercise (Koivisto, 1979). In NIDDM subjects, exercise does not usually cause hypoglycemia and, in obese diabetics, can be a vulnerable tool in losing weight. For these reasons no extra carbohydrate is needed with exercise. If blood glucose declines rapidly during exercise, as may occur in diabetics taking hypoglycemic agents, the dosage of the drug should be reduced or discontinue (Koivisto, 1979).

To avoid exercise-related hyperglycemia or hypoglycemia, individual with IDDM should:

1) Monitor blood glucose before, during, and after exercise;

2) Delay exercise when the blood glucose levels are >14 mmol/L (250 mg/dl) with ketones present, or blood glucose levels of $\leq$ 5.5 mmol/l (100mg/dl);

3) Eat a meal one to three hours before exercise and take supplemental carbohydrate feedings at least 30 minutes before vigorous or prolonged exercise;

4) Decline insulin dose before exercise and inject insulin into non-active musculature;

5) Learn individual glucose responses to different types of exercise and increase food uptake for up to 24 hours after exercising, depending on intensity and duration of exercise (Braunwald *et al.*, 2001; Colberg, 2001; White & Sherman, 1999).

IDDM subjects should avoid exercising in the late evening to reduce the risk of nocturnal hypoglycemia. People with diabetes who are in good metabolic control and do not have serious diabetic complications can engage in any type of exercise whether recreational or competitive (Colberg, 2001).

Exercise guidelines for NIDDM differ from that of IDDM, due to the difference in the origin of diabetes. IDDM exercisers have to take insulin injections whereas only a minimum of NIDDM exercisers uses insulin. The majority of NIDDM exercisers use a combination of diet, exercise and oral hypoglycemic agents to control their blood sugar and lessen their state of insulin resistance. The age of onset also varies, and older exercisers with NIDDM usually need a pre-exercise evaluation by their physician to ensure exercise will not worsen any other existing health problems (Colberg, 2001).

EXERCISE AND THE CARDIOVASCULAR SYSTEM

Exercise has long been recognized as a therapy in the management of diabetes mellitus. It is evident that exercise helps all persons with diabetes improve insulin sensitivity, reduce the risk factors, control weight, and bring about a healthier mental outlook (Graham *et al.*, 1990; Mahan *et al.*, 2000; Ruderman *et*

al., 1992). Although exercise training may not improve long-term blood glucose control, IDDM subjects are still encouraged to exercise on a regular basis to reduce cardiovascular disease and improve psychological wellbeing (Sherman & Albright, 1992; Campaigne & Gunnarsson, 1988). Exercise may help raise the diabetic's suppressed HDL levels (Ruderman & Schneider, 1992; Molitch, 1988) as well as blood coagulation time (Vitug *et al.*, 1988). Diabetics are also prone to hypertension, which is a known risk factor for atherosclerosis (Kumar *et al.*, 1997), and exercise has been shown to reduce moderate hypertension (Bennet *et al.*, 1984). Regular exercise often lowers the diabetics' insulin requirement, which in turn has a positive effect on blood pressure (Tipton, 1984). Elevated circulating insulin is associated with macrovascular diseases in IDDM (Vigorito, 1980), because insulin stimulates the growth of vascular smooth muscle (Stout, 1985), thus lowering the insulin requirements with exercise training would be beneficial in reducing the risk of macrovascular diseases, however recent research states that exogenous insulin is regarded as the best form of anti-inflammatory for the endothelial lining of the arterial wall, which is vascular protective (Distiller, 1994).

Combinations of aerobic and anaerobic exercisers are recommended for most diabetics (Colberg, 2000). It improves cardiovascular function, lipid profiles, weight control and insulin sensitivity (Delio, 1985; Lipman *et al.*, 1972; Horton, 1988). It has been recognized that exercise plays an important role in the treatment and prevention of specifically NIDDM (Horton, 1988). In a recent paper published by the American Diabetes Association (2000), inactivity was associated with major risk rates of death from heart disease in people with NIDDM.

South Africa is seen to have the third highest heart disease risk in the world, and the risk of heart attack or stroke is extremely high in patients with diabetes (Nova Nordisk Diabetes Lifeskill, 2000). Blair (1998), presented his findings from a

study analyzing the fitness levels of 25341 men and 7080 women. The subjects categorized as inactive, had the highest level of heart disease. Being inactive appeared to be a higher risk factor for heart disease than high blood pressure, high cholesterol, or being overweight. The above study revealed that as long as you were fit (even if you were overweight) you would have greater protection against heart disease.

EXERCISE AND HYPERTENSION

Arterial hypertension is more common in diabetics than in non-diabetic persons (Laragh & Brenner, 1995). Both IDDM and NIDDM are frequently associated with hypertension. Exercise training helps lower chronic high blood pressure. Hypertension has an effect on the smaller capillaries of the body and due to this the blood pressure needs regular monitoring in the diabetic person. According to Christensen *et al.* (1979) and McMillian (1979) insulin dependent diabetics have increased systolic and diastolic blood pressure values during exercise compared to non-diabetics. The research done by Jermendy *et al.* (1989) showed that abnormal diastolic pressures could appear earlier than systolic pressures in insulin-dependent diabetics. Moderate intensity aerobic exercise is generally recommended for those with elevations in blood pressure. Weight training can also be done as long as the focus is on low resistance, high-repetition training, which has a less dramatic increase in blood pressure than heavy weight lifting. High intensity (near maximal effort), isometric exercises, and valsalva maneuvers (breath holding), should be avoided due to the accompanying extreme increase in systolic and diastolic blood pressures (Colberg, 2000; Hanson, 1993). Effects of exercise on reducing blood pressure levels have been demonstrated most consistently in hyperinsulinemic subjects (Campaigne, 1997).

EXERCISE AND DIABETIC KETOACIDOSIS

Exercise also poses a problem in the presence of severe insulin alert. With the onset of exercise, peripheral glucose utilization is impaired, lypolysis is enhanced, hepatic glucose production and ketogenesis are stimulated, resulting in a rapid glucose concentration and the rapid development of ketosis (Fèry *et al.*, 1987; Horton, 1995). In this situation the poor metabolic control rapidly becomes worse, instead of lowering blood glucose, exercise causes a rapid deterioration of the metabolic state. To avoid ketosis the insulin dependent diabetic should check their blood glucose concentration and urine ketones prior to exercising. If ketones are present exercise should be postponed and supplemental insulin taken to re-establish good metabolic control (Horton, 1995).

EXERCISE AND NEPHROPATHY

Unfortunately the majority of diabetics with end stage renal disease (ESRD) are physically inactive for extended periods of time (American Diabetes Association, 1999b; Graham & McCarthey, 1990). The role and usefulness of exercise must be tempered and is dependent upon the degree of kidney failure and the chosen mode of therapy. Definitive goals of an exercise program need to be established in conjunction with these limitations, as exercise capacity is usually low. In nonuremic individuals, physical activity has a salutary effect on serum lipid and lipoprotein levels, cholesterol intolerance, insulin sensitivity and hypertension (Painter & Zimmerman, 1986). Research done by Goldberg *et al.* (1979) showed that physical training undertaken by young ESRD patients who were undergoing hemodialysis, showed improvements in physical working capacity, lipid abnormalities (decreased triglycerides and increased high density lipoprotein), glucose tolerance and hyperinsulinemia. Exercise training for 15-30 minutes at mild or moderate levels of exercise showed improvement in hemoglobin, hematocrit values and physical work capacity (Lowenthal, 1983).

Other reasons for maintaining strength and physical activity resides in the kidney's role in filtering phosphate. Diseased kidneys affect bone metabolism causing demineralization, thus weight-bearing exercise, done with dynamic physical activity, may result in improvement of bone volume (Lowenthal, 1983). A cornerstone of exercise therapy in diabetes is to reduce glucose intolerance and improve insulin sensitivity. Dialysis patients typically have hyperinsulinemia and glucose intolerance therefore the benefit of exercise in these patients will help reduce glucose intolerance, and increase insulin receptor density resulting in improved utilization of insulin (Lowenthal & Broderman, 1993; Painter, 1988). Painter and Zimmerman (1986) found that patients who performed recumbent cycling while undergoing dialysis showed significant improvements in maximum amount of oxygen consumed and control of blood sugar.

EXERCISE AND SENSORIMOTOR NEUROPATHY

Although exercise cannot reverse the symptoms of sensorimotor (peripheral) neuropathy, it can prevent the loss of physical fitness associated with disuse syndrome (Cyrus *et al.*, 1987). Adaptive shortening of connective tissue due to disuse syndrome immobilization, can begin within a week for patients with diabetes who are limited in their proprioception and ability to move. Daily range of movement for the major joints such as the ankle, knee, hip, shoulder, elbow, wrist and trunk is essential for preventing and minimizing contractures (Cyrus *et al.*, 1987).

Although exercising is of importance in patients with diabetes there are precautions that needs to be adhered to. With sensorimotor neuropathy loss of sensation to extremities creates a greater susceptibility to overstretching the muscles and connective tissue. Stretching exercises designed to prevent disuse syndrome, should be performed gently through the pain free range of movement

at all times. Diabetic persons with loss of sensation to the feet must limit weight-bearing exercises such as jogging and brisk walking. Shoes should not be worn more than 5 hours at a time and changing shoes will help distribute the shearing stress of walking and standing to new areas of the foot (Broadstone *et al.*, 1987).

Because sensorimotor neuropathy produces loss of proprioception (touch in the extremities), patients are more dependent on vision when performing motor skills. The following examples are strategies that a diabetic educator can employ to facilitate movement in patients with sensorimotor neuropathy:

1) Facilitate muscle contraction by using an assistant to rub and tap the skin over the muscle to be contracted;
2) Use visual aids such as foot prints placed on the floor to enhance walking proprioception;
3) Inspect feet before and after exercise to monitor any swelling, heat, redness or ulceration that may be developing; and
4) Suggest non-weight bearing activities such as arm exercises, swimming, and bicycling for persons with lost sensation on their feet (Broadstone *et al.*, 1987).

EXERCISE AND AUTONOMIC NEUROPATHY

Exercise conditions the organ system; optimal autonomic nervous system functioning essentially produces changes in the circulatory, hormonal, and metabolic adaptation to exercise. Therefore when identifying individuals with autonomic neuropathy one needs to ensure minimal dysfunction in the circulatory and hormonal response to exercise (Hilsted *et al.*, 1980). Patients with autonomic neuropathy may have decreased capacity for exercise, especially high intensity exercise due to an inadequate cardiovascular response to exercise,

such as an impaired increase in heart rate. These subjects are more prone to extreme hypoglycemia following exercise (Burr & Nagi, 1999).

The exercise tolerance in diabetics with autonomic neuropathy may be limited to the impairment of the sympathetic and parasympathetic nervous systems that normally augment cardiac output and redirect peripheral blood flow to the working muscles (Hilsted, 1982). Exercise in individuals with autonomic neuropathy should be gentle and limited to sessions of short duration (Burr & Nagi, 1999). Examples of suitable exercise in patients with autonomic neuropathy are stationary cycling and water exercise. Water exercise is good for individuals with orthostatic hypotension, as the pressure of the water surrounding the body helps maintain blood pressure. Sitting and semi-recumbence also helps maintain blood pressure and it maintains or increases muscular strength (Hilsted *et al.*, 1982).

Diabetic persons who display autonomic dysfunction should approach exercise with caution. Caution is needed because of the relationship of the cardiovascular components of the autonomic nervous system including baroreceptors, afferents, central nervous system processing, efferent, sympathetic and parasympathetic innervations of the heart and blood vessels (Graham & McCarthey, 1990). Because of the autonomic involvement, sub-maximal exercise testing is the most appropriate choice. The usefulness of the Borg Scale for rating of perceived exertion is applicable in these exercise situations because it is directed to the patient's subjective feelings (Hilsted *et al.*, 1982).

EXERCISE AND RETINOPATHY

The mode of exercise used in the presence of retinopathy may vary depending on the degree of vision remaining in an individual. The rise in systolic blood

pressure that normally accompanies exercise can aggravate proliferative retinopathy by causing pressure against weakened capillaries in the retina of diabetic patients (Margonato *et al.*, 1986; Colberg, 2001).

A study done by Mulder (1993) investigated whether regular training might improve body composition, oxygen capacity, glucose levels, contrast sensitivity and visual acuity in insulin-dependent diabetics. Three groups participated in the study, namely: a supervised and unsupervised exercise group and an inactive control group. A significant improvement resulted over total spatial frequency range of the contrast sensitivity in both eyes of the supervised group. They improved the visual acuity of the left eye. This improvement can be related to an overall improvement of their physiological condition after 12 weeks of regular training.

Before beginning an exercise program for diabetic persons with proliferative retinopathy, sub-maximal testing should be conducted under the guidance of trained personnel to establish a training heart rate according to blood pressure responses. Sub-maximal testing methods should be used because moderate exercise can raise systolic blood pressure to levels above 200mmHg, risking further damage to the retina. Persons with early stages of retinopathy can be tested using the guidelines provided by the American College of Sports Medicine (Hanson, 1993). Greenlee (1987) recommended that the heart rate should not exceed that which elicits a systolic blood pressure of 170mmHg. The blood pressure should be monitored during each exercise session, and exercise intensity adjusted accordingly. Cardiovascular endurance is particularly low in persons with vision impairments because of the loss of independent mobility (McCarthy, 1988). Exercise recommendations should consider the persons unique need, which include the development of muscle strength, balance, gait, cardiovascular endurance and/or social interactions.

At present there is no evidence to suggest that intensive physical training accelerates the progression of diabetic retinopathy, however as stated earlier by Morganato *et al.* (1986), certain types of exercise result in large increases in systolic blood pressure with increases in intra-occular pressure. These exercises are contra-indicators for moderate proliferation, examples being heavy weight training, power lifting and heavy valsalva maneuvers (Colberg, 2001). Functionally visually impaired individuals require environmental orientation to a workout facility, including where the hazards are located. Exercise is contraindicated if the person has recently undergone retinal photocoagulation treatment or eye surgery (Simmons, 1986).

Despite the potential risk associated with exercise, the benefits to people with diabetes far outweighs the risks (Colberg, 2001). Physical activity may not be a panacea for all ailments, but it has beneficial effects on the physical and psychological well-being of patients and has the potential to improve the quality of life (Burr & Nagi, 1999).

EXERCISE AND HYPERGLYCEMIA

IDDM is associated with elevated blood sugar levels termed hyperglycemia (Molitch, 1988). In contrast to sustained moderate–intensity, exercise during which blood glucose concentration remains constant or decrease slightly, high intensity exercise at 80% of maximal oxygen uptake (VO_2Max) or greater, is associated with a transient increase in blood glucose levels (Horton, 1995). The rise in blood glucose induced by exercise reaches a peak 5-15 minutes after exercise has stopped, and then gradually returns to the pre-exercise level within 40-60 minutes (Horton, 1995). This glycemic response to intense exercise results from a stimulation of hepatic glucose production, which exceeds the rate of glucose uptake in muscle, is associated with activation of the sympathetic nervous system, a sharp rise in glucose counter-regulatory hormones (glucagon,

catecholamines, growth hormone, and cortisol), and a suppression of insulin secretion (Berger *et al.*, 1977). Hyperglycemia with physical activity is more unusual and less dramatic than hypoglycemia. An increase in blood glucose during exercise has been demonstrated when the blood glucose level is initially high and the patients are ketotic (Berger, 1977; Beck *et al.*, 1984; Verity *et al.*, 1989). The threshold of the blood glucose levels, where exercise results in an increase instead of decrease in blood glucose, differs in individuals. In the absence of insulin, the levels of glucose and free fatty acids, as well as ketone body production by the liver, are greatly enhanced (Wahren *et al.*, 1975). There is a large increase in plasma free fatty acid and elevated ketone levels may result, by means of glucose-fatty acid cycle in an inhibition of glucose uptake by muscle (Randle *et al.*, 1964; Rennie & Holloszy, 1977; Randle *et al.*, 1963) which counterbalances the effect of exercise on the glucose transport process. These diabetics are characterized by an increase in the counter-regulatory hormones, such as glucagon, catecholemines and growth hormones. All of these contribute to an aggravation of the diabetic state. It is thus important to inform the diabetic that exercise must not be used as a means of decreasing hyperglycemia (Wallberg-Hendriksson, 1992). When exercise is stopped there is a two to three fold increase in plasma insulin, which has an inhibitory effect on hepatic glucose production and may enhance post exercise glucose uptake in muscle, thus the transiently elevated blood glucose concentration returns rapidly to normal (Calles *et al.*, 1983).

The most likely mechanism of hyperglycemic response to high-intensity exhausting exercise is the absence of and increases in plasma insulin during post-exercise recovery in diabetic subjects (Horton, 1995). Certain sport and recreational activities require relatively short periods of very high-intensity exercise, and the sustained hyperglycemic response to this type of exercise may present problems in diabetic children (Horton, 1995). At present there is no prevention or management of this response, although administration of insulin

following exercise might shorten the period of hyperglycemia (Horton, 1995). Careful self-monitoring of blood glucose levels before, during and following exercise of different intensities and duration may provide individuals with useful information that will allow them to develop strategies to minimize risk of hyperglycemia and/or hypoglycemia (Pickup & Williams, 1991).

EXERCISE AND HYPOGLYCEMIA

The most common disturbance of glucose homeostasis during exercise in IDDM is hypoglycemia (Vitug *et al.*, 1988; Wallberg-Hendriksson, 1992). IDDM individuals lack the basis for glucose homeostasis regulation i.e. a normal endogenous insulin production. The diabetics insulin levels does not respond to exercise, if no adjustments in medication dose are made, over-insulinization occurs (Wasserman & Zinman, 1994). The high insulin level prevents the liver from producing sufficient glucose to match the peripheral glucose uptake thereby resulting in hypoglycemia (Wallberg-Hendriksson, 1992; Vitug *et al.*, 1988).

The insulin level in persons with IDDM is governed mainly by the amount and timing of the last injection (Wallberg-Hendriksson, 1992; Burr & Nagi, 1999). The diabetic person must anticipate strenuous activity and make proper adjustment in the insulin dose (Burr & Nagi, 1999; Braunwald *et al.*, 2001), If adjustments in insulin dose is not adhered to, extra carbohydrates are recommended to compensate for an excess of circulating insulin (Burr & Nagi, 1999, Braunwald *et al.*, 2001; Wallberg-Hendriksson, 1992; Sherman & Albright, 1990).

Muscular contractile activity results in an increased glucose uptake and an increased insulin sensitivity several hours after the exercise session (Heath *et al.*, 1983; Ivy *et al.*, 1983). Hypoglycemia may not only occur during the physical activity, but may occur 4-6 hours after the exercise (Campaigne *et al.*, 1987; Vitug *et al.*, 1988; Burr & Nagi, 1999). If hypoglycemia poses a problem during

exercising even after the insulin dose has been lowered, the diabetic may benefit from not exercising at the time of peak insulin effect for their type of insulin. Also administering the insulin injections in a less active area is beneficial in preventing exercise-induced hypoglycemia (Sherman & Albright, 1990; Coram & Mangum, 1986). Repetitive contraction of the skeletal muscle immediately under the injection site can alter its absorption (Koivisto & Felig, 1978; Zinman *et al.*, 1977). When exercise takes place, accelerated absorption of insulin during exercise may result in hypoglycemia, at the time of exercise or shortly thereafter (Vitug *et al.*, 1988). Changing the site of insulin injection to an area away from the exercising muscle can correct the problem (Vitug *et al.*, 1988; Koivisto & Felig, 1978). When hypoglycemia occurs during exercise despite all efforts to avoid it, it is often difficult to treat (Burr & Nagi, 1999).

The following precautionary measures are suggested for the well controlled IDDM subjects who wishes to participate in strenuous exercise without the risk of hypoglycemia:

1) Consume CHO (15-30gm) for every 30 minutes of moderately intense exercise (Burr & Nagi, 1999; Vitug *et al.*, 1988; Chiarelli *et al.*, 1999; Braunwald et *al.*, 2001; Burge *et al.*, 1997).

2) Decrease insulin dose (Coram *et al.*, 1986; Vitug *et al.*, 1988; Wallberg-Hendriksson, 1992; Brenbaum *et al.,* 1989).

3) Avoid exercising muscles underlying the injection site (Coram & Mangum, 1986; Vitug *et al.*, 1988; Wallberg-Hendrikson, 1992).

CHAPTER 3

METHODOLOGY

The purpose of this study was to gain insight into the exercise practices, in conjunction with dietary habits and medication routine, of insulin dependent diabetics. In this chapter, the following methodological aspects are presented:

3.1 Subject Selection
3.2 Design and Instrumentation
3.3 Statistical Analysis

3.1 SUBJECT SELECTION

The subjects comprised of 200 insulin dependent diabetics making use of the outpatient service at twelve hospitals in Kwa-Zulu Natal, viz:

1) Newcastle Provincial Hospital
2) Vryheid Provincial Hospital
3) Ladysmith Provincial Hospital
4) Escourt Hospital
5) Addington Hospital (Durban)
6) Parklands Hospital (Durban)
7) Stanger Hospital (Kwa Duguza)
8) Mahathma Gandhi Memorial Hospital (Phoenix)
9) Port Shepstone Provincial Hospital
10) Murchison Hospital (Port Shepstone)
11) Christ the King-Ikopo Hospital (Ikopo)
12) Bay Hospital (Richards Bay)

The sample size was restricted to 200 on the basis of voluntary availability of respondents. The primary criterion for inclusion was that respondents had to be an insulin dependent diabetic. There was no restriction on gender, race or

physical activity status. Equal gender and juvenile/adult representation was ensured. It was observed during the pilot study that children under the age of 10 years were not capable of providing reliable data, and were thus excluded from the study. On this basis, the respondent's age ranged from 10 years and above.

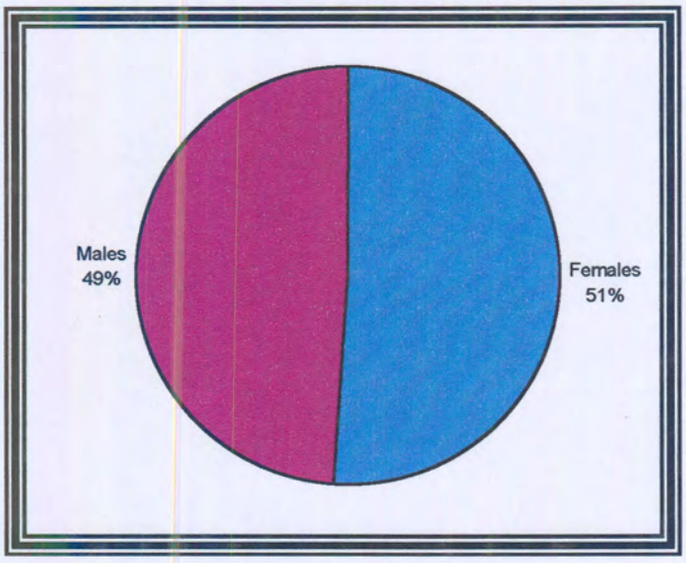
Biographic details with respect to age distribution, gender distribution, ethnic group distribution, diagnosis of diabetes, and family history of diabetes are presented henceforth:

TABLE 3.1: AGE DISTRIBUTION (ITEM 1)

AGE	10-20	21-30	31-40	41-50	OVER 50
n	61	42	39	27	31
%	30.5	21.0	19.5	13.5	15.5

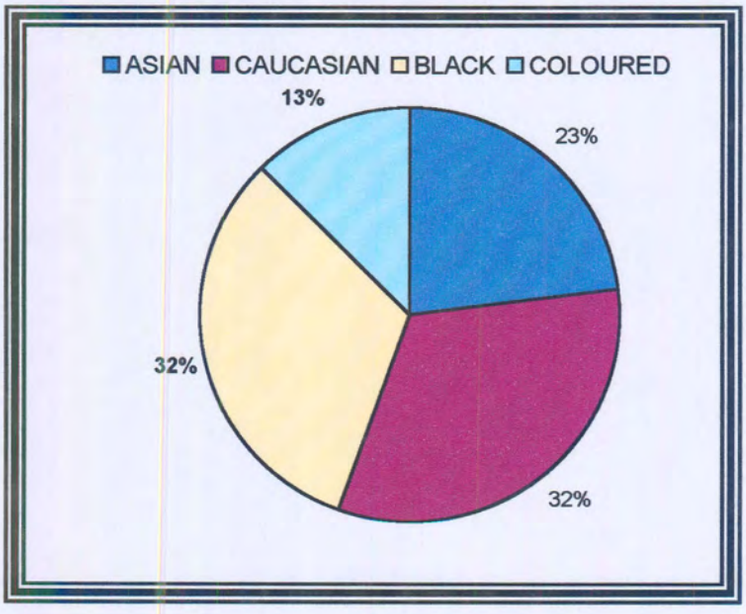
The majority of the respondents fell within the age group 10-20 years (30%), and 21-30 years (21%), corresponding with the "juvenile-onset " nomenclature of Bates (1986) indicating the prevalence of IDDM in adolescence and young adulthood (Table 3.1).

FIGURE 3.1: GENDER DISTRIBUTION (ITEM 2)



There was an equal gender representation (Figure 3.1). Males constituted 48.5% and females 51.5%, of the sample.

FIGURE 3.2: ETHNIC GROUP DISTRIBUTION (ITEM 3)



The ethnic origin of the respondents is graphically represented in Figure 3.2. The majority of respondents where of black African (32%) and European

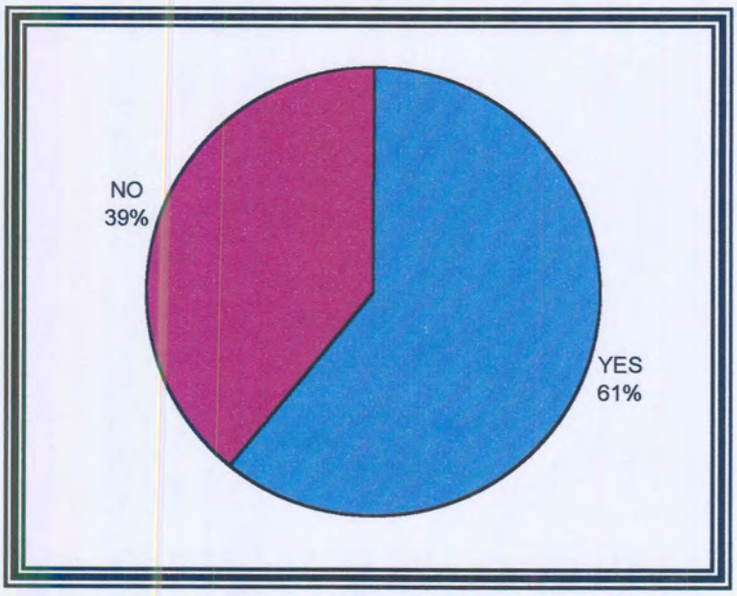
caucasian (32%) descent, whilst Asians 23% and coloreds 13%, made up the rest of the sample.

TABLE 3.2: MEAN AGE (YEARS) AT DIAGNOSIS (ITEM 1)

	TOTAL
n	195
Mean	21.5
Std Deviation	14.33

The mean age of diagnosis with IDDM among the sample was 21.5 years (Table 3.2). This age corresponds with the characteristic juvenile and young adulthood onset of the condition.

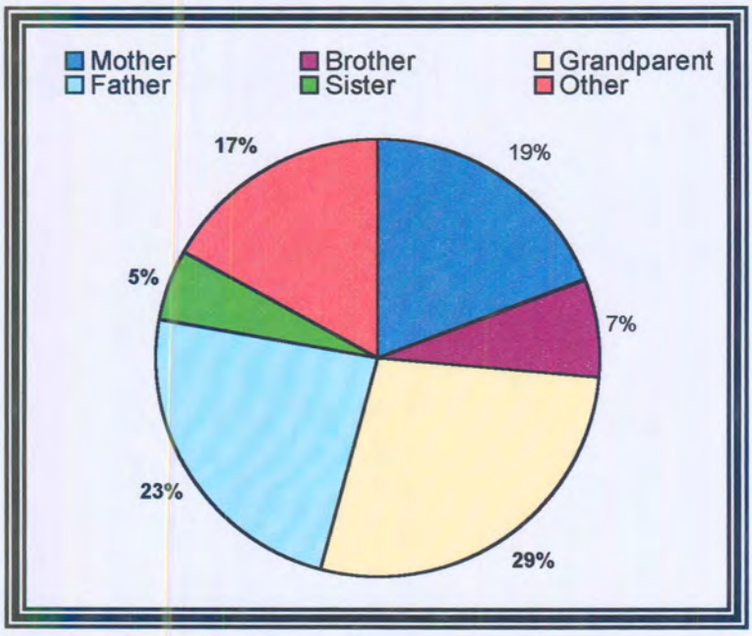
FIGURE 3.3: FAMILY HISTORY (ITEM 11)



From the data (Figure 3.3), 61% of the respondents had a family history of diabetes and 39% did not. This corresponds with research indicating that insulin dependent diabetics have genetic predisposition (identified by specific

human leukocyte antigens) together with an environmental risk (viral infection) (Pickup & Williams, 1991).

FIGURE 3.4: FAMILIAL HISTORY DESIGNATION (ITEM 12)



The highest risk for the development of IDDM resides with first-degree relatives of the diabetic proband, this risk being in the order of 2.9%, 6.6% and 4.9% for parents, siblings and children of probands respectively (Sandler, 1990). In this sample (Figure 3.4), the majority of respondents indicated their grandparents and fathers as having IDDM. In viewing the relationship of respondent with other family members that had diabetes, grandparents (28%) were the most common, followed by fathers (24%), mothers (19%), brothers (7%), sisters (5%), and lastly others-constituting of uncles, aunts and cousins (17%).

3.2 DESIGN AND INSTRUMENTATION

The design adopted for the study was that of a descriptive and analytical survey and was approved by the ethics committee of the Faculty of Humanities at the University of Pretoria. The gathering of data was conducted over a period of seven months using a questionnaire (Appendix 1)

as data-collection instrument. The questionnaire that was administered aimed to probe the knowledge, attitudes, beliefs and practices of insulin dependent diabetics with respect to exercise/physical activity, in conjunction with diet and medication, in the management of IDDM. Prior to administering the questionnaires, informed consent was procured from respondents based on the contents of a cover letter (Appendix 2), briefly explaining what the survey entailed. Administration of questionnaires was conducted on a self-report basis; however, if the respondents were confronted with difficulties they were assisted by doctors and nurses at the participating hospitals who co-operated in the research. Anonymity was ensured, no names were reflected on the questionnaire and the results were treated with confidence.

3.2.1 QUESTIONNAIRE CONSTRUCTION

The questionnaire was constructed following a thorough literature review, using the personal insight of the researcher as an insulin dependent diabetic and in consultation with the Department of Human Nutrition in the Faculty of Health Sciences at the University of Pretoria.

The questionnaire comprised of 72 items, containing categorical, closed and open responses. Variables were grouped into three categories i.e. medication usage incorporating variables 5-10, 44-47 & 70-71; dietary habits incorporating variables 52-62, 64-67; and exercise practices incorporating variables 13-43, 48-51, 63 & 68-69. In some items, duplicate responses were possible.

3.2.2 PILOT STUDY

A pilot study was conducted on a sub-sample of the population at a Diabetic Camp held at Pietermaritzburg (Kwa-Zulu Natal). The camp spanned an entire weekend. Questionnaires (n=24) were administered at the camp to diabetics ranging from ages eight years and above. A pre-test and post-test (1 day later) was administered, in order to evaluate the validity and reliability of responses. Questionnaires were administered directly by the researcher in

an interview situation, in order for confidentiality and anonymity to be maintained. The questionnaire was shown to observe content and face validity with acceptable repeatability (reliability) of responses. The following shortcomings were elicited and corrective steps were taken after the pilot study:

- Communication seemed to be a problem as the questionnaire was initially only available in English. The questionnaire was subsequently also translated into Zulu;
- With regards to few questions, more options were included when responding to an item on the questionnaire; and
- Some terminologies were simplified in order to compensate for respondents who were unfamiliar with certain technical/scientific terms.

3.3 DATA ANALYSIS

Data analysis was performed with the assistance of and independent statistician on the SAS System (copyright 1994 by SAS institute Inc., USA, version 6.12). Frequencies and percentages were calculated for responses and, where appropriate, means and standard deviations were calculated. The overall respondents amounted to n=200 unless stated otherwise, of which they were divided into exercisers and non-exercisers (Figure 3.5). The present exercising group (68%) was calculated as ($n=^{x}/_{197}$) where n=135 and present non-exercisers amounted (32%) was calculated as ($n=^{x}/_{197}$) where n=62. The Chi-Square test was used to determine significant differences between sets of data for the various nominal variables measured with alpha set at $p \leq 0.1$, as is the norm for survey research. The test is concerned with comparing differences in the actual (or observed) frequencies (or counts) with the expected frequencies (or counts) with respect to a certain attribute for the sample under investigation. The t-test was used to test for significant differences in ordinal data between groups, with alpha set at a minimum of $p \leq 0.05$ (Thomas & Nelson, 1996).

FIGURE 3.5: DISTINCTION BETWEEN EXERCISERS AND NON-EXERCISERS (ITEM 19)