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The Prevalence of Type 1 and Type 2 Diabetes and Other Altered Glucose States in Acute Hospital Admissions in Ireland.

By

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Declaration

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The work submitted in this thesis to Waterford Institute of Technology is entirely my own work and has not been submitted to any other higher education institution, or for any other academic award in this institute. Where the work of other people has been used in this thesis, it has been fully acknowledged and referenced.

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Abstract:

Abstract

The Prevalence of Type 1 and Type 2 Diabetes and Other Altered Glucose States in Acute Hospital Admissions in Ireland.

Author: Dorothy B. Moore

Background:
The prevalence of altered glucose states are rising exponentially due to population ageing, decreased physical activity and increasing obesity levels (WHO, 2005). Altered glucose states are associated with increased morbidity and mortality and place a major financial burden on healthcare budgetary resources (Rubin et al, 1994). Hospitalisation costs, to treat the avoidable complications of diabetes, are the most significant contributor to the costs of diabetes related healthcare expenditure. This survey was undertaken to ascertain the prevalence of altered glucose states in acute, medical, hospital admissions and to estimate the cost of this care to the Irish healthcare system.

Methods:
A prospective survey of an unselected sample was undertaken in acute medical admissions to a Regional hospital in Ireland. Between June 1st 2005 and 17th December 2006, 1273 individuals were enrolled in this survey. Of these, 419 eligible individuals had a known or new diagnosis of type 1 or type 2 diabetes, impaired glucose tolerance or impaired fasting glucose and a history of complication or risk factor for diabetes.

Findings:
34% of individuals hospitalised in this cohort had an altered glucose state. Type 2 diabetes was the most prevalent and was recorded in 21%. Impaired glucose tolerance was the principal newly diagnosed altered glucose state identified in 38% of individuals. All combined altered glucose states and type 2 diabetes alone were more prevalent in males however, a new diagnosis following screening did nor vary according to gender. Individuals with an altered glucose state were also older with new IGT becoming more prevalent with age. This was in contrast to negative OGTT results which decreased with increased age.   The cost of treating individuals in this cohort was estimated at €501,124 or €3,458,144 million, when applied to the total population of acute medical patients, admitted to this regional hospital.

Conclusions:
This study identified previously unavailable hospital admission data, for individuals requiring acute medical care in Ireland. In this study 34% of all acute medical hospital admissions had an altered glucose state. In addition, a significant number of individuals had a previously undiagnosed altered glucose state on admission. This study confirmed the significant cost of hospitalisation care, for altered glucose states in association with microvascular and macrovascular complications and the impact of this on the healthcare system.

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List of Abbreviations.

IDF	International Diabetes Federation
WHO	World Health Organisation
ADA	American Diabetes Association
WHO/IDF	World Health Organisation/International Diabetes Federation
IGT	Impaired Glucose Tolerance
IFG	Impaired Fasting Glucose
RoI	Republic of Ireland
DKA	Diabetic Ketoacidosis
EU	European Union
DoH&C	Department of Health and Children
WHO/FAO	World Health Organisation/Food and Agriculture Organisation of the United Nations
DECODE	Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe
GLUT	Glucose Transporters
ADP	Adenosine Diphosphate
ATP	Adenosine Triphosphate
IDDM	Insulin Dependent Diabetes Mellitus
NIDDM	Non-Insulin Dependent Diabetes Mellitus
OGTT	Oral Glucose Tolerance Test
US	United States
CDC	Centres for Disease Control and Prevention
NI	Northern Ireland
UKPDS	United Kingdom Prospective Diabetes Study
HbA1c	Haemoglobin A1c
HDL	High density lipoprotein
PAI-1	Plasminogen activator inhibitor-1
MODY	Maturity Onset Diabetes of the Young
HNF	Hepatocyte nuclear factor
BMI	Body Mass Index
WHR	Waist-Hip-Ratio
TNF	Tumour Necrosis Factor

CVD   Cardiovascular Disease

DCCT   Diabetes Control and Complications Trial

MRFIT   Multiple Risk Factor Intervention Trial

IUNA   Irish Universities Nutrition Alliance

CHD   Coronary Heart Disease

CVA   Cerebrovascular Accident

NSTEMI   Non ST Elevation Myocardial Infarction

ACS   Acute Coronary Syndrome

MI   Myocardial Infarction

TIA   Transient Ischaemic Attack

Chapter 1.

Introduction.

1.1 Diabetes Mellitus and Altered Glucose States.

Diabetes mellitus is a significant and growing global epidemic, and is considered the most common non-communicable chronic disease (International Diabetes Federation, 2008). Diabetes is a major contributor to global morbidity and mortality, with 50% of all global mortality attributed to chronic diseases such as, cardiovascular and respiratory disease, cancers and diabetes (Unwin and Alberti, 2006). Diabetes alone contributed to 1.7% of global mortality in 2002 (World Health Organisation, 2003a).

Diabetes and altered glucose states are a collection of metabolic disorders, in which chronic hyperglycaemia is a distinctive feature. These altered glucose states result from abnormal carbohydrate, protein and lipids metabolism. They are also characterised by an absolute or relative deficiency of insulin secretion, defects in insulin action or a combination of both (Krentz, 2000). Blood glucose abnormalities were first classified by the World Health Organisation (WHO) in 1980. This classification has been redefined over the intervening years by both the American Diabetes Association (ADA, 1997 & 2007a) and the WHO (1985 & 1999), to include intermediate and other glucose categories. The most recent World Health Organisation/International Diabetes Federation (WHO/IDF, 2006) guidelines classify diabetes as type 1 diabetes and type 2 diabetes, and intermediate hyperglycemias as, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT).

A significant growth in the worldwide prevalence of diabetes and other altered glucose states has occurred in recent years. Type 2 diabetes contributes approximately 90% of all diabetes while type 1 diabetes accounts for approximately 10% of all global disease. Conservative estimates from the WHO suggest that diabetes mellitus was prevalent in 30 million people globally in 1995. They predict this will grow substantially across all age groups (King et al, 1998). A significant growth has indeed occurred since 1995, with diabetes prevalence in 2003 estimated at 194 million or 5.1% of adults aged 20-79. This prevalence will continue to rise dramatically to 6.3% or 333 million by 2025 (IDF, 2008). Social factors such as a growing and ageing population, urbanisation, sedentary lifestyles and increasing obesity will accelerate this increase in diabetes prevalence (WHO, 2005).The contribution of other altered glucose states such as IFG and IGT will compound the diabetes situation. Given the increased risk of progression to type 2 diabetes and the elevated cardiovascular risk associated with IFG and IGT, these altered glucose states are predicted to contribute substantially to increased global morbidity and mortality (IDF, 2008).

The most recent prevalence data for type 1 diabetes in the Republic of Ireland (RoI) estimated a prevalence rate of 0.4% in 2005. This is equivalent to12,011 cases in the RoI and this number is rising (The Irish Diabetes Prevalence Working Group, 2007). Estimates have also demonstrated that 141,000 individuals in the RoI had type 2 diabetes in 2005. This reflects a prevalence rate of 4.7% and this is predicted to increase by 2015 to at least 193,944 people or 5.6% of population (The Irish Diabetes Prevalence Working Group, 2007).

Chronic disease places an enormous financial burden on healthcare resources (Wild et al, 2004). This arises from the need to detect, manage and prevent such chronic conditions (ADA, 2003). Chronic diseases such as cardiovascular disease, cancer and diabetes are among the most prevalent, preventable and costly chronic conditions (CDC, 2008a). The costs associated with diabetes primarily result from the treatment and management of the disease and its preventable complications (Rubin et al, 1994). Substantial global evidence is available to demonstrate that hospitalisation costs to treat the complications of diabetes are the most significant contributor to diabetes related costs (ADA, 2003, Simpson et al, 2003, Jonsson, 2002). In Ireland, inpatient care is the largest single contributor to diabetes related healthcare expenditure. Evidence has shown that hospitalisation costs account for 48% of overall diabetes costs in Ireland. These costs primarily result from the treatment of diabetes related complications (Nolan et al, 2006).

The escalating costs of diabetes are the major force driving the re-examination of current prevalence rates, service usage and service provision by healthcare planners (Health Canada, 1999). The WHO recognises the need to track the prevalence of the diabetes epidemic. Provision of prevalence data would assist future policy development and management of the escalating prevalence of altered glucose states. It would also facilitate management of the healthcare costs associated with treating altered glucose states and their long-term complications. While the WHO acknowledges that limited data is available to guide healthcare planning, it recognises the absolute need to acquire this epidemiological data (WHO, 2005).

1.2 Justification for this Research.

Given the projected rise in diabetes prevalence globally, the financial burden associated with treating diabetes is expected to increase substantially in the future. This increase in the prevalence of altered glucose states will also be reflected in the Irish healthcare setting and will compound the burden already placed on public healthcare resources. Hospitalisation costs account for a significant proportion of overall diabetes related costs and these arise primarily from the treatment of preventable complications of diabetes (ADA, 2003).

The provision of accurate and relevant prevalence data, to establish the true prevalence of diagnosed and undiagnosed altered glucose states, is necessary as advised by the WHO (2005). It is also appropriate to acquire this data for the acute hospital sector, in order to estimate the financial burden placed on hospital systems to treat altered glucose states and their complications. Systematic projections estimating the population prevalence of altered glucose states in Ireland by 2010 and 2015 are likely to underestimate the true prevalence of these states. Currently no published study has examined the prevalence of altered glucose states in individuals requiring acute hospital admission in Ireland and the contribution of such individuals to the overall cost of diabetes care in this country.

The purpose of this prevalence survey is to record the proportion of people with altered glucose states in an unselected sample of general medical adult patients, admitted acutely to hospital. It also intends to provide data for healthcare planners of the extent to which altered glucose states influence the health of people admitted to hospital, their requirement

for inpatient care, and to estimate the financial cost of healthcare provision. The availability of such data is essential to facilitate health service planning and delivery, for the future. This is particularly important in the context of the escalating prevalence rates of diabetes and altered glucose states and their associated costs.

Policy development to institute preventative treatment programmes could facilitate future reductions in the financial burden of diabetes. Such strategies could prevent future complications in individuals with diabetes and altered glucose states. In line with this, any decrease in the morbidity and mortality associated with these glucose states, would have significant benefits for individuals, their family and society. Preventative treatment programmes could also avert some of the hospital admission costs related to the complications of diabetes. Hospitalisation costs are the single biggest contributor to diabetes related healthcare costs for already struggling healthcare systems (IDF, 2005).

Some discussion has occurred in recent years in relation to the cost effectiveness of treating chronic conditions. This has centred on the cost implications of providing healthcare and decisions regarding the rationing of care (Cookson and Dolan, 2000). People are now living longer and as such their predisposition toward the development of chronic disease has increased. It has been suggested that the cost of treating individuals and maintaining life may be more expensive than letting people die (Walshe and Smith, 2006). Such opinions have been proposed against a background of increasing costs and demand for healthcare (Cookson and Dolan, 2000). However, while the economic benefits of withholding treatments and letting people die may be acceptable from a theoretical perspective,

decisions on the provision of healthcare resources continue to be made based on the benefits accrued by treatments, at a societal level (Walshe and Smith, 2006).

1.3 Research Objectives.

In light of the current dearth of knowledge related to the prevalence of diabetes and altered glucose states in acute hospital admissions in Ireland, this research intends to provide comprehensive prevalence data for altered glucose states amongst acute adult hospital general medicine admissions. The objectives of this research are:

1. To establish the prevalence of Type 1 diabetes, Type 2 diabetes, Impaired Glucose Tolerance, Impaired Fasting Glucose.

2. To explore and describe demographic data in relation to prevalence rates in this population.

3. To estimate the financial costs to the healthcare system of altered glucose states in acute hospital medical inpatient care.

Chapter 2.

Literature Review.

2.1 Chronic Disease Introduction.

Since the 1920's chronic disease has been a major public health concern (Beaglehole and Yach, 2003) with this escalating in recent decades (Unwin and Alberti, 2006). In both developing and developed countries the prevalence of chronic disease is increasing with the World Health Organisation predicting a global increase of 10-15% in chronic disease over the next decade (WHO, 2005). This increase in chronic disease has already placed a growing financial burden on healthcare systems. This increase has forced policy makers to review management strategies for many chronic conditions to improve healthcare quality and reduce the costs associated with these diseases (Cheah, 2001).

The rising prevalence of long-term chronic disease throughout the developed countries and the emergence of treatments to manage such conditions, has resulted in chronic diseases being the single biggest public healthcare challenge for countries in the Organisation for Economic Co-operation and Development (OEDC) (Walshe and Smith, 2002). These diseases pose a major health challenge within the European Union (EU). They contribute significantly to mortality rates with the highest rates from chronic disease occurring in central and eastern European countries. In the United Kingdom (UK) chronic diseases add significantly to rates of ill health and place a large financial burden on the National Health Service (NHS) (Lewis and Dixon, 2001). A similar situation exists in Ireland where

chronic disease is regarded as a major contributor to mortality and morbidity. It contributes enormously to the cost of care in the Irish healthcare system according to the Irish Department of Health & Children (2008).

2.1.1 Defining Chronic Disease.

The classification of an illness as a "chronic disease" can lead to confusion as an illness or disease can be classified and recorded in a different category, in different contexts (WHO, 2005). Chronic illnesses and diseases can be defined according to their underlying pathophysiology and classified into one of the three major disease categories, communicable disease, non-communicable disease or injury (Walshe and Smith, 2002). The term "non-communicable disease" is used to distinguish a disease from an infectious or communicable process, which may underlie the disease. However, this distinction is not always clear-cut as many chronic diseases such as cervical or liver cancer can have an infectious component to their development. For many chronic diseases, the influence of personal behavioural is a significant factor in the development of the illness or disease. Such illnesses or diseases are referred to as lifestyle-related diseases. While individual behaviour may contribute to the development of these chronic diseases, they generally do not result from individual choice alone, they are also strongly influenced by environmental factors (WHO, 2005).

Chronic diseases carry a lifelong burden for patients, their families and carers. They are long-term conditions that last for more than 6 months, involve some functional impairment or disability and are usually incurable (Department of Health & Children, 2008). These

require long-term treatment and follow up by a multidisciplinary team and have recurrent admissions to manage exacerbations of the condition (Lewis and Dixon, 2001). The term "chronic disease" includes a wide-ranging group of disorders such as chronic respiratory disease, cancers, cardiovascular disease, diabetes, musculoskeletal and mental health disorders (Unwin and Alberti, 2006).

2.1.2 Global Morbidity and Mortality from Chronic Disease.

The patterns of health, illness and disease have similarities and differences that exist between countries and across cultural and socio-economic groups within the same country. The contribution of diseases related to communicable disease, non-communicable disease or injury varies across countries. Poorer and developing countries are currently experiencing the highest mortality rates from infectious communicable diseases. In contrast developed countries have seen a shift from high rates of infectious diseases toward higher mortality from chronic non-communicable diseases (WHO, 2005).

Chronic disease is a significant contributor to morbidity and mortality in developed countries (Cheah, 2001) and is considered the major cause of adult death globally. Predictions of global deaths for 2005 suggested 35 million of the 58 million global deaths would result from a chronic disease. These deaths would result primarily from cardiovascular disease, in particular heart disease and stroke (Figure 1) (WHO, 2005).

The WHO mortality rates are not thought to be static and are expected to rise by 17% by

2015. According to the WHO 41 of the 64 million deaths that will occur in 2015 will result

from a chronic disease and these will occur equally across genders (WHO, 2005).

Figure 1: Chronic Disease Related Deaths.

(WHO, 2005)
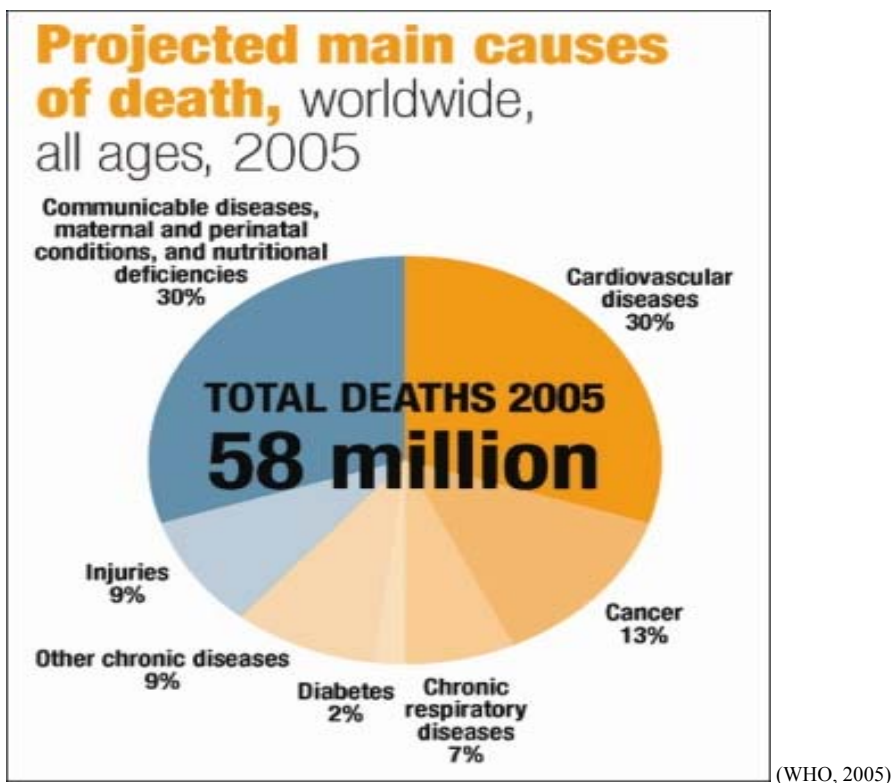
The geographical spread of chronic disease related morbidity and mortality differs across

income levels and countries, with approximately 80% of all chronic disease mortality

occurring in low to middle income countries. In these countries, 45% of deaths from

chronic disease will occur in people less than 70 years and 25% of these will be in people

less than 60 years. Individuals will develop chronic disease at a younger age, suffer longer

with their preventable complications and have a shorter life expectancy than those in higher

income countries. This high proportion of chronic disease mortality in low to middle income countries is partially explained by the high population levels in these countries, which account for 85% of the global population (WHO, 2005).

In developed and more prosperous countries chronic disease is also the leading cause of death (WHO, 2005). In the EU 86% of deaths and 77% of total morbidity is attributed to chronic disease. The principal contributors to these rates of chronic disease are cardiovascular disease and cancers (WHO, 2003a). Similarly in Ireland, mortality rates from chronic diseases are high with cardiovascular disease and cancers accounting for more than 66% of all deaths. These rates remain high despite significant reductions in mortality rates for heart disease and stroke (Department of Health & Children, 2008).

Of all chronic conditions cardiovascular disease, chronic respiratory disease, cancers and diabetes contribute to approximately 50% of global mortality (Unwin and Alberti, 2006). Cardiovascular disease remains the leading cause of chronic disease mortality accounting for 30% of global deaths. Cancer (13%) and respiratory disease (7%) are other significant contributors. Diabetes was responsible for 987,000 deaths or 1.7% of total global mortality in 2002 (WHO, 2003 a). This figure is however considered an underestimate as many deaths which were due to diabetes had a "complication of diabetes" recorded as their cause of death (WHO, 2005). People with diabetes most commonly die from complications of the disease such as cardiovascular or renal disease and not from complications unique to diabetes, such as hyperglycaemia and ketoacidosis (Roglic et al, 2005).

2.1.3 The Effects of Globalisation, Urbanisation and an Ageing Population.

The WHO predicted an increase in the prevalence of chronic disease from 28.1 million in 1990 to 49.7 million by 2020. They attribute this mainly to the effects of industrialisation, globalisation, urbanisation and ageing populations (WHO, 2005). According to the World Health Organisation/Food and Agriculture Organisation of the United Nations (WHO/FAO, 2003) enormous changes in living patterns have occurred in the last decade as a result of changing dietary patterns and lifestyle. This has occurred in association with industrialisation, market globalisation and urbanisation. These changes have impacted significantly on the health and nutritional status of global populations.

2.1.3.1 Ageing Populations and Chronic Disease.

The ageing population, which is linked primarily to decreased fertility rates and increased child survival rates, is a central component in non-communicable chronic disease epidemics (Beaglehole and Yach, 2003). The WHO has estimated that 17 million people, under the age of 70 years, will die from chronic disease related deaths annually. In low to middle income countries mortality rates are significantly higher and are thought to occur at a younger age, with 8.5 million individuals dying due to chronic disease in 2005 before age 60 (WHO, 2005). Evidence from some EU countries, with older populations, suggests approximately 40% of individuals live with a chronic disease (Department of Health & Children, 2008).

A rise in the total global population is forecast by the WHO and this will increase the number of elderly people aged greater than 70 years. It is estimated that those over 70

years will rise from 269 million to 1 billion between 2000 and 2050. Low to middle

income countries will see the most significant rise in population age with an expected

increase of 466% in those over 70 years. This will lead to an increase in the population

over 70 years from 174 million to 813 million in this timeframe. A more modest increase

from 93 million to 217 million is expected in higher income countries in people aged over

70, over the same period. It is envisaged that these increases in population age will

multiply the number of those living with chronic disease (WHO, 2005).

In Ireland similar changes in population age are predicted over the next 30 years

comparable with that experienced globally. These changes in population age will have a

significant impact on the number of people living with a chronic disease in Ireland and on

their requirements for healthcare (Department of Health & Children, 2008).

Ageing is an important marker for the accumulation of modifiable risks factors for chronic

disease. The development of adult chronic disease reflects a lifetime of exposure to

harmful environmental and social factors. (WHO/FAO, 2003). The impact of chronic

disease risk factors increases over the life course. It is possible however, to delay mortality

from chronic disease by several decades, particularly among middle-aged people, through

provision of healthcare intervention that give substantial short-term benefits. Primary

prevention through interventions in early life can also accrue significant health benefits by

reducing their initial development and subsequently the prevalence of chronic disease

(WHO, 2005). This has been identified in the treatment of individuals with both type

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1diabetes (The Diabetes Control and Compilations Trial Research Group, 1993) and type 2 diabetes (United Kingdom Prospective Diabetes Study (UKPDS) Group, 1998a).

2.1.3.2 Globalisation, Urbanisation and Chronic Disease.

Globalisation, which is the increased ability for travel and commerce between countries in relation to the openness of boarders to people, ideas and markets, imparts both positive and negative health benefits on individuals (Woodward et al, 2001). Globalisation has provided people with improved standards of living, a greater availability and more diversified range of food and greater access to services (WHO/FAO, 2003). It provides increased access to information and communication technology that supports health-care systems and makes health and lifestyle information more accessible. Significant consequences have also ensued including changes to dietary patterns, decreased physical activity and increased tobacco usage. Changes in the type of foods produced, food production patterns and increased global trading and marketing of products has driven the transition in food patterns (Beaglehole and Yach, 2003). This has led to an increase in dietary consumption of energy-dense foods with high sugar and fat contents, particularly saturated fats and foods low in unrefined carbohydrate (WHO/FAO, 2003). Commercial marketing of such foods, which are targeted at teenagers, has seen $200 million spent by 600 million 5-14 years olds globally each year with a substantial proportion of this spent on fast foods, soft drinks and tobacco (Beaglehole and Yach, 2003). These dietary changes have also been influenced by changing lifestyle patterns that result from increased income levels and reduced food preparation time (WHO, 2005).

Dietary changes have occurred in conjunction with a decrease in physical activity levels and energy expenditure. The development of labour saving devices and technologies for the home and workplace and increased access to motorised transport has led to more sedentary lifestyle patterns. Changes to urban planning and sprawl also encourage individuals to be less physically active (WHO, 2005). The combined effect of globalisation and urbanisation on dietary and lifestyle patterns has led to an increase in the prevalence of non-communicable chronic diseases including cardiovascular disease, obesity, diabetes and some types of cancers (WHO/FAO, 2003).

2.1.4 Chronic Disease Rick Factors.

The main causes of some chronic diseases are known, preventable and can be attributed to changing lifestyle patterns. Lifestyle factors such as physical inactivity, poor diet and excessive calorie intake, increasing levels of obesity, alcohol consumption and smoking in association with hypertension and hyperlipidaemia are the main risk factors for chronic disease (WHO, 2005). These chronic disease risk factors are a leading source of death and disease burden in all countries, regardless of their economic development status (Cheah, 2001). In the EU, the leading chronic disease risk factors of hypertension, alcohol, smoking, poor diet and physical inactivity contribute to almost 60% of the chronic disease burden (Department of Health & Children, 2008). These risk factors are clinically expressed by intermediate risk markers such as hypertension, hyperglycaemia, abnormal lipid levels, particularly raised low-density lipoprotein (LDLc), overweight (BMI>25 kg/m^2) and obesity (BMI>30 kg/m^2) (WHO, 2005).

It is recognised that chronic diseases cluster in people (WHO, 2005). In the US, 61 million of the 125 million adults with a chronic disease have been found to have multiple chronic diseases (Anderson and Horvath, 2004). In men aged over 60 years, approximately 75% have at least one chronic condition whilst 33% of have two. Each of these chronic diseases is influenced by two or more risk factors and each risk factor is often common to two or more diseases. In Ireland, severe depression is the co-morbidity suffered by 30% of people with cardiovascular disease, cancer or diabetes (Department of Health & Children, 2008).

2.2 Introduction to Altered Glucose States.

Diabetes is a metabolic disorder that is characterised by chronic abnormal blood glucose levels. These result from abnormalities in the metabolism of carbohydrate, protein and lipids. These metabolic abnormalities occur due to an absolute or relative deficiency of insulin secretion, defects in insulin action or a combination of both (Ferrannini, 1998). Pathogenic processes contribute to the development of diabetes and altered glucose states. These include autoimmune destruction of pancreatic β cells and resistance to insulin action (ADA, 2007 a). However, an understanding of normal glucose metabolism is necessary to appreciate the contribution of these pathogenic processes.

2.2.1 Normal Glucose Metabolism.

Normal glucose control depends on the action of insulin, the primary anabolic hormone in the body. Blood glucose control is mediated through the synthesis and secretion of insulin from the pancreatic β cells and its action on target tissues (Pessin and Saltiel, 2000). The release of insulin is dependent on circulating plasma glucose levels and this occurs in a

biphasic pattern (Henquin et al, 2002). In individuals with normal glucose tolerance, blood glucose levels are maintained between 4-7mmols/L. This achieved through a balance between circulating glucose, from ingestion and hepatic output, and glucose uptake in the peripheral tissues (Pessin and Saltiel, 2000). A background or basal rate of insulin is secreted throughout the day and this accounts for approximately 50% of daily secretion. The remaining insulin is secreted in response to elevated plasma glucose levels post-meal (Pessin and Saltiel, 2000). When blood glucose levels drop below 4.0mmols/L insulin release is inhibited however, when blood glucose is elevated such as post-prandially insulin is secreted at half its maximal level (Bhattacharjee et al, 1997).

Plasma glucose enters the pancreatic β cells via glucose transporters (GLUT 2), where it is phosphorlysed and oxidized, generating adenosine diphosphate (ADP) and adenosine triphosphate (ATP). The rise in ATP/ADP ratio closes the ATP sensitive potassium channels and depolarises β cells. Depolarisation of β cells opens the calcium channels and facilitates an influx of calcium into the cells. This increase in intracellular calcium facilitates insulin secretion into the blood (Bhattacharjee et al, 1997). On secretion, insulin binds to specific receptors which are present on the cell membrane of almost all human cells however, hepatocytes, adipocytes and skeletal myocytes have a particular affinity for insulin (Wollheim and Maechler, 2004). The principal physiological glucose lowering effects mediated by insulin includes;

- Stimulation of glucose uptake into cells, particularly skeletal and adipose tissue, through the translocation of GLUT 4 transporters which facilitate glucose entry. In

muscle cells glucose is stored as glycogen or converted to ATP for energy, while it
is stored as fat in adipose tissue (Quinn, 2002).

- Suppression of hepatic glucose production by inhibiting glycogenolysis (glycogen
  breakdown) and gluconeogenesis (formation of glucose from glycerol, lactate and
  amino acids) (Wollheim and Maechler, 2004).

- Suppression of lipolysis and hepatic ketogenesis (Krentz, 2000).

Glucose production in the liver is reduced by the action of insulin. Low levels of insulin
are required to suppress this function and this is reflected during times of basal insulin
secretion between meals or at night. In contrast, times of glucose uptake by skeletal and
adipose tissue, such as post-prandially, require higher levels of insulin release (Williams
and Pickup, 2004).

Blood glucose levels regulate the metabolic action of insulin however, counter regulatory
hormones also assist in maintaining blood glucose regulation in a negative feedback
fashion. Such hormones include glucagon, catecholamines, cortisol and growth hormone.
Glucagon, secreted from pancreatic α cells, and catecholamines are the principal hormones
that protect against or respond to hypoglycaemia. As blood glucose drops below normal
levels the sympathetic nervous system stimulates glucagon release to target its main site of
action, the liver. Glucagon increases hepatic glucose production through glycogenolysis
and gluconeogenesis and decreases glucose uptake by the tissues (Krentz, 2000).

Catecholamines inhibit insulin secretion as part of the autonomic response and facilitate

gluconeogenesis and glycogenolysis in the liver and muscles. In association with this,

insulin resistance is increased while glucose transport into cells is reduced in response to

low glucose levels and through the actions of catecholamines, cortisol and growth

hormones. Cortisol, growth hormone and catecholamines also facilitate proteolysis and

lipolysis to provide amino acids and glycogen for gluconeogenesis. These complex

hormonal interactions between insulin, glucagon, catecholamines, cortisol and growth

hormone maintain blood glucose levels within a tight normal range (Quinn, 2002). It is a

breakdown in the interaction between insulin secretion and insulin action that results in the

development of altered glucose states.

2.2.2 Classification of Altered Glucose States.

Assigning a diagnosis of an altered glucose state is dependent on the stage in the natural

history of the disease at which the individual presents and the symptoms, if any, they

present with. In 1980 the WHO Expert Committee (WHO,1980) categorised diabetes

according to two major classes, insulin dependent diabetes (IDDM) or type 1 diabetes and

non-insulin dependent diabetes (NIDDM) or type 2 diabetes. In 1985 the terms type 1 and

type 2 were removed from the classification (WHO, 1985) and the terms IDDM and

NIDDM were retained. This reflected the clinical requirement or non-requirement for

insulin however, these terms did not reflect the underlying aetiology of diabetes. In both

the 1980 (WHO, 1980) and 1985 (WHO,1985) classifications other types such as

pancreatic, drug induced and gestational diabetes were included with a new classification of

impaired glucose tolerance (IGT). In 1997, the American Diabetes Association (ADA)

further refined the classification system (ADA, 1997) and this adjusted classification was adopted by the WHO in 1999 (WHO, 1999).

The refined ADA (1997) and WHO (1999) classifications considered the underlying aetiology of the disease and the stage in the process of diabetes or other altered glucose categories. The new classification recognised the need to be aware of the underlying aetiology as these processes, such as the presence of islet cell antibodies in normoglycaemic individuals, could indicate potential progression to type 1 diabetes. They also acknowledge that diabetes may progress through many stages in its natural course and this course is independent of its aetiology. The new classification defined varying degrees of hyperglycaemia which can lead to diabetes and occur along a range from normoglycaemia to diabetes. The classification removed the term insulin-dependent and non-insulin dependent and replaced these with type 1 and type 2 diabetes. It also included stages of hyperglycaemia which could progress to diabetes namely, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). This allowed diabetes and the range of hyperglycaemia to be categorised according to clinical presentation and without the need for aetiological evidence. The classification of hyperglycaemia, regardless of the underlying cause, is categorised as;

- Insulin requiring for survival – type 1 diabetes
- Insulin requiring for control/non-insulin requiring – type 2 diabetes
- Not insulin requiring – IFG/IGT (Zimmet et al, 2004).

The most recent WHO/IDF guidelines classifying diabetes and altered glucose states (Appendix 1) retains the 1999 WHO changes and recommends the use of an Oral Glucose Tolerance Test (OGTT), in the absence of unequivocal hyperglycaemia, to determine the exact stage in the hyperglycaemic process (WHO/IDF, 2006).

2.3 Impaired Fasting Glucose and Impaired Glucose Tolerance.

The classification of altered glucose states acknowledges that hyperglycaemia passes through a number of stages which can lead to diabetes. These stages, while reflecting levels of hyperglycaemia that are higher than normal levels, do not meet the criteria for diabetes and are too high to be considered normal (ADA, 2007a). The 1980 and 1985 WHO classifications of diabetes recognised Impaired Glucose Tolerance (IGT) as a stage in the natural history of diabetes. The IGT stage was retained in the updated ADA (1997) and WHO 1999 and WHO/IDF 2006 classifications and a new stage, Impaired Fasting Glucose (IFG) was included. This new stage reflected fasting glucose levels that are higher than normal fasting glucose but not high enough to be classified as diabetes (Zimmet et al, 2004).

2.3.1 Prevalence of Impaired Fasting Glucose and Impaired Glucose Tolerance.

The burden of diabetes is compounded by the number of people with pre-diabetes (IFG and IGT). Currently, 314 million or 8.2% of the global adult population have IGT and this is expected to rise to 472 million or 9.0% by 2025. The prevalence rate of IGT in the EU, in 2003, was estimated at 10.2% (63.2 million) and this is expected to remain relatively unchanged at 10.9% (70.6 million) by 2025 (IDF, 2008).

The DECODE Study Group examined the impact of the revised 1997 ADA diagnostic criteria for the diagnosis of diabetes. They compared the use of the fasting plasma glucose to diagnose IFG and type 2 diabetes against the OGTT. In this study, data was collected from 26,190 participants in 13 European centres. The study showed the prevalence of impaired glucose tolerance (IGT), based on the OGTT results, increased with age in both genders (DECODE Study Group on behalf of the European Diabetes Epidemiology Group, 1998). In individuals aged 30-59 years, the prevalence was < 15% but this increased to between 15 and 30% in those over 60 years. In each age group the prevalence rates were higher in the UK, Polish and Spanish populations however, the highest rates of IGT were recorded among Finnish male and female individuals aged more than 60 years. While the prevalence of IGT was noted to increase linearly with age, a similar pattern was not obvious for impaired fasting glucose (IFG). The prevalence of IFG was higher in males and significantly so among those less than 70 years (DECODE Study Group on behalf of the European Diabetes Epidemiology Group, 1998). The most recent estimates for Ireland suggest that 260,836 individuals have IGT, based on current international prevalence data (Diabetes Federation of Ireland, 2006).

2.3.2 Diagnosis of Impaired Fasting Glucose and Impaired Glucose Tolerance.

The International Diabetes Federation has suggested that IFG and IGT differ in their prevalence, population and gender distribution, and risk of cardiovascular disease (Unwin et al 2002). Both IFG and IGT are generally asymptomatic, with many individuals being normoglycaemic in their daily lives and recording normal or near normal glycated haemoglobin levels (ADA, 2007a). A diagnosis of either IFG or IGT is generally made

following a glucose challenge and this may often be undertaken by a clinician following the diagnosis or detection of a macrovascular complication (Krentz, 2000). The WHO/IDF (2006) recommends the use of the Oral Glucose Tolerance Test (OGTT) as the gold standard test (Appendix 2) for clinical diagnosis of IGT and IFG and for epidemiological purposes. Categorisation is defined according to the WHO/IDF classification guidelines (Appendix 1). In contrast the ADA (2007a) advocates use of fasting plasma glucose as opposed to the OGTT for the diagnosis of IFG and in epidemiological situations. This was mainly recommended due to the difficulties in performing the OGTT in routine clinical practice (Zimmet et al, 2004).

2.3.3 Progression of Impaired Fasting Glucose and Impaired Glucose Tolerance.

While IFG or IGT are not associated with developing microvascular disease similar to individuals with type 2 diabetes (Williams and Pickup, 2004), they both have an increased risk of developing diabetes and cardiovascular disease (CVD). Progression to type 2 diabetes is prevalent in both IFG and IGT however their combined presence is strongly related to the development of diabetes (de Vegt et al, 2001). An increased risk of developing CVD is also associated with IFG and IGT however, this risk appears greater in the presence of IGT (Unwin et al, 2002). These stages of hyperglycaemia are also considered a feature of the metabolic syndrome which includes glucose intolerance, central obesity, hypertension, accelerated atherosclerosis, low high density lipoprotein (HDL) cholesterol and high triglycerides and very low density lipoprotein (vLDL) cholesterol (Reaven, 1988).

Both IGT and IFG are commonly known as "pre-diabetes" but they are not considered clinical (ADA, 2007a) or permanent entities (Krentz, 2000). Some individuals with IGT will revert to normoglycaemia, others will continue to have IGT, while some will progress to type 2 diabetes (Williams and Pickup, 2004). A number of lifestyle interventions have demonstrated the ability to prevent or delay the progression from IGT to type 2 diabetes. These interventions include a 5-10% reduction in body weight (Knowler et al, 2002) and increased physical activity (Toumilehto et al, 2001). Such interventions may have beneficial effects on further CVD and total mortality however, further studies are required to establish such benefits (Zimmet et al, 2004).

2.4 Incidence and Prevalence of Type 1 and 2 Diabetes.

Diabetes is a significant and growing global epidemic and is considered the most common non-communicable disease (International Diabetes Federation (IDF, 2008). Type 1 diabetes accounts for approximately 10% of all diabetes while type 2 diabetes contributes to about 90% of global disease (ADA, 2007a). Social factors such as growing and ageing populations, urbanisation, sedentary lifestyles and increasing obesity are the main factors contributing to the escalation in global diabetes (Wild et al, 2004). These social changes are leading to an exponential growth in the incidence of diabetes. This primarily results from the increase in obesity which is growing among all age groups, particularly in developing countries (WHO, 2008a).

Conservative WHO estimates in 1995 indicated the worldwide prevalence of both type 1 and 2 diabetes was 30 million however, it projected a rise in these rates for all ages (King et

al, 1998). A significant growth has occurred since 1995 with diabetes prevalence estimated at 194 million or 5.1% of adults aged 20-79 in 2003. The IDF suggested these figures would continue to rise dramatically to 6.3% or 333million by 2025 (IDF, 2008). The latest figures from the WHO concur with the IDF (2008) prevalence rates and suggest global diabetes prevalence will increase to 366 million by 2030 (WHO, 2008a). Currently people aged 40-59 years have the highest prevalence of diabetes and in line with trends for an ageing population, it is predicted 146 million 40-59 year olds and 147 million people over 60 will have diabetes by 2025 (IDF, 2008). The WHO suggests India, China and the US will have the highest prevalence of diabetes worldwide. The number of adults with diabetes are expected to rise from 19, 16 and 14 million cases to 57, 37, and 22 million cases in these countries, respectively (King et al, 1998).

2.4.1 Incidence and Prevalence of Type 1 Diabetes

Type 1 diabetes accounts for approximately 10% of all global diabetes (ADA, 2007a). It predominantly occurs in younger age groups with 70,000 children aged 0-14 years expected to develop type 1 diabetes annually (Tuomilehto et al, 1995). It is estimated 440,000 or 0.02% of the global population of children aged 0-14 years have the condition. This prevalence is increasing in both developed and developing countries with this trend more common in younger age groups (IDF, 2008).

A clear variation in the incidence of type 1 diabetes exists between and within populations. The highest rates of type 1 diabetes globally are found in European countries such as Finland, Norway, Sweden, Denmark and United Kingdom. In contrast China has the

lowest incidence of 0.1 per 100,000 of population (IDF, 2008). In the United States (US), incidence rates of 19.0 per 100,000 were reported in 2002-2003 with this highest in non-Hispanic white youths (Centres for Disease Control and Prevention, 2007).

Epidemiological studies of type 1 diabetes in Europe have shown a 10-fold difference between Finland (48.5 per 100,000) and Macedonia (3.4 per 100,000). The incidence of type 1 diabetes has been shown to be generally greater in north European countries with notable exceptions. An incidence rate of 37 per 100,000 was observed in Sardinia and this contrasted significantly with its surrounding countries where the incidence was far less. The occurrence in Sardinia contrasted with mainland Italy, with Sardinia 3-5 times higher than other regions of Italy (5.4 – 11.7 per 100,000) (Green and Patterson, 2001). The variation between these areas of Italy may reflect different genetic susceptibility pools, different or more predominant environmental factors, or a combination of both in the development of type 1 diabetes (Steck and Rewers, 2004).

Current estimates for the island of Ireland state that 0.4% of the population had type 1 diabetes in 2005. This was equivalent to 12,011 cases in the Republic of Ireland and 4,766 in Northern Ireland. While the number of people with type 1 diabetes is expected to rise by 2015 to reach 13.915 and 5,002 cases respectively, the prevalence rate will remain unchanged at 0.4% (The Irish Diabetes Prevalence Working Group, 2007).

2.4.2 Prevalence of Type 2 Diabetes

The most recent prevalence data for the US has shown that more than 24 million

individuals or 8% of the population have type 2 diabetes according to the Centre for

Disease Control and Prevention (CDC). This is an increase of more than 3 million over a

two year period. While this increase was observed in both male and female adults of all

ages, it disproportionately affected older adults, with almost 25% of adults over 60 years

having type 2 diabetes in 2007 (CDC, 2008b). In the US, disparities in prevalence exist

across ethnic groups (Qiao et al, 2004). The highest prevalence rates are noted among

Native American and Alaskan Natives (16.5%) compared to whites (6.6%), who have the

lowest rate (CDC, 2008b).

In the EU 48 million people currently have type 2 diabetes. This reflects a prevalence rate

of 7.9% (IDF, 2008) which is similar to that for North Americans at 8% (CDC, 2008b).

Despite large variations in diabetes prevalence across the EU, an increase is expected in

each state except Estonia by 2030 (WHO, 2008b). The IDF suggests the overall EU

prevalence rate for type 2 diabetes will rise to 9.1% by 2025 (IDF, 2008).

In the EU cohort of the DECODE study, the prevalence of type 2 diabetes was found to

increase with age, up to 70 and 80 years, in both genders. The study found type 2 diabetes

was prevalent in 10% of most populations less than 60 years however, this prevalence

increased to 10-20% in people aged 60-79 years. In this study the prevalence of type 2

diabetes was highest in each age group and both genders in Malta and among elderly

Finnish and Spanish ladies (DECODE Study Group on behalf of the European Diabetes Epidemiology Group, 1998b).

In Ireland the number of people with type 2 diabetes is rising significantly with 2007 estimates for the island of Ireland suggesting 67,000 adults in Northern Ireland (N.I.) and 141,000 in the Republic of Ireland (RoI) had type 2 diabetes in 2005. This reflects prevalence rates of 5.4% and 4.7% respectively. These rates are predicted to increase in both regions by 2015 to at least 193,944 people or 5.6% of population in the RoI and 84,226 (6.3%) in NI, if obesity rates increase in a linear fashion. This rise in prevalence equates to a 37% increase in the RoI by 2015. Should obesity rates increase in an exponential manner, the prevalence of diabetes in the RoI could reach 200,047 or 5.8% of the population (The Irish Diabetes Prevalence Working Group, 2007).

2.4.2.1 Prevalence of Undiagnosed Type 2 Diabetes.

Despite our increasing awareness of the risks and complications associated with altered glucose states, a large proportion of type 2 diabetes, IFG and IGT remains undiagnosed as evidenced in population based studies. The WHO has indicated that the prevalence of undiagnosed diabetes could exceed that of diagnosed diabetes (WHO, 2005).

In a US population study of African-American and white Americans (n=8,286) aged 53-75 years who were screened for altered glucose states using an OGTT and classified according to the WHO guidelines (WHO, 1999), 12% of the population were found to have undiagnosed type 2 diabetes. Furthermore, 32% were newly diagnosed with IGT/IFG.

(Schmidt et al, 2003). The more recent National Health and Nutrition Examination Survey suggested 2.8% of the adult US population have undiagnosed diabetes. Undiagnosed diabetes was found to be higher in males and increased with age, reaching 5.8% in those more than 65 years. Similarly the rate of undiagnosed IFG, which was 26.0%, also to increased with age (Cowie et al, 2006). When compared with the previous National Health and Nutrition Examination Survey (Harris et al, 1998) the prevalence of both undiagnosed diabetes and IFG (2.7% and 24.7%) was found to be unchanged. Determination of these US prevalence rates were based on the ADA guidelines which use fasting plasma glucose and 2 hour plasma glucose for diagnosis of IFG and type 2 diabetes. However, this method has been shown to underestimate the prevalence of type 2 diabetes and does not facilitate a diagnosis of IGT (DECODE Study Group on behalf of the European Diabetes Epidemiology Group, 1998a). Comparison between US rates of undiagnosed diabetes, IFG and IGT with studies using the OGTT for diagnostic purposes is therefore problematic.

In Australia, the population prevalence of undiagnosed type 2 diabetes in people aged more than 25 years, following OGTT, was 3.7% however, this equated to 50% of all those with type 2 diabetes. This study also found that IFG and IGT were undiagnosed in 5.8% and 10.6% of the population respectively (Dunstan et al, 2002).

In the EU a high proportion of undiagnosed altered glucose states have also been shown. In a Danish population based study, 65.6% of those with diabetes were previously undiagnosed. This equated to a prevalence rate of between 0.7% up to 9.7% with men more frequently undiagnosed (Glumer et al, 2003). The DECODE Study Group identified

the prevalence of diagnosed diabetes as 3.7% however, they projected this would increase to 7.2 – 7.7% when undiagnosed diabetes was incorporated (DECODE Study Group on behalf of the European Diabetes Epidemiology Group, 1998a). Similarly a Dutch study of Caucasian individuals, aged 50-74 years (n=2,484), established comparable prevalence rates for undiagnosed type 2 diabetes and IGT. These were found to be 4.8% and 10.3% respectively (Mooy et al, 1995).

The Irish Diabetes Federation suggests 200,000 people have type 2 diabetes with an equal number undiagnosed (Diabetes Federation of Ireland 2009). Two studies have identified high prevalence rates of diagnosed and undiagnosed diabetes and other altered glucose states, in general practice. In one study of patients aged more than 40 years and screened using the OGTT (n=3821), undiagnosed diabetes, IFG and /or IGT was detected in 23.5% and 3.9% of individuals respectively (Smith et al, 2003). These rates of under-diagnosis were consistent with the Cork and Kerry Diabetes and Heart Study which found a 30% underestimation of type 2 diabetes (Creagh et al, 2002).

2.5 Type 1 Diabetes.

Type 1 diabetes is characterised by an absolute insulin deficiency and accounts for approximately 10% of all diabetes. Insulin deficiency in type 1 diabetes is mediated primarily through the autoimmune destruction of pancreatic β cells. Autoimmune destruction is present in almost 90% of new type 1 diabetes (Notkins and Lernmark, 2001) and is the most common form in European children and adolescents (Karvonen et al, 2000). In the remaining 10% of type 1 diabetics, the exact aetiology is unknown and while there is

no clear evidence of autoimmune destruction, strong inherited links have been identified (Biros et al, 2005). This form of type 1 diabetes occurs in a small numbers of Caucasians (Steck and Rewers, 2004) and is more common among those of African and East Asian origin (Krentz, 2000). In this 10% of type 1 diabetics, the absolute need for insulin remains and many are prone to ketoacidosis. The requirement for exogenous insulin in this group is not constant and varies between episodes of ketoacidosis (Banerji and Lebovitz, 1989).

Diagnosis of type 1 diabetes typically occurs between 11-13 years however it can affect older people even up to 80 – 90 years (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). The incidence of type 1 diabetes peaks at ages 2, 4-6 years and 10-14 years, with the principal peak occurring before puberty. In females, the peak onset occurs 1 year before puberty. Approximately 60% of people with type 1 diabetes are diagnosed as adults. The diagnosis of adults with type 1 diabetes diminishes in the 3rd decade however autoimmune type 1 diabetes can present at any age and it's incidence increases again in the 5th to 7th decades (Steck and Rewers, 2004) and even into the 8th and 9th decades (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). In older adults the onset of type 1 diabetes is less dramatic and the requirement for insulin is initially delayed however, the absolute need for insulin remains (Steck and Rewers, 2004).

2.5.1 Onset of Type 1 Diabetes

The majority of type 1 diabetes results from the autoimmune destruction of pancreatic β cells (Notkins and Lernmark, 2001). Its causes are complex and not well understood

however, β cell destruction is probably triggered by environmental factors in people who are genetically predisposed to type 1 diabetes (Biros et al, 2005). In people with auto-antibodies a spontaneous loss of pulsatile insulin secretion and progressive loss of the acute insulin response to increased glucose levels occurs (McCulloch and Palmer, 1991). The occurrence of this preclinical state and the rate of β cell destruction vary in duration but can be present for up to 13 years before diagnosis (Bonifacio et al, 1990).

In type 1 diabetes, β cell destruction occurs at varying rates, developing more rapidly in infants and children and more slowly in adults (Foulis et al, 1986). For many individuals, especially children and adolescents, presentation with ketoacidosis is the first indication of the disease (Pinkey et al, 1994). Diabetic ketoacidosis (DKA) is one of the most serious acute metabolic complications of diabetes and is most common in type 1 diabetes (Chiasson et al, 2003). It is a state of severe uncontrolled diabetes that occurs due to inadequate levels or lack of insulin. When insulin is deficient, increased levels of counter-regulatory hormones stimulate hepatic glucose production through glycogenolysis and gluconeogenesis (Kitabchi and Wall 1995). Reduced insulin levels and elevated counter-regulatory hormones diminish the uptake of glucose in the peripheral tissues. The combination of raised hepatic glucose production and reduced peripheral glucose uptake are the primary causes of hyperglycaemia (Chiasson et al, 2003). In the absence of glucose as a fuel source, lipids are metabolised into triglycerides and free fatty acids and the fatty acids converted to ketone bodies by the liver (Foster, 1983). The accumulation of ketones in association with hyperglycaemia, dehydration and metabolic acidosis are some of the clinical signs of DKA (Krentz, 2000). Failure to treat DKA may precipitate a diabetic

coma or even death (ADA, 2009). Underlying factors which influence the development of

DKA include infection, which occurs in 20-25% of previously undiagnosed type 1 diabetes

(Umpierrez et al, 1996), or inappropriate or inadequate insulin doses (Krentz, 2000). In

2-10% of DKA cases, no precipitating factors are identified (Umpierrez et al, 1996).

Between 20-40% of type 1 diabetics who are less than 20 years old present with

ketoacidosis in industrialised countries (Pinkey et al, 1994). This results from a greater loss

of β cell function in children and adolescents, with children under 7 years presenting with

more severe symptoms as up to 80% of β cell function has been lost compared to a 60%

loss in 7-14 year olds and a 40% in adolescents more than 14 years (Foulis et al, 1986). In

adults, some residual β cell function may be present for a period of time after diagnosis thus

preventing ketoacidosis but these individuals eventually lose the majority of insulin

secretion and require insulin for survival (Bingley et al, 1994). In this group many will

experience a temporary fall in insulin requirements after diagnosis due to improved β cell

function (honeymoon period). This however is transient and these people will eventually

see a gradual or sudden rise in their insulin requirements (Steck and Rewers, 2004).

2.5.2 Clinical Presentation with Type 1 Diabetes.

Presentation with type 1 diabetes varies between patients with 20-40% presenting with

severe symptoms of diabetic ketoacidosis (Pinkey et al, 2004). In people with type 1

diabetes a marked reduction in β cell insulin secretion is evident on presentation (Notkins

and Lernmark, 2001). Insulin deficiency is associated with elevated plasma glucagon and

catecholamines levels although these normalise once insulin treatment is initiated.

Prolonged insulin insufficiency leads to lipolysis and hepatic conversion of fatty acid into ketones. Ketonuria in association with hyperglycaemia is the classic marker of insulin deficiency, as low levels of plasma insulin prevent lipolysis (Krentz, 2000).

Presentation with type 1 diabetes depends on the point reached in the natural course of the disease and for many symptoms will only be present for a number of weeks prior to diagnosis. Weight loss reflects protein and fat catabolism secondary to insulin deficiency and this may be associated with dehydration if hyperglycaemia is excessive.

The following indicates a number of the classic symptoms of type 1 diabetes;

- Thirst
- Polyuria
- Nocturia
- Weight Loss
- Fatigue
- Dehydration

Twenty to forty percent of patients diagnosed with type 1 diabetes present with life threatening ketoacidosis in industrialised countries (Pinkey et al, 1994). This may occur due to the rapid decline in β cell function below the critical level. When exposed to illness such as infections, the limited β cell reserves and insulin output are unable to prevent excessive hyperglycaemia in association with dehydration, acidosis, ketosis and electrolyte imbalance. These patients with diabetic ketoacidosis classically present with some of the following symptoms;

- Polyuria and polydipsia

- Nausea and vomiting

- Dehydration

- Acidotic (Kussmal) respiration and blood acidosis

- Ketosis

- Hyperglycaemia (Krentz, 2000).

2.6 Type 2 Diabetes

Type 2 diabetes is the most common form of diabetes in adults (King et al, 1998) however, its development in younger people is becoming apparent in western countries (WHO, 1999) with the rates among children and young adults increasing (Ludwig and Ebbeling, 2001).

2.6.1 Pathogenesis of Type 2 Diabetes

Type 2 diabetes is commonly undiagnosed for many years as hyperglycaemia develops over time and does not produce classic symptoms during this latent period (Fujimoto et al, 1987). Type 2 diabetes is characterised by the progressive decline of β cell function and increased insulin resistance, for which the pancreatic β cells are unable to compensate (Williams and Pickup, 2004). In type 2 diabetes, individuals are either predominantly insulin resistant with relative insulin deficiency or primarily have an insulin secretion deficiency with insulin resistance (Taylor et al, 1994). The contribution of either irregularity varies between people and as the disease progresses (Ferrannini, 1998).

At diagnosis both insulin resistance and defects in insulin secretion may be present, and this may lead to difficulties in determining the aetiology of type 2 diabetes (Gerich, 1998). In the United Kingdom Prospective Diabetes Study (UKPDS) of type 2 diabetes, β cell

function was reduced by approximately 50% at diagnosis and was found to worsen over time despite treatment (Hales and Barker, 1992). β cell dysfunction is associated with reduced first- and second-phase responses to intravenous insulin (Byrne et al, 1996) and a blunted or delayed response to mixed meals (Taylor et al, 1996). Insulin resistance in its primary target organs, the liver, muscle and adipose tissue, is compensated for initially by increased insulin secretion but this declines in time (Wayburn, 1935).

2.6.2 Insulin Resistance.

Insulin resistance plays a central role in the progression of type 2 diabetes (Williams and Pickup, 2004). Insulin resistance is considered the inability of insulin to generate its normal biological action at effective levels, in normal individuals. It can affect all elements of insulin action, the extent of which varies between and within individuals (Yki-Jarvinen, 2004). Insulin resistance is commonly associated with a cluster of clinical and biochemical features which group together and are commonly known as the "metabolic or insulin resistance syndrome" (Reaven, 1988). These features comprise of central obesity, glucose intolerance (type 2 diabetes or IGT), hypertension, atherosclerosis, decreased high density lipoprotein (HDL) cholesterol and high triglycerides and very low density lipoprotein cholesterol. Low HDL cholesterol and elevated triglyceride levels are distinctive features of type 2 diabetes. Raised levels of pro-coagulant factors such as plasminogen activator inhibitor-1 (PAI-1) and fibrinogen are also associated with the insulin resistance syndrome and increase the risk of atheroma development (Williams and Pickup, 2004). The presence of the insulin resistance syndrome predisposes individuals to a 2-3 fold risk of developing type 2 diabetes, or cardiovascular disease (King et al, 1998).

Insulin resistance develops early in the course of diabetes and occurs several years before symptom development. It occurs primarily in adipose, hepatic and muscle cells secondary to genetic and environmental factors such as physical inactivity, ageing and obesity. As insulin resistance increases, a corresponding rise in insulin production occurs to compensate for increasing hyperglycaemia. Over time, if insulin resistance persists or worsens, β cell function declines due to glucose or lipid toxicity or genetic defects (Guthrie and Guthrie, 2004).

Genetic defects in insulin receptors may also contribute to insulin resistance by preventing insulin attachment at receptor sites and thus cellular reactions within cells. Similarly, genetically mediated enzyme defects can also affect the action of insulin within cells. However, genetic factors are not singularly responsible for the development of type 2 diabetes, environmental factors such as obesity and sedentary lifestyle also contribute (Guthrie and Guthrie, 2004).

2.6.3 Insulin Deficiency.

In type 2 diabetes insulin secretion can be defective and insufficient to overcome insulin resistance (Krentz, 2000). Many patients with type 2 diabetes have normal or elevated insulin levels despite the presence of hyperglycaemia. If normal β cell function were present, individual insulin levels would be higher (Polonsky et al, 1996) however, in type 2 diabetics, β cell function can be reduced by up to 50% at diagnosis (UKPDS Group, 1995).

Insulin deficiency has been shown to become progressively worse as glycaemic control declines (Saad et al, 1989) however, tight control of glucose can enhance insulin secretion (Rosetti et al, 1990). Such observations have indicated that insulin deficiency occurs in part from glucose and lipid toxicity or from a combination of both (Ferrannini, 1998). Hyperglycaemia associated with β cell toxicity damages the β cells resulting in higher glucose levels and worsening β cell function (Robertson et al, 2003). Similarly changes to lipid function, resulting from decreased insulin levels, also effect insulin secretion. Insulin deficiency leads to activation of the enzyme lipase which subsequently breaks down fat into triglycerides, free fatty acids and glycerol (McGarry and Dobbins, 1999). In individuals with intra-abdominal adiposity, triglycerides pass directly into the hepatic system and the pancreas, causing β cells toxicity and leading to loss of β cell mass and function (Guthrie and Guthrie, 2004). The loss of β cell function may progress over time and become irreversible (Robertson et al, 2003). Indeed in such individuals, a substantial number will eventually require treatment to maintain glycaemic control, as identified by the UKPDS study group (UKPDS, 1998a).

2.6.4 Genetic Factors in Type 2 Diabetes

A number of genetic factors involving complex interactions are believed to influence the development of type 2 diabetes (Park, 2004). These insulin-mediated responses include β cell function, insulin secretion and action. Any defect in these processes can interfere with the production and action of insulin (Guthrie and Guthrie, 2004). However, these factors are complex and are not yet clearly understood (Ferrannini,1998). Indeed within this type

of diabetes, both monogenetic and polygenetic forms of the disease have been identified (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003).

A number of monogenic forms of type 2 diabetes have been clearly identified with such genetic defects effecting β cell function. Such monogenic forms of diabetes include Maturity Onset Diabetes of the Young (MODY) (Hitman and Sudagani, 1997). In this form of diabetes, insulin secretion is impaired however there appears to be minimal defect on the action of insulin (Byrne et al, 1996). Mutations at 3 different chromosomal loci have been identified in relation to MODY including mutations to chromosome 12 that relate to hepatocyte nuclear factor (HNF) -1α (Yamagata et al, 1996a). This is considered the most common form (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). Mutations also occur at chromosome 7p. This affects the metabolism of glucose to glucose-6-phosphate due to defects in the glucokinase molecule, and leads to reduced stimulation of insulin secretion by the β cells. Thus the "glucose sensors" on the β cell become impaired and require increased levels of glucose to stimulate normal levels of insulin secretion (Frogruel et al, 1992). A third form of monogenic MODY has been associated with abnormalities in HNF -4α at chromosome 20q. HNF -4α is required to regulate the expression of HNF -1α (Yamagata, 1996b).

Type 2 diabetes is believed to be a complex polygenic disease which interacts with environmental factors (Lyssenko et al, 2008). This has made it more difficult to identify the specific diabetic genes involved in the pathogenesis of the disease (Park, 2004). A number of genes have been identified as potential contributors to the development of type 2

diabetes with TCF7LE (Grant et al, 2006), KCNJ11 (Gloyn et al, 2003) and PPARG (Altshuler et al, 2000) being consistently associated with type 2 diabetes (Lyssenko et al, 2008). Indeed one study found the population-attributable risk associated with developing type 2 diabetes was 21% for those with a defect at TCF7LE (Grant et al, 2006). Similarly, variants in TCF7LE has been associated with an increased risk of progression from impaired glucose tolerance to type 2 diabetes (Florez et al, 2006).

In addition to genetic factors the development of type 2 diabetes is influenced by a number of environmental factors (Nolan et al, 2006). Obesity (Mokdad et al, 2003) and sedentary lifestyles (Helmrich et al, 1991) are particularly culpable, with obesity associated with a degree of insulin resistance and hyperinsulinaemia (Colditz et al, 1990). Not all obese individuals will develop type 2 diabetes. Only those that are genetically predisposed and have central obesity appear at risk (Guthrie and Guthrie, 2004).

2.6.5 Presentation with Type 2 Diabetes.

Presentation and diagnosis with new type 2 diabetes often occurs at a late stage of a long, pathological process (Krentz, 2000). Many individuals may have hyperglycaemia which does not produce classic symptoms for a number of years before diagnosis however, this hyperglycaemia carries a high risk of insidious tissue damage (Harris, 1992). In the UKPDS study, the researchers found the level of tissue damage in individuals with type 2 diabetes correlated closely with the glycated haemoglobin levels at diagnosis (UKPDS, 1998a).

Individuals present with new type 2 diabetes at various points along the natural course of the disease. The symptoms they exhibit on presentation are based on their stage in the disease process and these symptoms can range from having no symptoms to those associated with emergency hyperglycaemic states such as hyperosmolar non-ketotic syndrome (Table 1). Some of the common symptoms associated with new type 2 diabetes, although these may not be pronounced, are osmotic symptoms such as thirst, polyuria, nocturia and fatigue. Unlike new type 1 diabetics however, weight loss is not as aggressive and is generally not present. The absence of weight loss in people presenting with new type 2 diabetes reflects adequate endogenous insulin secretion reserves which prevent lipid and protein catabolism and therefore weight loss (Krentz, 2000).

Table 1: Presenting Signs and Symptoms in Type 2 Diabetes Mellitus

Presenting Signs and Symptoms in Type 2 Diabetes Mellitus
None – asymptomatic individuals identified by screening
Osmotic symptoms • Thirst • Polyuria • Nocturia • Blurred Vision • Fatigue/Lassitude
Infection • Recurrent Fungal infection • Recurrent bacterial infection
Macrovascular complications • Coronary artery disease (angina pectoris, acute myocardial infarction) • Cerebrovascular disease (transient ischaemic episodes, stroke) • Peripheral vascular disease (intermittent claudication, rest pain, ischaemic ulceration)
Microvascular complications • Retinopathy (acute or progressive visual impairment) • Nephropathy (proteinuria, hypertension, nephrotic syndrome) • Neuropathy (symptomatic sensory polyneuropathy, foot ulceration, amyotrophy, cranial nerve palsies, peripheral mononeuropathies, entrapment neuropathies)
Associated Conditions • Glaucoma • Cataracts
Hyperosmolar Non-Ketotic Syndrome • Marked Hyperglycaemia - usually greater than 50mmols/L • Profound dehydration with pre renal uraemia • Coma (Adapted from: Krentz, 2000).

2.6.6 Diagnosis of Type 2 Diabetes.

The diagnosis of an altered glucose state requires that an unequivocal elevation in plasma glucose be demonstrated (Krentz, 2000). A number of methods have been proposed to facilitate the diagnosis of altered glucose states namely, fasting plasma glucose, the Oral Glucose Tolerance Test and Glycosylated Haemoglobin A1c (HbA1c). Current consensus guidelines on diagnostic criteria have been adopted by the WHO/IDF (2006) and the ADA (2006) using some of these methods.

Fasting plasma glucose has been shown to be both sensitive and specific in its ability to diagnose both impaired fasting glucose and type 2 diabetes (Englelgau et al, 2000). It has been adopted by the ADA as its diagnostic tool due its convenience, reproducibility and being less costly to administer compared to the OGTT (WHO/IDF, 2006). Comparisons between fasting plasma glucose and the OGTT have demonstrated that these tests diagnose different people with diabetes. In one study, fasting plasma glucose alone, failed to diagnose 30% of people with diabetes (DECODE Study Group on behalf of the European Diabetes Epidemiology Study Group, 1998a). This has also been shown in a study of older adults where 48% of males and 70% of females were diagnosed with diabetes solely by 2-hour plasma glucose (Barrett-Connor et al, 1998). In addition, fasting plasma glucose is unable to diagnose IGT, this can only be diagnosed using the OGTT (WHO/IDF, 2006).

The use of HbA1c to diagnose diabetes has also been proposed. HbA1c has been shown to have a similar association with the incidence and prevalence of long term diabetes complications when compared to fasting and 2 hour plasma glucose concentrations, and

thus is considered a measure of glycaemia that could be used to diagnose diabetes (McCrane et al, 1994). HbA1c measurement is influenced by anaemia, abnormal haemoglobin, pregnancy and uraemia. The effect of these on HbA1c results varies. This effect is dependent on the laboratory test method used (Goldstein et al, 2004). Also while standardisation of the HbA1c test has begun (ADA, 2006), the current lack of a standardised test along with its biological variations (Kilpatrick et al, 1998) has prevented it's as a diagnostic tool (WHO/IDF, 2006).

In the absence of definitive hyperglycaemia either fasting plasma glucose or an OGTT can be performed to diagnose diabetes and IFG however, to determine IGT in individuals, an OGTT must be performed.

2.6.6.1 The Oral Glucose Tolerance Test.

The Oral Glucose Tolerance Test is considered the gold standard test for establishing a diagnosis of type 2 diabetes or altered glucose states. It examines the body's ability to metabolise glucose following a glucose challenge and provides evidence of undiagnosed diabetes and other glucose states such as IGT and IFG. The WHO/IDF guidelines recommend its retention as a diagnostic test on the following grounds:

- Fasting plasma glucose alone fails to diagnose approximately 30% of cases of previously undiagnosed diabetes
- The OGTT is the only means of identifying people with IGT
- The OGTT is frequently needed to confirm or exclude an abnormal glucose tolerance in asymptomatic people

The WHO/IDF guidelines on the diagnosis and classification of diabetes and altered glucose states also recommended an OGTT be carried out on individuals with a fasting plasma glucose of 6.1– 6.9mmol/l, to determine their glucose tolerance status The standard procedure for performing an OGTT is defined by the WHO and IDF guidelines (WHO/IDF, 2006), (Appendix 2).

The OGTT is affected by intercurrent illnesses such as major surgery, myocardial infarction, stroke, infections, malabsorption and drugs (steroids, thiazides, phenytoin, oestrogens, thyroxine), stress, nausea, caffeine and smoking. Therefore a final diagnosis of diabetes should not be confirmed by a single 2 h post-load glucose value, the result should be validated over subsequent days unless the person is symptomatic and the plasma glucose is unequivocally elevated (WHO/IDF, 2006). The results of an OGTT are interpreted according to the WHO/IDF recommendations for the diagnosis of Diabetes and Intermediate Hyperglycaemia (WHO/IDF, 2006), (Appendix 1).

2.7 Environmental Factors and Type 2 Diabetes.

Type 2 diabetes is most prevalent in metropolitan areas resulting from social deprivation, unemployment and poverty, in addition to diabetes related lifestyle factors, such as obesity, a westernised diet and decreased physical activity (WHO, 2005). The risk of developing type 2 diabetes is indeed increased by age, physical inactivity and obesity (Nolan et al, 2006). The prevalence of obesity is rising exponentially worldwide and this is predicted to significantly impact on the global diabetes epidemic (WHO, 2005).

2.7.1 Obesity and Altered Glucose States.

A significant rise in the prevalence of overweight and obesity has occurred globally, with a similar increase demonstrated in national data for Ireland (Irish Universities Nutrition Alliance, 2001). Obesity is the sixth most important risk factor for chronic disease globally (Haslam and James, 2005) and is significantly affecting the rise in rates in diabetes, hypertension and hyperlipidaemia (Mokdad et al, 2003). The escalating prevalence of diabetes has been closely linked to increased obesity levels. Approximately two-thirds of individuals with diabetes are obese (Shakher and Barnett, 2004). Obesity is a strong indicator for the development of diabetes, with the prevalence of diabetes is 3-7 fold in obese individuals compared to those of normal weight (Mokdad et al, 2003).

The value of anthropological measurements, such as body mass index (BMI), Waist-Hip-Ratio (WHR) and waist circumference, has been considered in determining the association between obesity and diabetes risk (Carey et al, 1997). In women with type 2 diabetes, WHR is 4.6 times more likely to be in the highest than the lowest tertile (Kaye et al, 1991). Waist-hip-ratio has also been shown to be an independent risk maker for predicting the development of type 2 diabetes. One study found the development of diabetes could be predicted in individuals in the top 5% of WHR and in the top 20% of waist circumference (Chan et al, 1994). In the Nurses' Health Study, WHR was also found to be predictive of type 2 diabetes however, both BMI and waist circumference alone were more highly predictive (Carey et al, 1997). The Nurses' Health Study also demonstrated a 5-fold risk of developing diabetes in women with a BMI > 25kg/m^2 compared to a BMI of 22 kg/m^2.

This risk was significantly increased to 28 and 93-fold in women with class 1 and 11 obesity (Appendix 3) (Colditz et al. 1990).

The development of impaired glucose tolerance, which affects 197 million individuals globally, has also been attributed to excess weight and the metabolic syndrome (Hossain et al, 2007). Overweight and obese individuals are predisposed to the clustering of metabolic risk factors, known as the metabolic syndrome. These factors include impaired glucose tolerance, diabetes, hypertension and dyslipidaemia (raised triglycerides, low HDLc and elevated LDLc) (Reaven, 1988).

The excess intake of calories leads to visceral adiposity and increases the risk of developing glucose intolerance and diabetes. This is principally mediated through the effects on insulin action and metabolism (Kopleman and Hitman, 1998). Obesity is associated with increased insulin resistance with the incidence of insulin resistance increasing as BMI levels rise (Colditz et al, 1990). Many studies have demonstrated the beneficial effects of weight reduction, in particular visceral weight loss, in improving insulin sensitivity (Lebovitz, 2003). Moderate weight loss of 5% - 10% has been shown to improve insulin action (McCauley et al, 2002) and reduce fasting glycaemic levels (Williams and Kelly, 2000). However, those with long-standing diabetes and β cell dysfunction do not achieve the same beneficial effects as those with less extensive disease (Klein et al, 2004). Moderate weight loss has also been shown to prevent or delay the development of diabetes from impaired glucose tolerance. The Finnish Diabetes Prevention Study investigated the impact of lifestyle interventions, including diet and exercise modifications, on the

prevention of diabetes in individuals with IGT. This study found that such interventions

reduced the development of diabetes in overweight (BMI > $25kg/m^2$), middle aged (40-64

years) individuals with IGT by 58% (Toumilehto et al, 2001). In a similar study, the

Diabetes Prevention Programme in the US found increased physical activity reduced

weight by 7% and decreased the 4-year incidence of type 2 diabetes by 58% in individuals

with IGT (Knowler et al, 2002).

The accumulation of adipose tissue is thought to be influenced by neuronal (Kreier et al,

2002) and hormonal factors (Stefan et al, 2001). These alter the levels of carbohydrate,

fatty acid and adipocyte derived factors such as tumour necrosis factor (TNF), leptin,

adiponectin and resistin. They also affect the distribution and metabolism of adipose tissue.

The distribution of body fat is also a factor in the development of diabetes, glucose

intolerance and atherosclerosis. Central obesity which is the accumulation of abdominal

fat, principally subcutaneous and omental fat has been shown to impact on mortality

(McTernan and Kumar, 2004). It is considered an independent risk factor for the

development of diabetes mellitus (Ohlson et al, 1985) and cardiovascular disease (Larsson

et al, 1984).

2.7.2. Physical Activity and Altered Glucose States.

Physical activity is considered an essential component in the prevention and treatment of

type 2 diabetes. A number of studies have highlighted the benefits of exercise in

preventing type 2 diabetes and maintaining glycaemic control. In a US study, an inverse

relationship between energy expenditure during leisure time activity and progression to

type 2 diabetes was identified. Indeed this study found a 6% reduction in the incidence of type 2 diabetes for every 500 kcal expended through exercise each week (Helmrich et al, 1991). Similarly, a study of women aged 39-54 years, who exercised vigorously at least once a week, found a significant reduction in the risk of developing type 2 diabetes compared to those who exercised less vigorously and less frequently. It also found that the protective effect of physical activity was not influenced by weight and BMI (Manson et al, 1991). The Physicians' Health Study among males aged 40 – 84 years confirmed a relationship between frequency and vigorous exercise. It found the age adjusted relative-risk of developing type 2 diabetes was reduced as exercise frequency increased, with the relative risk of type 2 diabetes 0.77 for once weekly exercise, 0.62 for two to four times weekly and 0.58 for exercise at least five times a week (Manson et al, 1992). Although the greatest risk of developing type 2 diabetes was thought to occur in individuals who were the least physically active, recent evidence from the Women's Health Study contrasted with this. This study showed that an elevated BMI was a more significant risk factor for type 2 diabetes than decreased physical activity levels (Weinstein et al, 2004).

The ability of increased exercise levels to prevent or reduce the progression of IGT to type 2 diabetes has been shown in a number of studies. The Finnish Diabetes Study of overweight, middle-aged men (Toumilehto et al, 2001) and the Da Qing Study of lean Chinese participants (Pan et al, 1997) identified a 58% and 41-46% reduction in the progression from IGT to type 2 diabetes in these respective studies. The US Diabetes Prevention Programme also found increased physical activity reduced weight by 7% and

decreased the 4-year incidence of type 2 diabetes by 58% in individuals with IGT (Knowler et al, 2002).

While the beneficial effects of lifestyle interventions on reducing the progression to diabetes have been demonstrated in these short term studies (average follow-up 2.8 – 6 years), achieving these benefits required considerable effort from trained staff. In addition those who encountered difficulty in meeting the study weight loss and exercise goals were given counselling and incentives to assist in meeting their targets. Having considered the targets for each study, which were 5% weight reduction and 150 min/week of moderate exercise in the Finnish Diabetes Prevention Study (Toumilehto et al, 2001) and 7% weight reduction and 150 min/week of moderate self-reported exercise in the Diabetes Prevention Programme (Knowler et al, 2002), only 43% and 50% of participants achieved the weight loss targets and 36% and 74% achieved the exercise goals in these respective studies.

The benefits of lifestyle interventions have not been confirmed by long-term studies. Achieving and maintaining lifestyle intervention targets is difficult and many individuals regain any weight loss (Jeffery et al, 2000). Over time individuals often fail to persist with the lifestyle changes that have been made because the lifestyle change itself is no longer positively viewed or the benefits of the change are no longer considered an adequate reward (Jeffrey et al, 2004).

Despite the difficulties encountered by individuals in achieving and maintaining lifestyle changes, recent updates from the Da Qing Study group have demonstrated the benefits of

any lifestyle changes extend beyond the intervention period. They have found diabetes can be prevented or delayed for up to 14 years after the intervention has ceased (Li et al, 2008). This reflected similar findings from follow up of participants in the Finnish Diabetes Prevention Study. Again it was found that the benefits of lifestyle interventions, in people with IGT, were sustained and the reduction in diabetes incidence was maintained after the individual lifestyle counselling had stopped (Lindstrom et al, 2006).

2.8 Healthcare Costs of Chronic Disease.

The increased prevalence of chronic diseases, which are predicted to escalate, has placed an enormous financial burden on healthcare systems globally (Wild et al, 2004) due in part to the need for strategies to detect, manage and prevent diseases (ADA, 2003). Chronic diseases such as cardiovascular disease, cancer and diabetes are among the most prevalent, preventable and costly chronic conditions (CDC, 2008a). Costs associated with chronic disease can be classified as either direct or indirect, with direct costs related to the resources used to treat the condition (medical care) and indirect costs resulting from consequences of the disease (loss of production and premature death) (Triomphe et al, 1993).

Individuals with chronic diseases disproportionately access and use healthcare. The escalation in chronic disease, in recent decades, has led to a significant rise in the cost of direct healthcare for such diseases. In 1997, the direct cost of chronic care in the US was estimated at $272.2 billion dollars. In this year, 76% of total US healthcare expenditure was used by the 46% of people who reported having a chronic disease (Hoffman et al, 1996). In 2005, 133 million people in the US had at least one chronic disease with the cost

of care for these individuals accounting for more than 75% of the nation's $2 trillion healthcare bill (ADA, 2007b). One of the principal contributors to the increased prevalence of chronic disease is obesity which currently accounts for 16% of the global disease burden. In 2001, obesity accounted for $123 billion in direct and indirect costs in the US alone (Hossain et al, 2007).

In the UK, eight chronic diseases have been recorded in the top 11 causes of hospital admissions, with 42% of all acute bed days used by the 5% of patients with long-term or chronic conditions. In Ireland an estimated 75% of healthcare spending is required to manage chronic disease. The majority of this cost results from GP visits (80%) and avoidable inpatient hospital admissions (60%) to manage a chronic disease or its complications. It is estimated that chronic diseases represent 75% of all emergency admissions to hospitals in Ireland (IDF, 2005).

2.9 Financial Cost of Diabetes and Altered Glucose States.

Diabetes is a chronic disease which places an enormous financial burden on global healthcare systems. This burden results from the costs associated with the management and treatment of the disease and its complications. Individuals with diabetes are significant users of healthcare services which provide assistance with the management of glycaemia and diabetes risk factors (Rubin et al, 1994). These people have a higher incidence of hypertension and dyslipidaemia (Stamler et al, 1993) and have an increased risk of developing macrovascular and microvascular complications. These factors significantly increase the risk of morbidity and mortality which in turn impact on healthcare resources

(Morrish et al, 2001). As a result, healthcare costs for people with diabetes have been estimated to be 2-3 times higher than the average cost of healthcare for the entire population (Rubin et al, 1994).

Data from the International Diabetes Federation (IDF) estimated the annual direct cost of diabetes care globally, for individuals aged 20-79 years, was at least 153 billion international dollars (Appendix 4). This figure is now believed to be an underestimate. Revised projections suggest diabetes care costs will reach 213 to 396 billion by 2025, if the prevalence of diabetes escalates as expected. Should the prevalence of diabetes rise as anticipated, 7% to13% of the global healthcare budget will be required to provide diabetes healthcare (IDF, 2005).

2.9.1 Cost of Diabetes in North and Latin America.

In the US the direct cost of diabetes care was estimated at $44.1 billion dollars (USD) in 1998 with the treatment of complications accounting for 27% of this expenditure (ADA, 1998). By 2002 the direct cost had doubled to $91.8 billion and included $23.2 billion for general diabetes care and $24.6 billion to treat complications. Hospitalisation was the most significant contributor to expenditure requiring 43.9% of the total cost of diabetes care (ADA, 2003). More recent data demonstrated the financial requirement for diabetes care rose vastly by 2007 to $174 billion. This reflected the increased prevalence of diabetes and its associated lifestyle factors such as obesity. Again, the ADA found the treatment of diabetic complications, which amounted to $58 billion, was the principal contributor to diabetes related expenditure (ADA, 2007b).

Similar increases in the cost of diabetes care have been experienced by the Canadian healthcare system. The economic impact of the whole diabetes epidemic and its complications were estimated at $9 billion Canadian dollars in 1999, based on data extrapolated by the Canadian Diabetes Association (Health Canada, 1999). The direct cost of care was estimated as $2.6 billion or 8% of total medical expenditure in1998 (Dawson et al, 2002). In the Saskatchewan study of 38,124 Canadian individuals with diabetes (3.6% of population), the cost of diabetes care was estimated based on service usage data and expenditure data for medication, physician services, hospitalisation, day care, cardiovascular, renal and ophthalmic services. The study found the cost of diabetes care was $134.3 million, which equated to 15% of the total expenditure for hospitalisation care, physician care and medication. This established the most significant contributor to diabetes expenditure was the management of co-morbidities which required 36.4% of diabetes related spending. Hospitalisation to treat cardiovascular, renal and ophthalmic complications accrued costs of $35.5 million (26.4%), $10 million (7.5%) and $3.3 million (2.5%) respectively (Simpson et al, 2003). These costs compared to those reported from a study of a managed care programme in the US, which reported 33.9% of total diabetes expenditure was required to treat the complications of diabetes (Selby et al, 1997)

In Latin-American countries and the Caribbean, many people have limited access to healthcare and in these countries the indirect costs of diabetes care exceeds those for direct care. Recent data suggested the total cost of diabetes care was $65,216 million US dollars with direct and indirect costs accounting for $10,721 and $54,496 million respectively. Of the direct costs, $1,012 million was required to support hospital care with the treatment of

complications requiring $2,480 million dollars. This reflects the similar pattern of diabetes expenditure which has occurred in developed countries, where the principal sources of direct diabetes costs are hospitalisation and the treatment of complications (Barcelo et al, 2003).

2.9.2 Cost of Diabetes in Europe.

In Europe, the CODE-2 study investigated the cost of type 2 diabetes in 8 countries. This study estimated the direct cost of diabetes care was €29 billion, in 1999, with this accounting for up to 6% of total healthcare spending in some countries. Approximately 53% of this expenditure related to inpatient care. As with other global estimates, the CODE-2 study found the enormous costs associated with diabetes care were primarily due to the management of the preventable complications of type 2 diabetes (Jonsson, 2002). In the UK, the cost of direct diabetes care amounted to 4-5% of the total health budget (Laing and Williams, 1989).

Recent estimates of the total cost of direct care for type 2 diabetes in Ireland have indicated that €377.2 million was required to treat diagnosed diabetes (Nolan et al, 2006) based on a prevalence rate of 3.9%. This estimated cost corresponded to 4.1% of public healthcare spending in 2003. This data is likely to underestimate the true prevalence and cost of diabetes in Ireland as evidence suggests the rate of undiagnosed diabetes equals that of diagnosed diabetes (WHO, 2003b). Using a prevalence estimate of 6%, which included both diagnosed and undiagnosed diabetes, the CODEIRE study proposed the true cost of direct diabetes care would rise to €580.2 million or 6.4% of Irish healthcare expenditure

(Nolan et al, 2006). Consistent with other studies (Jonsson, 2002, ADA, 2003), CODEIRE identified inpatient care as the single biggest contributor to diabetes related healthcare costs. The study found 60% of people with diabetes in Ireland developed complications. Hospitalisation costs accounted for 48% of overall diabetes expenditure with the treatment of diabetes related complications the predominant reason for inpatient care. This study also noted the presence of microvascular or macrovascular complications, increased the cost of treatment 1.8 and 2.9 fold respectively (Nolan et al, 2006).

Individuals with diabetes require inpatient care more frequently, with the total cost of this care per capita almost twice that of people without diabetes (ADA, 1998). In healthcare, the majority of care and costs are attributed to a small proportion of patients. In a US study of Medicare diabetes patients, 56% of total diabetes costs were consumed by the top 10% diabetic recipients of Medicare expenses (Krop et al, 1998). Olveira-Fuster et al (2004) found that people with diabetes accounted for 13.8% of total hospital stays and 14.1% of total hospitalisation expenditure. They noted 58.3% of these costs were directly related to the presence of diabetes and in particular, to the management of acute or chronic complications. One contributing factor to the total costs of diabetes care is the incidence of multiple hospitalisations. A review of hospitalisation data for 648,748 diabetics, found 30% of patients with diabetes were admitted on two or more occasions. Although only 30% of individuals had multiple admissions, these individuals accounted for 55% of all hospitalisations and 54% of all hospital expenses. The cost of care per patient requiring multiple admissions is 3 times that needed to treat single stay patients ($23,119 vs. $8,508) (Jiang et al, 2003).

Evidence clearly indicates the principal contributor to the considerable and rising costs of diabetes healthcare is hospitalisation for the treatment of diabetes complications. Escalating costs are a major driving force behind the re-examination of current prevalence data, service usage and service provision, by healthcare planners. Unequivocal evidence demonstrates that maintaining glycaemic levels at normal or near-normal levels in type 1 and type 2 diabetes (The Diabetes Control and Complications Trial Research Group, 1993 & United Kingdom Prospective Diabetes Study, 1998a), in addition to control of blood pressure (United Kingdom Prospective Diabetes Study, 1998b), is effective in delaying or preventing the development of microvascular (eye, kidney, nerve) complications of diabetes. Policy development to institute preventative treatment programmes could facilitate future reductions in the financial burden of diabetes. This could be achieved particularly through the treatment of complications and could avert some hospital admission costs for already struggling healthcare systems (IDF, 2005).

2.10 Hospitalisation for Diabetes Related Care.

Hospitalisation to treat the complications of diabetes is the principal source of the rising healthcare costs of diabetes care. Individuals with diabetes have an enormous requirement for healthcare and healthcare resources to manage the disease and its co-morbidities (Ahern and Hendryx, 2007). Hospitalisation in these patients is common with the rate of admission increasing with age. The presence of co-morbidities in patients with diabetes generates a disproportionate use of hospital resources in this group (Olveira-Fuster et al, 2004).

A large volume of evidence is available to support the notion that hospitalisation costs for diabetes related care places the most significant drain on healthcare resources (Moss et al, 1999). A Spanish study of hospitalisation costs found that 60% of all avoidable diabetes expenditure related to acute or chronic complications in particular, cardiovascular complications (Olveira-Fuster et al, 2004). This study may be of limited relevance in the Irish setting due to the contribution of diet and lifestyle factors to the development of diabetes complications in this Spanish population (Buzina et al, 1991) however, the CODEIRE study also demonstrated that inpatient care, to treat macrovascular and microvascular complications of diabetes, were the most significant contributor to the cost of diabetes care in Ireland (Nolan et al, 2006).

Many episodes of diabetes inpatient care are avoidable (Ahern and Hendryx, 2007). A modest reduction in hospitalisation rates, through the identification of those at high risk of admission and the modification of risk factors in these individuals, could achieve substantial reductions in the cost of diabetes care (Moss et al, 1999). A UK study, comparing hospital admission rates between individuals with type 1 and 2 diabetes and the non-diabetic population, found 0.64% of those admitted to hospital had a diagnosis of type 1 diabetes and 5.4% had type 2 diabetes during a year-long study. These admission rates suggested 25% of the total diabetic population in the study region (n=7,735) were hospitalised at least annually (Donnan et al, 2000). This corresponded with previous data, reported in a US study, of hospital admissions rates for insulin requiring patients. This study found 25.5% and 30.8% of people with diabetes, diagnosed before and after age 30 respectively, were hospitalised at least once annually. However, this study also highlighted

that 31% of those diagnosed before 30 years and 37% diagnosed after 30 years required

multiple admissions annually to manage diabetes related complications (Moss et al, 1999).

2.10.1 Complications of Diabetes Requiring Hospital Admission.

Analysis of admission records, to determine primary admission diagnosis in both type 1

and 2 diabetics, has shown cardiovascular disease (CVD) is the largest contributor to

hospital admissions. In type 2 diabetes, CVD has accounted for 27% of admissions

compared to 12% in the general population (Donnan et al, 2000). In individuals diagnosed

with diabetes before age 30, hypertension has a higher odds ratio for hospitalisation (Moss

et al, 1999). Jiang et al support this, having found hypertension, ischaemic heart disease

and heart failure were the most common cardiovascular co-morbidities, with each requiring

multiple admissions. They also noted that 40% of multiple adult hospital admissions were

attributed to lower limb disease (Jiang et al, 2003).

Hospitalisation, for the treatment of heart failure in type 2 diabetes, has been shown to be a

major contributor to the requirement of hospital care (Aksnes et al, 2007). The risk of

hospitalisation for the treatment of heart failure is two-fold in patients with type 2 diabetes

(Davis et al, 2006). In the UK, heart failure has been shown to be responsible for

approximately 5% of all medical admissions (Smooke et al, 2005).

Individuals with type 2 diabetes also have a higher incidence of neurological admissions

(6%) compared to the general population, while renal complications are more prevalent in

type 1 diabetics primarily due to renal failure. Both type 1 and type 2 diabetics have higher

admission rates for ophthalmic complications (24% and 15% respectively) compared to non-diabetic patients (4.1%) with treatment for cataracts being the most common ophthalmic complication requiring hospitalisation in type 2 diabetes (Donnan et al, 2000).

Factors predictive of hospital admission in both type 1 and type 2 diabetes include elevated glycosylated haemoglobin (Moss et al, 1999). A recent US study of individuals admitted with a primary diagnosis of type 1 or 2 diabetes (n = 97,526) confirmed the contribution of uncontrolled diabetes to hospitalisation rates. Ahern and Hendryx found that 36% of individuals with diabetes were admitted with an avoidable short-term complication (ketoacidosis, hyperosmolarity, hypoglycaemic coma) or uncontrolled diabetes. Of these admissions 25.7% were associated with short-term conditions while 10.5% related to uncontrolled diabetes. They found 68.7% of all hospital admissions which were related to avoidable complications, occurred in people with type 2 diabetes (Ahern and Hendryx, 2007).

Diabetes is a chronic disease which is invariably associated with the development of long-term complications (Williams and Pickup, 2004). Hospitalisation to treat these complications places a substantial burden on all healthcare resources (Rubin et al, 1994). Many episodes of inpatient care to treat diabetes complications are avoidable (Ahern and Hendryx, 2007).

The inextricable links between microvascular and macrovascular disease has been clearly demonstrated in both type 1 and type 2 diabetes. The benefits of tight blood glucose

control, in reducing the microvascular complications of type 1 and type 2 diabetes, has been well documented (The Diabetes Control and Complications Trial Research Group, 1993 & United Kingdom Prospective Diabetes Study Group, 1998a) however, a comparable benefit has been less well defined for all macrovascular diseases (United Kingdom Prospective Diabetes Study Group, 1998a). Macrovascular disease, which includes coronary heart, cerebrovascular and peripheral vascular disease (Williams and Pickup, 2004), is responsible for an enormous proportion of morbidity and mortality associated with diabetes and altered glucose states (Krentz, 2005). The following section will outline the increased morbidity and mortality related to macrovascular complications in people with altered glucose states and their requirement for hospitalisation care to treat and manage these complications.

2.11 Macrovascular Disease and Altered Glucose States.

An elevated risk of atherosclerotic cardiovascular disease (CVD) exists in people with diabetes and this is responsible for the majority of diabetes related serious illness (Haffner et al 1998). The presence of type 1 diabetes, type 2 diabetes, IFG or IGT imparts a significantly higher risk of developing atheroma affecting the coronary, cerebral and peripheral arterial vasculature (Beckmann et al, 2002).

The Multiple Risk Factor Intervention Trial (MRFIT) of 35,000 men established that people with diabetes are not only at a higher risk of CVD but the condition is also more aggressive in diabetes patients (Stamler et al, 1993). The UKPDS study demonstrated a relationship between elevated glycaemic levels and the risk of macrovascular disease, in type 2 diabetes (United Kingdom Prospective Diabetes Study Group, 1998a) while the

DCCT also identified a similar association in type 1 diabetes (The Diabetes Control and Complications Trial Research Group, 1993). However, despite the associations demonstrated in the UKPDS and the DCCT trials and the overall ability of intensive glycaemic control to reduce all cardiovascular events by 41% in the DCCT (The Diabetes Control and Complications Trial Research Group, 1993) and the risk of MI by 16% in the UKPDS study (United Kingdom Prospective Diabetes Study Group, 1998a), neither trial established a significant reduction in macrovascular events. Thus, the presence and aggressive nature of diabetes ensures its vascular complications are enormous challenges in relation to the management and treatment of diabetes and IGT (Gray and Yudkin, 2002).

2.11.1 Epidemiology, CVD and Altered Glucose States.

CVD is a principal source of morbidity and mortality in diabetics (ADA, 2006). It has been shown to confer a 2-4 fold risk of Coronary Heart Disease (CHD), Cerebrovascular Accident (CVA) and Peripheral Vascular Disease (PVD) in those with type 1 and 2 diabetes (Haffner, et al, 1998). The MRFIT study confirmed this identifying a three-fold risk from all CVD in type 2 diabetes with the specific risk of CHD, CVA and other CVD increased by 3.2, 2.8 and 2.3 respectively (Stamler et al, 1993).

Studies are now indicating that diabetes confers a major risk of CVD mortality (Haffner et al, 1998). Atherosclerosis is thought to account for a 30% reduction in life expectancy in diabetic patients in the UK. Type 2 diabetes is associated with a 2-5% risk of fatal and non-fatal cardiovascular events (Beckmann et al, 2002). Evidence has suggested that overall CVD mortality has declined in the general population in the US (Gu et al, 1999), UK

(Stephenson et al, 1992) and Ireland (Department of Health & Children, 1999) in recent years however, a similar reduction in diabetes related CVD mortality has not been seen, in fact it has escalated (Gu et al, 1999, Department of Health & Children, 1999). An increased risk of CVD mortality has also been identified in type 1 diabetes. Evidence suggests 35% of type 1 diabetics die from CVD (Gray and Yudkin, 2002).

Individuals with IGT are also exposed to an increased risk of CVD mortality. IGT increases the risk of CVD, CHD and all cause mortality however, this risk is not extended to those with IFG thereby suggesting IFG and IGT do not carry similar CVD prognosis (Mykkanen et al, 1992). In the DECODE study higher rates of CVD and all cause mortality were noted in individuals with diabetes or IGT but this was not evident in those with IFG or normoglycaemia. Of note, the largest number of absolute CVD deaths occurred in those with IFG and normal glucose levels. They also found the age-standardised mortality from all causes was higher in males across all glucose ranges, particularly the normoglycaemic range. This increase in deaths in normoglycaemic individuals reduced the relative risk of CVD mortality among diabetic males. It also emphasised the impact of classical risk factors on male CVD mortality in comparison to altered glucose states alone (DECODE Study Group, 2001).

2.11.2 Coronary Heart Disease and Altered Glucose States.

The contribution of CHD to mortality rates in those with diabetes is enormous (Gray and Yudkin, 2002). Coronary heart disease is a term which covers a number of clinical manifestations of heart disease and includes unstable angina, Non ST Elevation Myocardial

Infarction (NSTEMI), myocardial infarction, heart failure and sudden death (Gray and Yudkin, 2002). Coronary Heart Disease has been shown to account for up to 50% of all diabetes deaths (Morrish et al, 1990). In the sixteen-year follow up of the MRFIT study, CHD was the principal cause of death amongst black and white males with type 2 diabetes, with this equating to 31% and 44% mortality respectively (DECODE Study Group, 1998b). A number of studies have confirmed the 2-5 fold risk of CHD mortality in type 2 diabetes (Fuller et al, 1980, Lotufo et al, 2001) and have demonstrated the age-adjusted risk of CHD mortality was 2-4 times higher in diabetics than their non- diabetic counterparts (Stengard, 1992).

Unstable angina and NSTEMI are the two conditions that encompass the term Acute Coronary Syndrome (ACS). In those with type 2 diabetes the signs and symptoms of angina are similar to non-diabetics however, presentation with painless myocardial infarction is more common in diabetics (Gray and Yudkin, 2002). Recent studies of patients with ACS (n=2786) found no difference in the frequency of atypical symptoms between diabetic and non-diabetic individuals (Mudespacher et al, 2007) however, the prevalence of asymptomatic myocardial ischemia and infarction was greater in the diabetic population. In diabetic individuals 10-20% presented with a silent MI compared to 1-4% in the non-diabetic population (Janand-Delenne et al,1999). Some authors have suggested the lack of ischemic pain in diabetics was due to autonomic neuropathy which led to sensory denervation and differing pain sensitivity levels but there is little evidence to support this theory (Gray and Yudkin, 2002).

Acute coronary syndrome is also associated with poorer outcomes in diabetics compared to non-diabetics. In one study, the 2 year relative risk for MI was 1.44 and was 1.84 for death. This study also noted a 27% increased mortality rate in diabetics was independently related to diabetes (Malmberg et al, 2000).

2.11.3 Coronary Artery Disease.

Diabetics have a 2-4 fold risk of developing CAD (Feskens and Kromhout, 1992) however, the tendency toward increased CVD mortality is more apparent in females where mortality rates have increased (Barrett-Connor et al, 2004, Kanaya et al, 2002). The Rancho Bernardo study demonstrated the absolute risk of developing CAD in diabetics was similar in both genders however, they found an elevated relative risk of CAD in females (Barrett-Connor et al, 1991). The DECODE Study confirmed a higher mortality for women with diabetes from all causes, but they found this was only statistically significant in CHD (DECODE Study Group, 2001). This suggested the CVD protection normally afforded to pre-menopausal females was negated in the presence of type 2 diabetes (Barrett-Connor et al, 2004) however, this loss has also been associated with the presence of other classic CVD risk factors such as hypertension, cholesterol and smoking (Kanaya et al, 2002).

2.11.4 Myocardial Infarction.

Diabetes is the principal risk factor associated with myocardial infarction (MI) (Yusuf et al, 2004). In patients admitted to hospital following acute myocardial infarction and screened for diabetes, the prevalence of altered glucose states was 66%, with 35% diagnosed with IGT and 31% with diabetes (Norhammer et al, 2002). The high prevalence of altered

glucose states in people with stable and unstable CAD was confirmed by the Euro Heart Survey (n = 4961) where 31% had known diabetes while 12% and 25% were newly diagnosed with diabetes and IGT (Bartnik et al, 2004). In a 7 year population based study, the incidence of first MI in diabetics was 20% compared to 3.5% in non-diabetics. In this study a history of previous MI was found to increase the incidence of recurrent MI or CVD death by 45% in diabetics as opposed to 18.8% in normoglycaemic individuals. This confirmed that diabetics with no previous CVD had an equal risk of MI and CVD event as those with a previously diagnosed MI and no diabetes (Haffner et al, 1998).

Recent data demonstrates a poorer outcome post MI (Mukamal et al, 2001) in those with newly diagnosed type 2 diabetes or IGT compared to non-diabetics (Bartnik, et al, 2004). Diabetes influences the risk of re-infarction (Malmberg et al, 1999) with the risk of fatal/non-fatal MI significantly increased in those with diabetes and a previous MI (Haffner et al, 1998). Mortality rates in diabetics following MI are twice that for their non-diabetic counterparts (Otter et al, 2004). In-hospital data demonstrated a 10% mortality rate among diabetic individuals post MI compared to 5% in non-diabetics (Mudespacher et al, 2007). These outcomes are similar following percutaneous coronary intervention (Laskey et al, 2002) or coronary artery bypass grafting (Krentz et al, 2005). Mortality post MI is elevated in the immediate (Mudespacher et al, 2007) and long-term course of the condition mainly due to increased heart failure and cardiogenic shock (Gray and Yudkin, 2002).

2.11.5 Cerebrovascular Disease and Diabetes.

Cerebrovascular disease covers a number of clinical conditions, including reversible transient ischaemic attack (TIA) and established Cerebrovascular accident (CVA)/stroke with its long-term neurological deficits (Gray, 2002). It is a major health concern with significant associated mortality and morbidity. The risk of CVA is increased in altered glucose states with population studies identifying a higher prevalence of CVA in individuals with known diabetes (Davis et al, 1999), IGT, and undiagnosed diabetes (Bell, 1994). As a proven risk factor, diabetes confers a 2-4 fold risk of CVA over normoglycaemic individuals (McGuire et al, 2000, Beckman et al, 2002). The MRFIT study identified a similar 3 fold risk of CVA in participants treated with anti-diabetic medications (Stamler et al, 1993) with this considerably greater in patients less than 55 (You et al, 1997).

Evidence of an increased stroke risk has also been demonstrated in association with IGT (Gray et al, 2004) and IFG (Kernan et al, 2005). One recent study identified a 50% prevalence rate for IGT or diabetes in patients with a previous CVA or TIA (Kernan et al, 2005). Another study (n=238) investigating glucose metabolism following haemorrhagic or ischaemic stroke found 20.2% of patients had known diabetes. They also identified new type 2 diabetes in 16.4%, IGT in 23.1% and IFG in 0.8% of participants (Matz et al, 2006).

Cerebrovascular accident is the second largest cause of mortality in type 2 diabetes (Krentz et al, 2005) and is also a major contributor to CVA morbidity (Levetan, 2004). The risk of CVA mortality is 2-4 fold in people with type 2 diabetes (Bell, 1994). It also appears that

women have a higher risk of mortality post CVA than males with mortality rates 16% in diabetic men and 33% in diabetic women in one Finnish study (Toumilehto et al, 1996). This increased risk of CVA mortality in women was also confirmed by the DECODE study group (DECODE Study Group, 2001). Similarly, admission hyperglycaemia has been found to be an independent risk marker for poorer outcomes following CVA. It was associated with increased mortality, particularly death within the first month, higher morbidity, impaired long-term recovery and increased length of hospital stay (Levetan, 2004). Those with IGT and diabetes have also been found to have more severe strokes, a more complicated recovery course and were more prone to infections (Matz et al, 2006).

2.11.6 Heart Failure and Diabetes.

A strong and independent relationship has been identified between heart failure and diabetes (Masoudi and Inzucchi, 2007). The Framingham study identified this association more than 3 decades ago and found diabetics had a higher incidence of heart failure than non-diabetics (Haffner, et al, 1998). Recent data from the UKPDS study of type 2 diabetes established a direct association between HbA1c and the risk of heart failure. It indicated a 12% increased risk of heart failure for each 1% increase in HbA1c (Stratton et al, 2000).

Prevalence data has demonstrated that diabetes was present in 7.7 – 44% of individuals with heart failure. In the US, 44% of patients admitted to hospital with heart failure were found to have diabetes (Adams et al, 2005) with a similar rate (42%) identified in a study of patients (n=48,612) hospitalised with new or worsening heart failure (Greenberg et al, 2007). In contrast, much lower rates have been identified in a retrospective analysis of

health maintenance organisation records (n=19,000). In this study, prevalence rates of heart failure were 11.8% and 4.5% in those with and without diabetes (Nichols et al, 2001). Comparable rates of heart failure have been observed in a community based prospective screening sub-study (n=1062) in the UK with definitive heart failure diagnosed in 2.3% of all participants however, this increased to 7.7% in the diabetic group (Davis et al, 2002).

Diabetes has been shown to confer poorer outcomes in those with established heart failure. A recent study of diabetes treatment and outcome in patients with advanced heart failure (n=554) found survival rates worse for insulin treated patients (78.5%) at year 1 compared to non-insulin treated (85.8%) and non-diabetic patients (89.7%). By year 2, a narrowing of survival rates was evident between both insulin treated and non-insulin treated diabetics. The rates of survival at year 2 were 62.6% and 66.7% for insulin treated and non-insulin treated diabetics however, these rates were significantly poorer than those for non-diabetic individuals (85.5%) (Smooke et al, 2005). The increase in mortality in individuals with heart failure and diabetes has been shown to be independent of age, gender, ejection fraction, comorbidities and creatinine clearance (From et al, 2006) however, the duration of diabetes does appear to enhance this risk of morbidity (Shindler et al, 1996).

2.12 Summary and Conclusion.

Chronic conditions such as diabetes mellitus and altered glucose states are the most significant public healthcare challenge facing countries, worldwide (Walshe and Smith, 2002). Type 2 diabetes is by far the most prevalent form of diabetes mellitus and accounts for approximately 90% of global cases, with type 1 diabetes prevalent in the region of 10%.

The prevalence of these conditions has risen dramatically in recent years, with the WHO predicting a further increase in the global prevalence of diabetes mellitus to 49.7 million by 2020 (WHO, 2008b).

This rise in diabetes prevalence is primarily attributed to type 2 diabetes which is now believed to have reached epidemic levels (Nolan et al, 2006). In addition to type 1 and 2 diabetes, other altered glucose states such as IGT, add significantly to the burden of chronic diseases. The current prevalence of IGT is 8.2% of the global population and this is expected to rise to 9.0% by 2025 (IDF, 2008). While IGT is not considered a disease state, it is classified as an intermediate hyperglycaemia and a stage in the progression to type 2 diabetes (WHO/IDF, 2006). The diagnosis of IGT is associated with an increased risk of developing cardiovascular disease (de Vegt et al, 2001).

Social factors such as an ageing population, reduced physical activity levels and changing dietary patterns, which have led to an exponential growth in obesity levels, are the principal contributors to the escalation in type 2 diabetes (WHO/FAO, 2003). Type 2 diabetes is characterised by progressive β cell dysfunction (Saad et al, 1989) and insulin resistance (Taylor et al, 1996). Insulin resistance plays a central role in the development of type 2 diabetes and is frequently associated with a cluster of factors known as the metabolic or insulin resistance syndrome (Reaven,1988) and comprises of factors such as; central obesity, hyperlipidaemia, hypertension, accelerated atherosclerosis and glucose intolerance (Williams and Pickup, 2004). The presence of the metabolic syndrome confers a 2-3 fold risk of developing type 2 diabetes or cardiovascular disease (King et al, 1998).

In type 2 diabetes insulin secretion can be defective or insufficient to overcome insulin resistance (Krentz, 2000). Many patients with type 2 diabetes have normal or elevated insulin levels despite the presence of hyperglycaemia. If normal β cell function was present, individual insulin levels would be higher (Polonsky et al, 1996) however, in type 2 diabetics, β cell function can be reduced by up to 50% at diagnosis (UKPDS Group, 1995). Insulin deficiency has been shown to become progressively worse as glycaemic control declines (Saad et al, 1989) however, tight control of glucose can enhance insulin secretion (Rosetti et al, 1990).

Obesity is the sixth most important risk factor for chronic disease globally (Haslam and James, 2005) and has significantly influenced the rise in rates in diabetes, hypertension and hyperlipidaemia (Mokdad et al, 2003). A clear association between IGT (Hossain et al, 2007), type 2 diabetes (Mokdad et al, 2003) and obesity has been demonstrated. Obese individuals have a 3-7 fold risk of developing type 2 diabetes, while approximately 66% of people with diabetes are obese (Shakher and Barnett, 2004). Obesity, particularly visceral adiposity, is associated with increased insulin resistance and this worsens as obesity levels rise (Colditz et al, 1990). Similarly, physical inactivity is also indicated in the development of type 2 diabetes. While the exercise mechanisms that prevent the development of type 2 diabetes are not yet clearly understood, improved insulin sensitivity is believed to contribute (Bjorntorp and Rosmond, 1999).

Weight reduction (Toumilehto et al, 2001) and increased physical activity (Weinstein et al, 2004) has significant benefits for individuals and can prevent the development of type 2

diabetes. Comparable results have also been demonstrated in people with IGT, with

lifestyle interventions shown to delay or prevent the progression from IGT to type 2

diabetes (Knowler et al, 2002). No long-term studies have confirmed the benefits of

lifestyle interventions as individuals frequently give up the change (Jeffrey et al, 2004).

However, follow up of participants in the Da Quing and the Finnish Diabetes Prevention

Study found the benefits of lifestyle interventions, in delaying the progression to type 2

diabetes, were sustained in individuals with IGT for up to 14 years after the intervention

had ceased (Li et al, 2008, Lindstrom et al 2006).

Diabetes like all other chronic conditions is a significant contributor to global morbidity

and mortality. In 2002, it was responsible for 1.7% (n=987,000) of deaths worldwide. This

figure probably underestimates the true contribution of diabetes to global morbidity and

mortality, as many deaths which are due to diabetes, have a complication of diabetes

recorded as their cause of death (WHO, 2005). In terms of morbidity, chronic conditions

such as type 2 diabetes carry a lifelong burden for patients. Diabetes is a lifelong condition

that requires long-term monitoring of the condition by the individual and their medical

team, and may necessitate recurrent hospital admissions to treat and manage the

complications associated with the disease (Lewis and Dixon, 2001).

The cost of treating diabetes and its associated complications places an enormous burden

on healthcare resources (Wild et al, 2004). Individuals with diabetes are significant users

of healthcare services to manage glycaemia and diabetes risk factors. This results in

healthcare costs for people with diabetes being 2-3 times higher than the average for the

entire population (Rubin et al, 1994). Unequivocal evidence indicates the most significant contributor to the cost of healthcare in diabetes patients is hospitalisation costs, to treat and manage the complications of diabetes (Nolan et al, 2006).

Limited evidence is available of the extent to which individuals with diabetes access hospital care and the prevalence of altered glucose states among acute hospital admissions. Available data shows that individuals with diabetes complications disproportionately access hospital care and this increases with age (Hoffman et al, 1996). Those who do require care, need treatment for avoidable acute complications such as ketoacidosis or hypoglycaemia (Ahern and Hendryx, 2007), or long-term complications. Long-term complications can be categorised as microvascular and macrovascular diseases. An elevated risk of cardiovascular disease exists in diabetes, IFG and IGT (Beckmann et al, 2002). In both type 1 and type 2 diabetes, cardiovascular disease is the single biggest contributor to hospital admissions (Donnan et al, 2000). The presence of any cardiovascular complication is associated with increased morbidity and mortality in these people (Morrish et al, 2001).

Many episodes of hospital care to treat and manage the complications of diabetes are avoidable and a reduction in these admissions could be achieved by targeting high risk cases and treating modifiable risk factors such as weight loss (Toumilehto et al, 2001) and increased physical activity (Weinstein et al, 2004). This strategy could also attain a substantial reduction in diabetes related costs (Moss et al, 1999). Indisputable evidence demonstrates that maintaining glycaemic levels at normal or near-normal levels, in type 1 and type 2 diabetes (The Diabetes Control and Complications Trial Research Group, 1993

& United Kingdom Prospective Diabetes Study Group, 1998a), in addition to control of blood pressure (United Kingdom Prospective Diabetes Study Group, 1998b), is effective in delaying or preventing the development of diabetes complications. Identifying individuals at high risk of developing an altered glucose state and implementing strategies to prevent the development of complications and the need hospital care to treat such conditions, could reduce avoidable hospital admissions and the significant costs associated with managing complications, at a time of challenging financial healthcare resources.

Chapter 3.

Research Methodology

3.1 Introduction.

The purpose of this research study is to provide comprehensive prevalence data for diabetes and altered glucose states among acutely unwell adults admitted to a regional hospital in Ireland. In this chapter the research methodology is described in terms of, the design chosen to measure disease occurrence, ethical issues, research sample, data collection and data analysis.

3.2 Research Methodology.

A quantitative research method was used to examine the prevalence of altered glucose states amongst acute hospital admissions. This method allowed the researcher to collect observable data which could be statistically analysed. It also allowed general tendencies in this population to be evaluated and its specific features to be identified.

3.3 Epidemiology and Disease Measurement.

Prior to the selection of an appropriate research design, it was essential that the researcher had an awareness of the underlying principles of epidemiology and the indicators available to measure disease occurrence. The following section will outline the role of epidemiology in relation to the current research study and the instruments available to measure disease frequency.

3.3.1 Epidemiology.

Epidemiology is a study of the determinants (aetiology), distribution and risk factors associated with disease in human populations (Bowling, 2002). The two central elements in epidemiology are to try to establish "*who is developing a disease, where and when*" and "*why they are developing it?*" (Webb et al, 2005). Epidemiology facilitates the examination of environmental and other risk factors that contribute to disease development and the frequency of disease occurrence (Bowling, 2002). It also allows variations in the geographical distribution of diseases and characteristics of individuals affected by a specific disease, to be identified (Barker et al, 1998). Patterns reflecting the frequency of exposure over specific time periods can also be examined.

3.3.2 Disease Measurement.

To accurately measure the frequency of a disease, a clear definition of the disease or diagnosis under investigation is required. A diagnosis can be made using a number of markers such as; subjective symptoms reported by the individual, signs or objective indicators observed by the clinician, or using clinical tests and reference ranges. These can be used either alone or in combination (Webb et al, 2005). Once a diagnosis is clearly defined, the determinants and frequency of a disease can be precisely measured (Silman and Macfarlane, 2002). A clearly defined set of signs and symptoms for type 1 and type 2 diabetes are available (Appendix 6 & 7) along with the OGTT (Appendix 2) and the WHO/IDF (2006) diagnostic criteria for diabetes and intermediate hyperglycaemia (Appendix 1). The use of these clearly defined signs and symptoms, clinical test and diagnostic reference ranges can facilitate the precise diagnosis of altered glucose states and the accurate measurement of their occurrence, in this study population.

3.3.3 Disease Measurement Indicators.

The two measurement indicators used to reflect the frequency of disease occurrence are incidence and prevalence. The frequency measure used in a particular study depends on the nature of the disease under investigation (Silman and Macfarlane, 2002).

3.3.3.1 Incidence Rates.

Incidence, refers to the number of new cases of a disease, that occurs in a defined time period. It reflects the number of people who are newly diagnosed with the disease in a particular timeframe and how quickly these individuals are developing the disease (Webb et al, 2005). The incidence of a disease does not consider the size of the population under investigation, so comparisons between populations are problematic. For this reason the calculation of the incidence rate is generally used. This allows the incidence of a disease to be divided by the population from which it is drawn. Incidence rates are usually expressed as a multiple (e.g. 1000, 10000) to facilitate interpretation and comparison between populations.

Incidence rates are calculated as follows;

$$\text{Incidence Rate} = \frac{\text{Number of people newly diagnosed with a disease in specific timeframe}}{\text{Average Number of people in the population in the timeframe}}$$

(Silman and Macfarlane, 2002).

3.3.3.2 Prevalence Rates.

The prevalence of a disease reflects the number of people in a population who have the disease or attribute under investigation. Prevalence rates are calculated in a similar manner to incidence and are also recorded as multiples of the population (e.g. 1000, 10,000).

Prevalence is used to record the proportion of people with the disease or attribute at a specific point in time. It preferentially identifies chronic disease states and reflects the status of individuals living with the disease at particular points, in a specified timeframe. All those who have the disease are deemed to be in the disease state on "prevalence day". Prevalence is therefore sometimes referred to as point prevalence, giving a "snapshot" of the problem at a particular point in time (Silman and Macfarlane, 2002).

Other approaches used to document prevalence rates include period prevalence. Period prevalence is more complex than point prevalence, as it captures both the prevalence and incidence of the disease during the timeframe (Webb et al, 2005). It accounts for situations where the clinical manifestation of the disease varies within individuals. In such cases, the person may have the condition, but may not be suffering from it at the specific point in time, for example those suffering from migraine (Silman and Macfarlane, 2002).

Cumulative prevalence records all individuals who have had a particular disease at any point in their lives or between two specific time points (e.g. 40-70years). This includes those diseases with a variable natural history. It captures illnesses where an individual has had a single resolved episode at some point prior to the survey, and also those who are in the disease state at the time of the survey. Cumulative prevalence is a similar measure to cumulative incidence and should record the same individuals. They differ in that cumulative incidence allows all individuals who developed the disease during their lives, or within the specified timeframe and who subsequently died, to be recorded, while cumulative prevalence retrospectively analyses only those who are alive (Silman and Macfarlane, 2002).

Prevalence rates are calculated as follows;

$$\text{Prevalence Rate} = \frac{\text{Number of people with the disease at a given point in time}}{\text{Total Number of people in the population}}$$

(Webb et al, 2005).

Prevalence rates are affected by factors such as; changes in the duration of the disease under investigation, an increase in incidence rates will subsequently raise prevalence rates, and the requirement for a clear definition of the disease under investigation. Prevalence rates are not an adequate measure to ascertain the underlying factors effecting disease occurrence however, it is a valuable tool to assess disease frequency. It is particularly important when describing the overall burden of a disease in a population and to provide evidence for policy makers of population healthcare needs (Webb et al, 2005).

The choice of disease measurement used in this study was determined following consideration of the characteristics of the disease. Type 1 diabetes generally has a clearly defined onset and is a chronic state that requires long-term management. Similarly, type 2 diabetes is a chronic state, with a gradual and less well defined onset, which also requires long-term management (Williams and Pickup, 2004). IFG and IGT are considered stages in the natural history of type 2 diabetes. People who have these states, have a strong risk of progression to type 2 diabetes. They also have an increased risk of developing other chronic diseases such as CVD (Unwin et al, 2002). In each of these cases, point prevalence is considered an appropriate measure of disease occurrence.

The purpose of this study was to record the proportion of adults with altered glucose states, admitted acutely to hospital in a specific timeframe. It also intended to provide data for

healthcare planners regarding the extent to which altered glucose states influence the health of people admitted to hospital, the requirement for inpatient care for this population and to estimate the financial cost of healthcare provision. The most appropriate measurement of disease occurrence, which considered both newly diagnosed cases and previously diagnosed cases of altered glucose states, was point prevalence, and so this was the method chosen for measuring disease occurrence in this study.

3.4 Research Design.

A non-experimental, descriptive research design was chosen for this prevalence survey, as it facilitates the description of population characteristics or prevalence rates (Polit and Beck, 2004). A descriptive research design allows naturally occurring phenomena to be observed, explored and described in their natural setting (Silman and Macfarlane, 2002). This design can be used to identify the distribution of health states, the prevalence of a disease and the characteristics of a group under investigation (Bowling, 2002).

The survey method is commonly used to measure phenomena in descriptive research. It can disclose information about the attitudes, opinions and trends of a population including prevalence data (Webb et al, 2005). A descriptive or cross-sectional survey collects data regarding the phenomena of interest, at one point in time in a cross section of a population. Such surveys are used to study the cause of disease, to screen for previously undiagnosed cases, and to describe the burden of a disease in a population (Barker et al, 1998). A cross-sectional survey is considered an appropriate method for counting prevalence or rates of chronic conditions, in a given population (Bowling, 2002). The cross-sectional survey approach is also practical and economical however, it does allow changes in disease

patterns, which occur over time, to be examined (Polit and Beck, 2004). The terms cross-sectional survey and prevalence survey are interchangeable terms which are used to describe this type of survey. This study did not seek to examine changes in disease patterns rather, the intention of the study was to establish the prevalence of altered glucose states amongst acute hospital admissions therefore, a cross-sectional survey was an appropriate approach to achieve the aims of this research.

3.5 Gaining Access to the Research Setting.

This study was conducted in Waterford Regional Hospital in the Republic of Ireland. This is a general hospital serving the Waterford community and defined areas of south Kilkenny and Tipperary. It is also a regional referral centre for specialist services in the South East - Health Services Executive. The research was carried out through the Endocrinology Department of Waterford Regional Hospital. A request was made to the Endocrinology Department for access to data relating to acute hospital admissions, under the care of the Consultant Physician, during the study period. This approval was granted by the Endocrinology Department. This access allowed the researcher to attend routine and post on-call ward rounds, to access the Consultant Physician computerised inpatient lists, and to review patient medical records to verify the accuracy of documented diagnosis' and blood test results.

3.6 Research Population.

The study sample was derived from the total number of patients admitted to hospital between June 1st 2005 and December 17th 2006 under the care of an adult Consultant Physician. This consultant was one of eight adult Consultant Physicians who equally

shared a scheduled on-call rota in Waterford Regional Hospital in the Republic of Ireland. Data from hospital inpatient admissions data show that the study population admitted to this hospital was similar to those located in other urban areas, during the timeframe of this prevalence survey (Hospital Inpatient Enquiry, 2009).The sample drawn was an unselected sample of the total population however, the purpose of this study was to gather local hospital admissions data associated with altered glucose states and was not designed to allow the extrapolation of prevalence rates to the general population.

The study population was drawn from a review of local hospital admission data for all consecutive patients, admitted under the care of the Consultant Physician. The Consultant inpatient list is a computerised hospital printout of all admissions under the care of a specified Consultant and provides a comprehensive, accurate and legal record of all patients under their medical care. The researcher attended each routine and post on-call ward round to ensure the inpatient list accurately recorded all patients under the care of the Consultant Physician between June 1st 2005 and December 17th 2006.

The complete Consultant Physician inpatient list was reviewed to identify patients meeting the inclusion criteria for this study, including those with new or previously diagnosed type 1 diabetes, known type 2 diabetes, IFG or IGT. The list provided clinical information regarding patient past medical history and current admission episode. It was used to identify individuals with a known diagnosis of an altered glucose state and those who were screened for an altered glucose state as part of their routine clinical care or within the

Origin International, Multicentre, Randomised Controlled Trial (Population Health Research Institute, 2004).

As part of routine clinical patient care, only individuals who were considered high risk based on their previous or current medical admission history were screened for an altered glucose state. Such opportunistic screening of high risk cases is recommended where the opportunity presents itself such as hospital or general practice contact (WHO/IDF, 2006) however, the routine screening of every person admitted to hospital is not performed due to the lack of resources and financial constraints. Therefore in this admission cohort, only people who had a history or a new diagnosis of a diabetes complication or risk factor (Appendix 5 & 8) were considered a high risk case. It was these individuals who were screened for an altered glucose state as part of their routine clinical care. Similarly those people screened within the Origin International Trial were high risk cases with a history or new diagnosis of cardiovascular disease, a cardiovascular complication of diabetes or cardiovascular risk factors. The aim of the Origin Study was to evaluate the effect of insulin Glargine versus standard care, and Omega 3 fatty acids versus placebo, in reducing cardiovascular morbidity and mortality in patients with IFG, IGT and type 2 diabetes (Population Health Research Institute, 2004). Individuals with a positive screen test result and those with a known altered glucose state, who met the inclusion criteria for this study, were included in the numerator of this prevalence survey (Appendix 9).

The denominator for the study was provided by calculating the total number of consecutive patients admitted to the hospital, under the care of the adult Consultant Physician, in the study time period. Every individual admitted to hospital under the care of the Consultant

Physician and recorded on the accurate Physician inpatient list, was counted once for an admission episode.

3.6.1 Criteria for Inclusion and Exclusion from the Study Numerator.

Inclusion Criteria:

- ➢ Unselected sample of all consecutive individuals admitted under the care of a specified adult Consultant Physician to Waterford Regional Hospital between June 1st 2005 to December 17th 2006
- ➢ 18 years or older
- ➢ Male or Female
- ➢ Previous diagnosis of type 1 diabetes based on patient self report and existing medical records from a previous admission to Waterford Regional Hospital, to include diagnosis, test results and treatments.
- ➢ Previous diagnosis of IFG, IGT and type 2 diabetes based on existing medical records from a previous admission to Waterford Regional Hospital, test results, prescribed treatment strategies and screening associated with participation in the Origin International Multicentre Trial.
- ➢ New diagnosis of type 1 diabetes based on physiological symptoms on presentation, routine screening of fasting plasma glucose and blood gas analysis during current hospital admission.
- ➢ New diagnosis of IFG, IGT and type 2 diabetes based on screening of high risk individuals with an OGTT during this admission. High risk individuals screened included those with clinical evidence or a history of a diabetes complications (Macrovascular or Microvascular disease - Appendix 5) or risk factors for altered glucose states (obesity, hypertension, hyperlipidaemia - Appendix 8).
- ➢ New diagnosis of overt type 2 diabetes based on physiological symptoms on presentation and routine screening of random blood glucose during this admission. Overt type 2 diabetes is recorded when two random plasma glucose levels are elevated > 11.1 mmols/litre (WHO/IDF, 2006).

Exclusion Criteria:

- ➢ < 18 years

  In Ireland individuals who are less than 18 years are often managed under the care of a Consultant Paediatrician therefore, any cases less than 18 years who were admitted in this study cohort were excluded from the analysis as they did not represent the standard patient admitted under the care of an adult physician. It is therefore likely that the diagnosis of new type 1 diabetes in people who were greater than 18 years in this study, will under-represent the true prevalence of type 1 diabetes.

- ➢ Endocrinopathy   –   Acromegaly

  Cushing's Disease

  Hyperthyroidism

  Phaeochromocytoma

3.7 Data Collection.

The purpose of this study was to identify the prevalence of type 1 and type 2 diabetes, impaired glucose tolerance (IGT), and impaired fasting glucose (IFG) in acute hospital admissions. This required the identification of cases with both known and newly diagnosed type 1 and 2 diabetes, IFG and IGT.

Data was obtained using a researcher administered pro-forma (Appendix 8) to collect demographic data such as age and gender, new or a previous diagnosis of an altered glucose state and evidence of a microvascular or macrovascular complication (Appendix 5), or risk factors associated with an altered glucose state.

Data on known and newly diagnosed altered glucose states were captured from documented evidence in medical records and/or following review of previously documented laboratory

results. Participants were not required to undergo any diagnostic or invasive tests for this prevalence survey, results of screening tests undertaken previously as part of routine clinical care or associated with participation in the Origin International Multicentre Trial were recorded to classify new diagnoses. Demographic data including age and gender and information regarding the patient's medical history, in terms of microvascular and macrovascular complications, were recorded from the patient medical records based on previous medical evidence and treatment of such complications. Confirmation of a diagnosis was based on agreed criteria including;

- Documented physical examination and test results

- Agreed criteria set out by the investigator and drawn from contemporary records, such as medical records are considered the most ideal source of information to accurately verify cases (Silman and Macfarlane, 2002).

3.7.1 Previously Diagnosed Altered Glucose States.

Previously diagnosed type 1 or type 2 Diabetes, IFG and IGT was recorded following confirmation of the diagnosis in the following manner:

➢ Documented evidence of the diagnosis and its treatment by medication, diet and exercise recorded in the patient's medical records.

➢ Review of previously recorded laboratory results for random blood glucose, blood gas analysis or Oral Glucose Tolerance Test results, and validation of altered glucose states using the WHO/IDF diagnostic criteria for diabetes and intermediate hyperglycaemia (WHO/IDF, 2006).

3.7.2 Newly Diagnosed Altered Glucose States.

New cases of type 1 diabetes were recorded from patient medical records. Diagnosis of new cases was based on the presence of standard physiological signs and symptoms for type 1 diabetes or ketoacidosis (Appendix 6), review of venous blood glucose and blood gas analysis.

Individuals newly diagnosed with type 2 diabetes, IFG or IFG were identified and classified following;

> ➢ Random plasma glucose tests undertaken during screening and as part of routine clinical care, plus or minus the standard signs and symptoms present in people with type 2 diabetes (Appendix 7), were used to identify overt type 2 diabetes. Overt type 2 diabetes is recorded when two random venous blood glucose levels are elevated > 11.1 mmols/litre (WHO/IDF, 2006).
> ➢ Oral Glucose Tolerance Test (OGTT) results for those screened at Waterford Regional Hospital for type 2 diabetes, IFG and IGT.

3.7.2.1 Standard Procedure for the Oral Glucose Tolerance Test.

The Oral Glucose Tolerance Test is the standardised diagnostic instrument used to diagnose type 2 diabetes, IFG and IGT and is performed in the following manner in Waterford Regional Hospital.

1. The OGTT is carried out on individuals during hospital admission.
2. All individuals are fasting for 12 hours from the night prior to the test.
3. Medication is held on the morning prior to test.
4. Smoking and exercise are not permitted prior to and during the test.
5. A standardised glucose drink (Polycal 120mls) containing an oral glucose load of 75g is administered to adults over 5 minutes.
6. Plasma glucose samples are taken:

- Immediately prior to ingestion of the 75g glucose load (Polycal 120mls)
- 2 hours (120 minutes) post glucose challenge (WHO/IDF, 2006).

The researcher was aware that the OGTT could be affected by intercurrent illnesses such as major surgery, myocardial infarction, stroke, infections, malabsorption or other factors such as drugs (steroids, thiazides, phenytoin, oestrogens, thyroxine), stress, nausea, caffeine and smoking. The WHO/IDF recommends that a final clinical diagnosis of diabetes should not be confirmed by a single 2 hour, post-load glucose value, but that this result should be validated over subsequent days, unless the person is symptomatic and the plasma glucose is unequivocally elevated (WHO/IDF, 2006). In epidemiological surveys, such as a prevalence survey, a single analysis of the OGTT it deemed appropriate for diagnostic purposes (Barker et al, 1998).

3.7.2.2 Analysis of Venous Blood Samples.

Random plasma glucose samples, and plasma glucose samples taken pre and 2 hour post glucose load, are analysed using the Beckman LX 20 (chemistry analyser) in Waterford Regional Hospital. The coefficient of variation between samples for this analyser was 2.4 for a mean glucose value of 6.8mmols and 1.5 for a mean glucose value of 16.5 mmols. These are analysed using a glucose oxidase method to establish blood glucose levels in these plasma samples.

3.7.2.3 Interpretation of Random and Oral Glucose Tolerance Test Results.

Laboratory results of random blood glucose samples and OGTT venous sample were interpreted and verified according to the WHO/IDF (2006) *Diagnostic Criteria for Diabetes and Intermediate Hyperglycaemia*, in this prevalence survey (Appendix 1).

3.8 Data Analysis.

All data was entered into Microsoft Excel for Windows XP (Microsoft Corporation © 2008). This data was transported into the MINITAB 15 (Minitab Inc. © 2009) computer software package for statistical analysis. Statistical analysis was undertaken with the guidance of a statistician and the research supervisor. Prevalence data is presented as percentages and mean values.

3.9 Reliability and Validity.

Reliability and validity form the basis upon which the quality of a research study is assessed. Reliability refers to the consistency, stability and dependability of the measuring tool and the data collected, while validity is concerned with the robustness of the study's evidence (Polit and Beck, 2004). The researcher considered these concepts during the design phase of this study.

Study reliability can be affected by both intra-observer and inter-observer variation. Intra-observer variation tends to be random and unpredictable and may result from variation in the subject or the researcher. Random variations tend to cancel each other out and are therefore not a significant issue in epidemiological studies, where a population is under consideration, and a large sample has been used (Barker et al, 1998).

Systematic error is introduced when the instrument used to measure a state is consistently inaccurate (Webb et al, 2005). This has a greater affect in epidemiological studies than random error. The following measures were undertaken in this study to reduce the risk of random and systematic error;

- Single data collector

- Eighteen month study period to increase the study sample size

- Strict inclusion/exclusion criteria

- Standard signs and symptoms for type 1 and type 2 diabetes (Appendix 6& 7)

- Evidence of altered glucose states documented in contemporaneous medical records

- Standard diagnostic tests such as the OGTT or random plasma glucose sampling were undertaken by trained phlebotomy staff

- Analysis of blood samples was undertaken by trained medical scientists in an accredited laboratory subject to external quality control

- Classification of test results to diagnose type 2 diabetes, IFG and IGT was in accordance with the WHO/IDF recommendations for diabetes and intermediate hyperglycaemia (Appendix 1)

- Monthly review of case data by researcher and supervisor

Validity is the ability of an instrument to measure what it proposes to measure. Threats to validity can be random or systematic (Barker et al, 1998). Validity can be considered as two separate issues; internal and external validity. Internal validity is the extent to which the study results reflect the true situation within the study population, while external validity is concerned with the generalisability of the study results. Systematic sampling error can affect the validity of a study and this can occur when a systematic difference

exists between those included and excluded from the study (Webb et al, 2005). An independent standard reference that is accepted as trustworthy, to facilitate the determination of cases, can support the validity of a research study (Barker et al, 1998).

Measures adopted to reduce threats to the validity of this study included:

- Clearly defined inclusion/exclusion criteria
- Prospective analysis of contemporaneous data recorded in an individual's medical record to detect cases (Silman and Macfarlane (2002)
- A clear outline of criteria for defining cases using signs, symptoms and test results
- Analysis of standard diagnostic tests including the OGTT, which is considered the Gold standard test to determine type 2 diabetes and altered glucose states
- Classification of test results according to internationally accepted guidelines
- Researcher attendance at routine and post-on call Consultant Physician ward rounds to ensure accuracy of admissions data

Accurate measurement and collection of data related to the particular exposure was essential, to ensure the validity of the data was not affected by random errors. To reduce the risk of random errors, the data was reviewed monthly by the researcher and her supervisor. A participant's eligibility for inclusion as a case and verification of their altered glucose classification, was assessed by the research supervisor on every 10th individual admitted under the Consultant Physician.

3.10 Ethical Considerations.

Ethical approval to conduct this cross-sectional prevalence survey was requested from and granted by the Ethics Committees of both Waterford Regional Hospital and Waterford Institute of Technology. Ethical issues considered as part of this prevalence survey related to, participant anonymity and confidentiality, data collection, data analysis and presentation of the findings of this prevalence survey.

To ensure participant confidentiality, all data collected prospectively between June 1st 2005 and December 17th 2006 was anonymised to prevent participant identification and to eliminate the risk of inappropriate disclosure of information. Minimal personal demographic data was collected, with only standard data such as age and gender recorded (Bowling, 2002). Data collected was held on computerised record by the researcher. This electronic copy was kept securely and confidentially by the researcher during this research, with access limited to the research supervisors and statistician.

Participants were not required to undergo any diagnostic or invasive tests as part of this prevalence survey. Diagnostic test data, including random plasma glucose and OGTT, were collected from test results undertaken by participants as part of routine clinical practice in high risk patients. Test results were reviewed against standard diagnostic criteria for diabetes and intermediate hyperglycaemia to ensure the accurate diagnosis of altered glucose states (WHO/IDF, 2006). Data collected for this research was used purely to achieve the defined objectives of this study.

The results are reported as aggregate data to protect the confidentiality and anonymity of subjects. This required survey results which identified a small number of participants with a particular altered glucose state, to be combined for both genders, in order to eliminate the potential disclosure of an individual's identity. The researcher intends to publish the results of this prevalence survey in current peer reviewed medical and nursing journals. This data will be published as aggregate and anonymous prevalence data on altered glucose states in acute hospital admissions, and no individuals will be identified.

3.11 Pilot Study.

A pilot study was undertaken for one month (April 2005) to determine the feasibility of the proposed research study. A pilot study allows the researcher to examine aspects of the proposed research (Polit and Beck, 2004). In this research, the pilot study was used to review the proposed recruitment strategy, to establish a realistic estimate of the number of participants suitable for inclusion in the survey and to review the proposed data collection process prior to the main study (Silman and MacFarlane, 2002).

The pilot study identified 40-50 people admitted under the care of the Consultant Physician over a one month period. This figure suggested an appropriate sample size could be obtained, over the proposed eighteen month study period, to accurately record the prevalence of altered glucose states. As the aim of this study was to identify local hospital admissions prevalence data and there was no intention to extrapolate from the data to the general population, it was not necessary to undertake a power calculation. The primary issue identified from the pilot study was the need for the researcher to attend all routine and post on-call ward rounds to ensure accurate recording of data.

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Chapter 4.

Research Findings

4.1 Introduction.

Between June 1st 2005 and December 17th 2006, 1237 admission episodes of adult patients requiring acute hospital care were recorded under one Consultant Physician. This included 601 (48.58%) females and 636 males (51.41%). The total number of individuals admitted for acute general medicine care, under all 8 Consultant Physicians in Waterford Regional Hospital during the defined study period, was 8569 (Hospital Inpatient Enquiry, 2009). Therefore the population cohort examined in this prevalence survey represented 14.4% (n=1237) of all acute general medical adult admissions to this regional hospital between June 2005 to December 17th 2006. This was an unselected sample which was representative of all emergency cases admitted to this general regional hospital. The prevalence of altered glucose states was calculated as a proportion of all admissions under the care of the Consultant Physician (n=1237). The results are shown below, along with corresponding 95% confidence intervals. The figures are given for known and new occurrences combined and separately.

4.2 Excluded Participants.

Of all hospital admission episodes recorded under the care of one Consultant Physician in this prevalence survey (n=1237), 719 cases were known to have normal glucose tolerance or did not meet the criteria for screening in this prevalence survey. The remaining 518 cases

were found to have either an existing diagnosis of an altered glucose state, overt type 2

diabetes which was recorded when an individual presented with unequivocal symptoms of

type 2 diabetes and had two random plasma glucose levels greater than > 11.1 mmols/litre

(WHO/IDF, 2006), or were screened as part of their routine clinical care for a new altered

glucose state. From these 518 cases, ninety-nine cases (19.11%) were excluded. Twenty

cases (3.86%) of all known or new altered glucose states (20/518) were excluded according

to the defined exclusion criteria due to Cushing's disease, phaeochromocytoma,

acromegaly or age (Table 2 & 3). A further 79 (15.25%) individuals had a negative OGTT

screening result. The remaining 419 cases were included in the calculations for this

prevalence survey.

Table 2. Breakdown of Total Population According to Exclusion Criteria

Exclusion Criteria	Count	Percent
0	79	6.38
1	7	0.56
2	0	0.00
3	11	0.88
4	2	0.16
5	719	58.12
Total Excluded -	818	66.12

Table 3. Exclusion Criteria Codes

0 = OGTT Negative Screening Test
1 = 18 years
2 = Acromegally
3 = Cushing' Disease
4= Phaeochromocytoma
5 = Known Normal Glucose Tolerance or Did Not Meet Criteria for Screening

Type 2 diabetes was the most predominant altered glucose state in those who were

excluded followed by type 1 diabetes. All excluded episodes of type 1 diabetes occurred in

individuals less than 18 years. One excluded individual with a negative OGTT result also a

simultaneous new diagnosis of Cushing's disease (Table 4).

Table 4: Excluded Altered Glucose States.

Excluded	Count	Percent
Excluded IGT	2	2.02%
Excluded Type1	6	6.06%
Excluded Type2	12	12.12%
Excluded OGTT Screen Negative (n=99)	79	79.79%

4.3 Prevalence of Combined Known and New Altered Glucose States in Acute Adult Hospital Admissions.

Four hundred and nineteen cases were found to have an altered glucose state and were eligible for inclusion in the study numerator. These included admission episodes for known or new type 1 diabetes, type 2 diabetes, impaired fasting glucose or impaired glucose tolerance. The prevalence of each altered glucose state was calculated as a proportion of the total hospital admissions. These figures are shown below, along with the corresponding 95% confidence intervals. The findings indicate that altered glucose states were present in 34% of the population (95% CI 0.31-0.37), with type 2 diabetes the most common altered glucose state. This occurred in 21% of the population (95% CI 0.19-0.24). Impaired glucose tolerance was present in 10% of the population (95% CI 0.08-0.12) with the lowest rate of an altered glucose state attributed to the 3% in the type 1 diabetes category (95% CI 0.02-0.04) (Table 5).

Table 5: Prevalence of Altered Glucose States in Acute Hospital Medical Admissions

Occurrence	Altered state	Prevalence (95% CI)
Known & New occurrences	All altered states	0.34 (0.31, 0.37)
	Type I diabetes	0.03 (0.02, 0.04)
	Type II diabetes	0.21 (0.19, 0.24)
	IGT	0.10 (0.08, 0.12)
Known occurrences	All altered states	0.22 (0.19, 0.24)
	Type I diabetes	0.02 (0.01, 0.03)
	Type II diabetes	0.16 (0.14, 0.19)
	IGT	0.03 (0.02, 0.04)
New occurrences	All altered states	0.12 (0.10, 0.14)
	Type I diabetes	0.005 (0.002, 0.011)
	Type II diabetes	0.05 (0.04, 0.06)
	IGT	0.07 (0.05, 0.08)

4.4 Prevalence of Type 1 and Type 2 Diabetes, Impaired Fasting Glucose and Impaired Glucose Tolerance.

A breakdown of participants with known and newly diagnosed altered glucose states was performed. The number of cases with previously diagnosed type 1 and type 2 diabetes, and IFG or IGT were identified.

In this cohort, 34% of individuals had a diagnosis of an altered glucose state (Table 5). Of these 419 individuals, 22% (95% CI 0.19-0.24) or 269 cases ($p<0.001$) were admitted to hospital with pre existing type 1 or 2 diabetes, or IGT (Table 5 & 6). These known cases were confirmed by patient self report or following review of existing medical records from previous admissions to Waterford Regional Hospital and included recorded diagnosis, test results and treatments.

Type 1 diabetes accounted for 3% (n=32) of all altered glucose states in this survey. This was previously diagnosed in 2% (n=26, 95% CI 0.01-0.03) of cases admitted. The prevalence rates for type 1 diabetes (Table 5) observed in this survey are unlikely to accurately reflect the true admission rates for both known and particularly new diagnoses of type 1 diabetes as the inclusion criteria for this survey targeted adults greater than 18 years of age. In this prevalence survey 6 cases (0.5%) of new type 1 diabetes (95% CI 0.01-0.03) (Table 5 & 6) were admitted for care during the study period however as previously outlined, a further 6 cases were all excluded due to the age related exclusion criteria (Table 2, 3 & 4).

Type 2 diabetes was the principal pre-existing altered glucose state found in individuals in this survey. It was present in 16% of individuals (95% CI 0.14-0.19) on admission with this confirmed by review of existing medical records (Table 5). Type 2 diabetes was previously diagnosed in 75% (n=203) of all known altered glucose state cases (p <0.001) prior to hospital admission (Table 6).

Previously diagnosed and new cases of impaired glucose tolerance were present in 10% (n=124) of all cases of altered glucose states (95% CI 0.08 – 0.12) in this survey. Impaired glucose tolerance was known in 3% (n=40, 95% CI 0.02-0.04) of the whole admission population (Table 5 & 6) and was a diagnosis in 15% (n=40) of all known altered glucose state cases on admission (p<0.001). The results identified the prevalence rate for known IGT was in contrast to the high prevalence of new IGT diagnosed in this survey (Table 6). Impaired glucose tolerance was the most prevalent new altered glucose state with 56%

(n=84) of all new cases diagnosed as IGT (p< 0.001). No cases of known IFG were

admitted during the timeframe of this survey.

Table 6: Number and Percentages, Gender, and Age Profiles for Known, New and
Combined Altered Glucose States.

Group	Type I diabetes Number (%)	Type II diabetes Number (%)	IGT Number (%)	P-value
Combined Known and New Diagnosis	32 (8%)	263 (63%)	124 (30%)	
Known Diagnosis	26 (10%)	203 (75%)	40 (15%)	**<0.001**
New Diagnosis	6 (4%)	60 (40%)	84 (56%)	
Female	23 (13%)	102 (58%)	50 (29%)	**0.002**
Male	9 (4%)	161 (66%)	74 (30%)	
Age 18-39	23 (70%)	8 (24%)	2 (6%)	**<0.001**
Age 40-59	8 (13%)	40 (66%)	13 (21%)	
Age 60-79	1 (0.5%)	151 (75%)	50 (25%)	
Age 80+	0 (0%)	64 (52%)	59 (48%)	

4.5 New Diagnosis of an Altered Glucose State.

In this prevalence survey, 12% of individuals (n=150 95% CI 0.10 – 0.14) were newly

diagnosed with an altered glucose state during their hospital admission (Table 6). An

analysis of prevalence rates for new type 1 and type 2 diabetes and IFG or IGT was carried

out. In this survey, new occurrences of an altered glucose state were primarily attributed to

IGT. This was undiscovered in 56% (n = 84) of all new cases of an altered glucose state

(p < 0.001) (Table 5 & 6)

4.5.1 New Type 1 Diabetes.

All 6 new cases of type 1 diabetes (0.5% - 95% CI 0.002 – 0.011) were diagnosed from their physiological symptoms on admission, routine analysis of fasting plasma glucose levels and blood gas tests. The rate of newly diagnosed type 1 diabetes is unlikely to represent the true prevalence of new type 1 diabetes in a hospital admission population. In Ireland, individuals who are less than 18 years are often managed under the care of a Consultant Paediatrician therefore any cases less than 18 years, who were admitted in this study cohort, were excluded from this analysis as they did not represent the standard patient admitted under the care of an adult physician. It is therefore likely the diagnosis of new type 1 diabetes in people who were greater than 18 years in this study, will under-represent the true prevalence of new type 1 diabetes in a hospital admission population.

4.5.2 New Type 2 Diabetes, Impaired Fasting Glucose and Impaired Glucose Tolerance.

New diagnoses of type 2 diabetes or IGT accounted for 96% (n=144) of all new cases of altered glucose states in this survey (p = <0.001). Sixty new cases of type 2 diabetes were diagnosed (5% - 95% CI 0.04 – 0.06). Of these cases, overt type 2 diabetes was diagnosed in 6 (10.00%) individuals (6/60) and 1 individual (1.66%) was diagnosed as MODY (1/60). Both these diagnoses were based on physiological symptoms at presentation and routine screening of random plasma glucose levels during admission. The remaining 53 individuals (88.33%) were diagnosed with new type 2 diabetes following screening with an OGTT (53/60). Individuals were screened for an altered glucose state if evidence or a history of a diabetes complication (Macrovascular or Microvascular disease - Appendix 5), or risk

factors for an altered glucose state (obesity, hypertension - BP > 140/90, dyslipidaemia –

Appendix 8) were identified. In these 53 cases (24%), the standardised OGTT was used to

identify undiagnosed cases of type 2 diabetes.

Overall, the OGTT was required to diagnose type 2 diabetes, IFG and IGT in 17.4%

(n=216) of the total admission population. In the group of individuals screened using the

OGTT, 63% (137) had a diagnosis of an altered glucose state (Figure 2).

Figure 2: Altered Glucose States Diagnosed by Oral Glucose Tolerance Test.
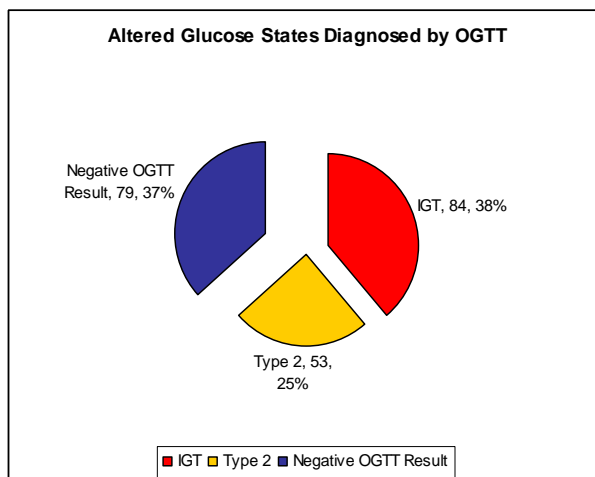
Impaired glucose tolerance was the most common new altered glucose state diagnosed in

this survey. New IGT was diagnosed in 7% (95% CI 0.05 – 0.08) of the total admission

population (Table 5). A new diagnosis required screening with the OGTT and IGT was

found to be prevalent in 39% (n=84) of individuals screened (Table 7) and accounted for

56% (p < 0.001) of all new diagnosis of an altered glucose state. This compared to 15% for

known altered glucose states (p< 0.001) (Table 6).

IFG was diagnosed on OGTT in 1 case (0.46%). This case was in association with IGT and

was included in the IGT group for statistical analysis

Table 7: Summary of Oral Glucose Tolerance Test Results According to Diagnosis, Gender and Age.

Group	Type II diabetes Number (%)	IGT Number (%)	Negative Number (%)	P-value
All combined	53 (24%)	84 (39%)	79 (37%)	
Female	29 (31%)	31 (33%)	35 (37%)	0.12
Male	24 (20%)	53 (44%)	44 (36%)	
Age 18-39	3 (25%)	2 (17%)	7 (58%)	**0.006**
Age 40-59	7 (15%)	12 (26%)	27 (59%)	
Age 60-79	25 (27%)	38 (42%)	28 (31%)	
Age 80+	18 (27%)	32 (48%)	17 (25%)	

4.6 Prevalence of Altered Glucose States by Gender and Age.

The prevalence of each altered glucose state in this population of acute hospital admissions,

was recorded according to gender. Analysis of the results indicated that the occurrence of

an altered glucose state, gender, and age were all associated with the type of altered glucose

state. Type 2 diabetes was the most prevalent altered glucose state present in this

population, with 21% either known or newly diagnosed (Table 5). Type 1 diabetes was

prevalent in 3% of hospital admission episodes however, this is unlikely to be a true

prevalence rate as previously outlined. Impaired glucose tolerance was present in 10% of

the population with this including the one case diagnosed with both IFG and IGT (Table 5).

The results demonstrated a significant difference in prevalence rates between males and females when altered glucose states were combined and for type 2 diabetes separately. From the total population cohort of 1237 individuals admitted to hospital during the study timeframe, 51.41% (n=636) were male and 48.58% (n=601) were female. Overall, all altered glucose states were more prevalent in males than females (p<0.001) (Table 8). In this survey of acute hospital medical admissions 38% (95% CI 0.35 – 0.42) of males (n=244) and 29% (95% CI % 0.26 – 0.33) of females (n=175) had an altered glucose state (Table 6 & 8). Similarly, a significant difference (p < 0.001) was also noted in the prevalence of type 2 diabetes, with males (25%, CI 0.22-0.29) also more likely to be admitted with this diagnosis compared to females (17%, CI 0.14-0.20) (Table 6 & 8).

Table 8: Prevalence of Altered Glucose States by Gender.

Altered state	Females Prevalence (95% CI)	Males Prevalence (95% CI)	P-value
All altered states	0.29 (0.26, 0.33)	0.38 (0.35, 0.42)	**0.001**
Type I diabetes	0.04 (0.02, 0.06)	0.01 (0.006, 0.03)	**0.008**
Type II diabetes	0.17 (0.14, 0.20)	0.25 (0.22, 0.29)	**<0.001**
IGT	0.08 (0.06, 0.11)	0.12 (0.09, 0.14)	0.05

There was also slight evidence that IGT was more prevalent in males than females but this result was only of borderline statistical significance (p < 0.05). Impaired glucose tolerance was prevalent in 12% of males (CI 0.09 – 0.14) and as opposed to 8% of females (CI 0.06 – 0.11) (Table 8). An illustration of overall prevalence rates of altered glucose states according to gender is shown below (Figure 3).

Figure 3: Altered Glucose States According to Gender.
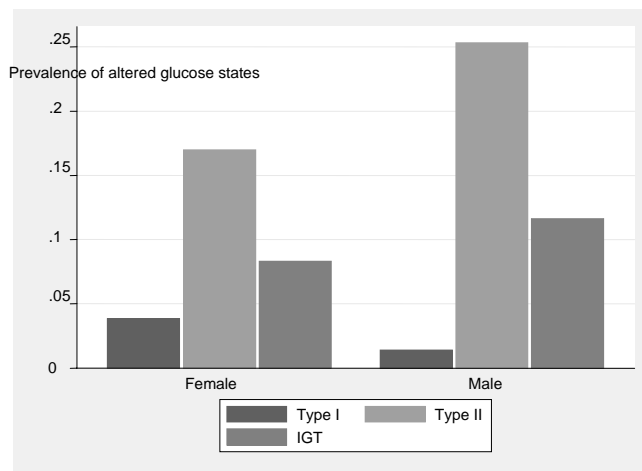
When analysis of the OGTT were stratified according to gender, the results indicated the prevalence of new altered glucose states did not vary between genders. While more males (44%) than females (33%) were newly diagnosed with IGT (Table 7) this was not statistically significant ($p < 0.12$). Similarly, no gender difference was observed in those who screened negative for an altered glucose state on OGTT (M – 36% vs. F – 37%).

In this cohort of people with an altered glucose state, the modal age was 60-79 years (48.2%). This study found 77.5% of the population were more than 60 years. Across all age groups, type 2 diabetes was the principal altered glucose state except in those aged18-39 years. In the 18-39 year age group, a greater proportion of individuals with type 1 diabetes were represented. Of note, the prevalence of IGT was found to increase with age from 6% in individuals less than 39 years compared to 48% in those greater than 80 years ($p < 0.001$)(Table 6).

A significant difference was observed across the four age ranges for new altered glucose states diagnosed on OGTT. The findings suggested the proportion of new type 2 diabetes did not vary particularly by age however, there was an increase in the prevalence of new IGT according to age. In the youngest age category (18-39 years), IGT was prevalent in 17% of cases however, this rose to 48% in the oldest category (> 80 years) (Table 7). Conversely, the proportion of negative OGTT results fell with age from 58% in the youngest age group to 25% in patients over 80 years of age (p < 0.006).

4.7 Cost of Altered Glucose States in Acute Hospital Admissions.

The substantial and increasing costs associated with treating diabetes is primarily related to the management of the preventable complications of the disease. Hospitalisation to treat the complications of diabetes mellitus is the single biggest contributor to the cost of care. The total cost of direct medical care per patient requiring hospitalisation in the Republic of Ireland has been identified as €1196 (Nolan et al, 2006). Using this figure to estimate the cost of care for individuals with known type 1 diabetes and known and new type 2 diabetes (n=289 – Table 6) in this cohort, the cost of hospitalisation care was €345,644. This figure excludes new type 1 diabetics in order to give a representative view of the costs associated with hospitalisation for acute and chronic complications of diabetes mellitus (Appendix 5). When new diagnoses of type 1 diabetes were included (n=295), the cost of hospitalisation care increased marginally to €352,820. Impaired glucose tolerance is associated with an increased risk of macrovascular complications, when known and new IGT were included with type 1 and 2 diabetes (n=419 – Table 6) to estimate the total cost of hospitalisation care for all glucose states, the cost of care rose to € 501,124.

The sample used in this prevalence survey represented 14.4% of all general admissions over the 18 month study period. Of these patients, 34% had a diagnosis of a known or new altered glucose state. Hospital data was used to extrapolate the prevalence of altered glucose states amongst acute medical admissions to this Regional Hospital during the study timeframe (18 months). During this period, 8569 patients were admitted to this regional hospital for acute adult medical care under all 8 Consultant Physicians. Over a 12 month period, admissions rates for acute adult medical care were estimated at 5712 admissions based on Hospital Inpatient Enquiry data for the study period. Of these acute hospital admissions for all 8 Consultant Physicians, 2914 individuals were estimated to have had a diagnosis of an altered glucose state over the 18 month study period or 1942 over a 12 month period. Using this admissions data and the prevalence rate for altered glucose states (34%), identified in this study population, to estimate the cost of providing care in this regional hospital, the total cost of inpatient care for cases with type 1 and type 2 diabetes, impaired fasting glucose and impaired glucose tolerance was estimated at €3,485,144 over 18 months or €2,322,632 per annum.

Chapter 5.

Discussion.

5.1 Introduction

This study provides prevalence data for altered glucose states in acute hospital medical admissions, in an Irish setting. The research population in this prevalence survey was an unselected sample, representing 14.4% (n=1237/8569) of the acute adult general medicine population, admitted to a regional hospital. These cases were admitted under the care of one of eight medical consultants in this regional hospital. The findings of this research indicates a high prevalence of altered glucose metabolism in medical patients requiring acute hospital care. This study identified a prevalence rate of 0.34 or 34 per 100 acute adult medical admission cases for altered glucose states.

5.2 Type 1 Diabetes.

Type 1 diabetes was found in 3% of hospital admissions in this cohort (n=32), with this newly diagnosed in 0.5% of all new cases. Type 1 diabetes is a condition that is predominantly diagnosed in children aged 0-14 years (Tuomilehto et al, 1995) and in Ireland individuals who are less than 18 years are often managed under the care of a Consultant Paediatrician. It is therefore likely that the prevalence rates for type 1 diabetes identified in this study, which excluded people under 18 years, under-represents the true prevalence of type 1 diabetes in acute hospital admissions. This is similar for those admitted for management of the complications of type 1 diabetes. Despite the exclusion of those under 18 years, the prevalence rates identified for type 1 diabetes in this study were

greater than previously published rates, which found type 1 diabetes in 0.64% of hospital admissions (Donnan et al, 2000). This higher admission rate for known type 1 diabetes may reflect the multiple admissions required by a number of type 1 diabetics in this survey. Such an influence on admission rates would correspond with previous data which highlighted the need for multiple admissions to manage the complications of diabetes in individuals with type 1 and type 2 diabetes (Moss et al, 1999).

5.3 Type 2 Diabetes and Impaired Glucose Tolerance.

Type 2 diabetes was the most prevalent altered glucose state present in this population of patients requiring hospital care, with 21% either known or newly diagnosed. A number of studies have considered the prevalence of altered glucose states in hospital admission populations. In one study, type 2 diabetes was identified in 5.4% of hospital admissions (Donnan et al, 2000) however, this was considerably lower than that found in this survey. In contrast, the rates of type 2 diabetes identified in high risk populations requiring hospital care were greater than those identified in this survey. Studies in high risk populations have shown prevalence rates for type 2 diabetes of 31% in CAD (Bartnik et al, 2004), 35% post myocardial infarction (Norhammer et al, 2002), 44% in heart failure (Greenberg et al, 2007), 20.2% post haemorrhagic stroke (Matz et al, 2006) and 50% for type 2 diabetes or IGT post CVA or TIA (Kernan et al, 2005). In comparison with these studies, type 2 diabetes in both known and new cases had a lesser impact however, the impact on high risk individuals who were screened for a new altered glucose state in this survey was similar.

Impaired glucose tolerance was prevalent in 3% of all acute cases admitted to hospital for medical care. It was previously diagnosed in 15% of all known altered glucose state cases on admission. Due to a dearth in the knowledge of IGT prevalence in acute hospital admissions, it was difficult to compare the prevalence data identified in this survey. The rate of IGT demonstrated in this survey was found to be similar to EU population based prevalence studies (10.2%) (IDF, 2008) however, the prevalence rate for all hospital admissions in this survey were shown to be considerably less than those identified in studies of high risk individuals post MI. In these studies 35% were found to have known IGT (Norhammer et al, 2002) and 25% were newly diagnosed (Bartnick et al, 2004) however, such high prevalence rates in individuals post MI could be expected, as IGT is known to increase the risk of developing CAD (Mykkanen et al, 1992).

5.4 Newly Diagnosed Altered Glucose States following Opportunistic Screening during Hospital Admission.

In addition to known altered glucose states, a substantial proportion was unknown on admission to hospital. This study demonstrated that targeted screening of high-risk hospital admission cases can diagnose a substantial number of new cases of altered glucose states prior to discharge. In high-risk individuals screened for an altered glucose state during their hospital admission, new type 2 diabetes, IFG and IGT was diagnosed in 63% of cases. Although type 2 diabetes was diagnosed in 25% of cases screened on OGTT, IGT was the principal new altered glucose state detected through screening procedures and was prevalent in 38% of individuals. When these findings were evaluated against previous studies of high risk populations, the prevalence of new IGT was found to be considerably

higher in this study compared to prevalence rates of 25% in CAD (Bartnik et al, 2004) and 28% in CVA or TIA admissions (Kernan et al, 2005).

As found in this study, opportunistic screening during hospital admission detected a subset of people who were asymptomatic for type 2 diabetes and were undiagnosed for both type 2 diabetes and IGT. Opportunistic screening of these high risk patients, with established microvascular or macrovascular disease, or those who had risk factors for both, was shown to be both effective and practical in the acute hospital setting. In this study, opportunistic screening of high risk cases demonstrated that altered glucose states place a significant burden on the acute hospital system and that undiagnosed type 2 diabetes and IGT were an important issue. Diabetes and IGT remained undiagnosed in at least 63% of high risk individuals screened in this hospital population.

Screening for these specific categories of altered glucose states in males and females using the OGTT was effective and facilitated a targeted approach for lifestyle interventions and treatment with secondary prevention strategies in people who had risk factors or a diagnosis of diabetes related complications. Such individuals have a higher risk of cardiovascular disease (Haffner et al, 1998, Unwin et al, 2002) and all cause mortality (DECODE Study Group, 2001). Evidence from clinical trials has established the complications of type 1 and type 2 diabetes can be delayed or prevented with tight glucose control (DCCT, 1993, UKPDS, 1998a). Similarly engaging in lifestyle modification strategies has been shown to prevent or reduce the progression from IGT to type 2 diabetes (Toumilehto et al, 2001, Pan

et al, 1997). These benefits were maintained for up to 14 years after a lifestyle intervention has ceased (Li et al, 2008, Lindstrom et al 2006).

Individuals with chronic diseases disproportionately access and use healthcare, with the majority of healthcare costs associated with avoidable inpatient hospital admissions to manage the disease or its complications. The findings of this study has confirmed the value of the OGTT as a screening tool in the hospital setting. Given the high proportion of new type 2 diabetes and IGT identified in this study, the findings justify and strengthens the case for greater systematic screening of altered glucose states, in high risk patients, in acute hospital admissions. This may be particularly in effective in males and all patients more than 60 years.

5.5 Altered Glucose States, Age and Gender.

In this prevalence survey age and gender were found to be associated with the type of altered glucose state. Overall, a statistically significant difference was found for gender across all altered glucose states, with all altered glucose states and type 2 alone more prevalent in males than females. This contrasted with new cases of IGT. Slight evidence of its increased prevalence in males was demonstrated however, this was only of borderline statistical significance. Of note, a new diagnosis of type 2 diabetes or IGT following an OGTT did not vary with gender.

Individuals with an altered glucose state were found to be older, with such states highest in people aged 60 years or more. In this study, 77.5% of all cases were more than 60 years of

age. This was most apparent in people with type 2 diabetes. Type 2 diabetes was also the principal altered glucose state across all age groups. Comparison with international data would suggest that those admitted to hospital requiring acute care in the Republic of Ireland are older than their international counterparts. This finding, which demonstrated a higher prevalence of an altered glucose state in older people was expected, as diabetes is clearly a chronic age related disease (WHO, 2005). Evidence states that the peak age of onset for type 2 diabetes is 60-70 years and this is higher in males (Harris et al, 1998) however, its prevalence does increase with age in both genders up to 70-80 years (DECODE Study Group on behalf of the European Diabetes Epidemiology Group, 1998b). The findings of this study concur with this.

New diagnoses of type 2 diabetes and IGT occurred predominantly in individuals aged more than 60 years. While no difference was observed for new type 2 diabetes diagnosed following OGTT, a significant difference was identified across the age ranges for new IGT and for those screened negative on OGTT. In this study, IGT became more prevalent with age however, this was in contrast to the decline in negative OGGT results as age increased. Epidemiological evidence has identified similar findings in population based studies which demonstrated that IGT prevalence increased linearly with age and was present in at least 30% of people over 60 years (DECODE Study Group, 2003). Ageing has been shown to be an important risk marker for the accumulation of chronic disease. The development of adult chronic disease reflects a lifetime of exposure to harmful environmental and social factors (WHO/FAO, 2003). In men aged over 60 years approximately 75% have at least one chronic condition whilst 33% of have two. Each of these chronic diseases is influenced by

two or more risk factors and each risk factor is often common to two or more diseases (WHO, 2005).

5.6 Hospitalisation Costs of Altered Glucose States.

This study shows that diabetes and other altered glucose states place a considerable burden on the financial resources available in healthcare settings. The sample population in this study of unselected patients represented 14.4% of all acute general admissions to a regional hospital. In this sample, altered glucose states were present in 34% of the population. The cost of treatment for individuals with type 1 diabetes, type 2 diabetes, IFG and IGT in this cohort was estimated at €501,124 or €3,485,144 when applied to the total population of acute medical patients admitted to this regional hospital. The total cost of care for those with undiagnosed type 2 diabetes and IGT was estimated at €163,852. The findings of this study were similar to other studies (Jonsson, 2002, Simpson et al, 2003) in that the cost of hospitalisation to treat the complications of diabetes was considered excessive.

Of note, all individuals with a known altered glucose state or those who screened positive for an altered glucose state in this study had a complication, risk factors or required hospital care to manage the altered glucose state. Healthcare costs for people with diabetes are 2-3 three times higher than those in the general population (Rubin et al, 1994). In addition the cost of treating the compilations of diabetes are 1.8 and 2.9 times higher in individuals who have a microvascular or macrovascular complication. Indeed, the presence of both complications increases the cost of treatment 3.8 fold (Nolan et al, 2006). The costs identified in this study are likely to exceed this figure as that data used to derive these

calculations is now a historical figure and furthermore, only high risk individuals were screened for an altered glucose state. Presentation and diagnosis with new type 2 diabetes often occurs at a late stage in a long, pathological process and individuals may have hyperglycaemia which does not produce classic symptoms for a number of years before diagnosis (ADA, 2007a), however this hyperglycaemia carries a high risk of insidious tissue damage (Krentz, 2000). Such individuals would not have been captured for screening in this study unless they met the criteria as a high risk case.

In conclusion, this study found the cost of hospital care, associated with altered glucose states, was €501,124 or €3,485,144 when applied to this total population while undiagnosed type 2 diabetes and IGT accounted for €163,852. These findings represent a substantial financial burden for individual hospitals and the healthcare system as a whole.

5.7 Limitations of the Study.

Extrapolation of the results from this prevalence survey of altered glucose states in an unbiased sample of acute hospital medical admissions, is limited from a population health perspective. This occurs because the whole population does not access acute healthcare in a uniform manner. Hospitals disproportionately attract individuals who require a certain type of medical care such as; emergency or planned surgical care or acute medical care (Barker et al, 1998). Individuals captured in this study cohort self-selected medical care and these may possess different characteristics or medical problems than a randomly selected sample of the general population (Polit and Beck, 2004) however, this prevalence survey never intended to provide population prevalence rates for altered glucose states for the entire

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population. The objective of this survey was to establish the extent to which altered glucose states impact on the requirement for healthcare in the acute hospital setting and to estimate the financial cost of this care.

Methodological limitations associated with this prevalence survey reflected issues relating to the inclusion criteria. This study examined the prevalence of altered glucose states in an adult population aged more than 18 years. In Ireland, individuals who are less than 18 years are frequently managed under the care of a Consultant Paediatrician therefore any cases less than 18 years who were admitted in this study cohort were excluded from the analysis. As type 1 diabetes is a condition that is predominantly diagnosed in children aged 0-14 years (Tuomilehto et al, 1995) it is likely that the true prevalence of type 1 diabetes is under-represented in this study.

Similarly, individuals with known renal or eye disease directly accessed renal and ophthalmological care directly through their specialised medical teams. These individuals were not processed through the general medical admissions system. This may underestimate the true prevalence of altered glucose states in hospital admissions, as both these cohorts are known to have a high prevalence of diabetes (CDC, 2008c, Klein et al, 1998).

Individuals in this study were screened for an altered glucose state if they met the defined criteria for high risk. Such criteria included presentation with known risk factors or complications of diabetes. In this study 32.6% of all altered glucose states were diagnosed

in asymptomatic people on screening. This suggests that the OGTT should be

systematically employed to screen for type 2 diabetes, IFG and IGT. Without such

screening these individuals would remain undiagnosed. Presentation and diagnosis with

new type 2 diabetes often occurs at a late stage in a long, pathological process and

individuals may have hyperglycaemia which does not produce classic symptoms for a

number of years before diagnosis however, this hyperglycaemia carries a high risk of tissue

damage. Similarly people with undiagnosed IFG and IGT, which may progress to type 2

diabetes, have a high risk of cardiovascular disease and do not present with symptoms. In

this study, such individuals would not have been captured for screening unless they met the

criteria as a high risk case. As such the true prevalence of undiagnosed type 2 diabetes, IFG

and IGT may be in excess of that identified in this study, however practical implications

and financial restraints did not allow for each individual to be screened routinely on

admission using the OGTT. As this prevalence survey used a targeted screening approach

for acute general medical admissions with a known complication or risk factors for diabetes

mellitus, it does present the minimum prevalence of altered glucose states in this cohort.

Despite these limitations, this data provides new insights into the influence of altered

glucose states on acute general medical admissions and the extent to which care for such

individuals impacts financially on the Irish healthcare system.

5.8 Summary.

Chronic conditions such as diabetes mellitus and altered glucose states are highly important

public healthcare challenges facing countries, worldwide (W.H.O, 2005). Type 2 diabetes

is by far the most prevalent form however, the prevalence of all altered glucose states has

risen dramatically in recent years (W.H.O, 2008b) with the rise in type 2 diabetes now reaching epidemic levels (Nolan et al, 2006). In addition, IGT and IFG will add significantly to the burden of chronic diseases due to their increased risk of progressing to type 2 diabetes (WHO/IDF, 2006) and developing cardiovascular disease (de Vegt et al, 2001).

Unequivocal evidence indicates the most significant contributor to the cost of healthcare in diabetes patients is hospitalisation costs, to treat and manage the complications of diabetes (Nolan et al, 2006). This results in the cost of healthcare for people with diabetes mellitus being 2-3 times higher the average for the entire population (Rubin et al, 1994). Available data shows that individuals with diabetes complications disproportionately access hospital care and this increases with age (Olivera-Fuster et al, 2004). Those who do require care, need treatment for avoidable acute complications such as ketoacidosis or hypoglycaemia (Ahern and Hendryx, 2007) or other long-term complications. An elevated risk of CVD exists in diabetes, IFG and IGT (Beckmann et al, 2002) with this being the single biggest contributor to hospital admissions in type 1 and 2 diabetes (Donnan et al, 2000). Similarly, microvascular complications such as renal disease, eye complications and neuropathy confer poorer outcomes in these cases.

Many episodes of hospital care to treat and manage the complications of diabetes are avoidable and a reduction in these admissions could be achieved by targeting high risk cases, to treat modifiable risk factors. Available evidence demonstrates that maintaining glycaemic levels at normal or near-normal levels, in type 1 and type 2 diabetes (The

Diabetes Control and Complications Trial Research Group, 1993 & United Kingdom Prospective Diabetes Study Group, 1998a), in addition to control of blood pressure (UKPDS, 1998b) is effective in delaying or preventing the development of microvascular (eye, kidney and neuropathy) complications of diabetes. The implementation of strategies to prevent the development of such complications and their excessive requirement for hospital care could significantly reduce costs required to manage these cases (Moss et al, 1999), at a time of challenging budgetary constraints for healthcare providers.

5.9 Conclusion.

This study has identified prevalence data for altered glucose states in individuals requiring acute medical care in Ireland. While data has been published in relation to the prevalence of altered glucose states in a community population in Ireland, this author was unable to identify similar published data in relation to the prevalence of altered glucose states in acute, medical, adult hospital admissions in Ireland. The availability of such data and the extent to which hospitalisation for altered glucose states impact on the health of people admitted to hospital and their requirement for inpatient care is essential for future health service planning. This study highlighted the excessive financial burden placed on healthcare systems in the Republic of Ireland, from altered glucose states due to avoidable hospital admissions to treat complications. In this study, 34% of all acute medical admissions had an altered glucose state however, this was higher than those previously identified in similar studies. The highest prevalence of a known altered glucose state was attributed to type 2 diabetes while IGT was the most frequent newly diagnosed state. This was expected as population prevalence rates were lower at the time such studies were

undertaken. In addition, a substantial number of individuals admitted to hospital had a previously undiagnosed altered glucose states. In this study 63% of those screened had unknown type 2 diabetes or IGT. This would suggest that high risk individuals would benefit from opportunistic screening for an altered glucose state, during hospital admission. Such a strategy would facilitate tighter management of diabetes related risk factors.

Inpatient care is the principal contributor to the cost of diabetes care. This study does provide an estimate of the significant financial costs associated with the provision of hospital care for people with altered glucose states in the Republic of Ireland. Any assessment based on the analysis provided in this study is likely to underestimate the degree of this problem, as this study did not allow for the increased cost of hospital care associated with more than one complication of diabetes or for direct admissions to specialised care. The availability of this data does provide a basis for any future health service planning however, healthcare planners would need to acknowledge and take account of the predicted future escalation in the prevalence of all altered glucose states.

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Appendix 1:

World Health Organisation Recommendations for the Diagnostic Criteria for
Diabetes and Intermediate Hyperglycaemia 2006.

	Fasting plasma glucose		2–h plasma glucose*
Diabetes	≥7.0mmol/l (126mg/dl)	or	≥11.1mmol/l (200mg/dl)
Impaired Glucose Tolerance (IGT)	<7.0mmol/l (126mg/dl)	and	≥7.8 and <11.1mmol/l (140mg/dl and 200mg/dl)
Impaired Fasting Glucose (IFG)	6.1 to 6.9mmol/l (110mg/dl to 125mg/dl)	and	<7.8mmol/l (140mg/dl) (if measured)**

* Venous plasma glucose 2 hours after ingestion of 75g oral glucose load
**If 2–h plasma glucose is not measured, status is uncertain as diabetes or IGT cannot be excluded

Appendix 2:

World Health Organisation/International Diabetes Federation Guidelines for Performing an Oral Glucose Tolerance Test.

The Oral Glucose Tolerance Test is performed in the following manner:

1. The OGTT should be carried out on individuals following three days of unrestricted carbohydrate rich diet and activity.

2. 12 hour fast from the night prior to the test.

3. Medication should be held on the morning prior to test.

4. Avoid smoking and exercise prior to and during test.

5. Administration of an oral glucose load of 75g of glucose in adults.

6. Venous plasma glucose sampling occurs:

   - Immediately prior to ingestion of 75g of glucose load

   - 2 hours (120 minutes) post glucose challenge (W.H.O./I.D.F, 2006).

Appendix 3:

<u>World Health Organisation Classification and Calculation of Body Mass Index.</u>

Classification of Adults According to Body Mass Index:

Classification	BMI (kg/m^2)	Risk of Comorbidities
Underweight	18.5 kg/m^2	Low (but risk of other clinical problems increased)
Healthy Weight	18.5 – 24.9 kg/m^2	Average
Overweight		
Pre Obese	25.0 – 29.9 kg/m^2	Increased
Obese Class 1	30.0 – 34.9 kg/m^2	Moderate
Obese Class 11	35.0 – 39.9 kg/m^2	Severe
Obese Class 111	>40.0 kg/m^2	Very Severe

Calculation of Body Mass Index:

<u>Weight in kilograms (kg)</u>
Height in metres ^{2} (m^2)

W.H.O, 2000.

Appendix 4:

International Dollars .

The international dollar or Geary-Khamis dollar is a hypothetical unit of currency that has the same purchasing power as a dollar spent in the U.S economy. It is based on the concept of purchasing power parities (PPP) of currencies and the international average prices of goods. It is not widely used however, it is used for statistical purposes by organizations such as the World Bank and the International Monetary Fund.

International dollars cannot be converted to a particular country's currency using standard market exchange rates. It must be converted by the country's purchasing power parity (PPP) exchange rate used in a particular study.

Purchasing power parity is an indicator used by the World Bank to measure the performance and size of an economy. This indicator considers the relative prices of goods and services, especially non-tradeable goods, in different countries. It identifies the value of a local unit of currency within it's own borders. This is used to make comparisons between countries and over time (World Bank, 2009).

Appendix 5:

Macrovascular and Microvascular Complications of Diabetes

Macrovascular	Microvascular
Coronary Heart Disease	Nephropathy
Cerebrovascular Disease	Retinopathy
Peripheral Vascular Disease	Neuropathy

(Adapted From: Williams and Pickup, 2004)

Appendix 6:

Classic Signs and Symptoms of Type 1 Diabetes and Ketoacidosis.

Signs and Symptoms of Type 1 Diabetes	Signs and Symptoms of Diabetic Ketoacidosis in Type 1 Diabetes
Thirst	Polyuria/Polydipsia
Polyuria	Weight Loss
Nocturia	Nausea and vomiting
Weight Loss	Dehydration
Fatigue	Hypotension, Tachycardia
Dehydration	Ketosis (Acetone Breath)
	Acidotic Respiration (Kussmal)
	Acidotic Blood Gas
	Abdominal pain, Leg cramps
	Confusion, Drowsiness (10% of Cases)

(Adapted From: Williams and Pickup, 2004)

Appendix 7:

Presenting Signs and Symptoms in Type 2 Diabetes Mellitus

None – asymptomatic individuals identified by screening

Osmotic symptoms

- Thirst
- Polyuria
- Nocturia
- Blurred Vision
- Fatigue/Lassitude

Infection

- Recurrent Fungal infection
- Recurrent bacterial infection

Macrovascular complications

- Coronary artery disease (angina pectoris, acute myocardial infarction)
- Cerebrovascular disease (transient ischaemic episodes, stroke)
- Peripheral vascular disease (intermittent claudication, rest pain, ischaemic ulceration)

Microvascular complications

- Retinopathy (acute or progressive visual impairment)
- Nephropathy (proteinuria, hypertension, nephrotic syndrome)
- Neuropathy (symptomatic sensory polyneuropathy, foot ulceration, amyotrophy, cranial nerve palsies, peripheral mononeuropathies, entrapment neuropathies)

Associated Conditions

- Glaucoma
- Cataracts

Hyperosmolar Non-Ketotic Syndrome

- Marked Hyperglycaemia - usually greater than 50mmols/L
- Profound dehydration with pre renal uraemia
- Coma

(Adapted from: Krentz, 2000).

Appendix 8:

<u>Data Collection ProForma</u>

Date of Birth: _____

Gender: Male   □   Female   □

Known Type 1 Diabetes: Yes   □   No   □

Confirmed By;   Documentation   □   Treatment_____

                                    Signs and Symptoms □ _____

                                    Blood Results   □

                                    Blood Glucose Level □ _____

                                    Blood Gas Analysis   □ _____

Known Type 2 Diabetes, IFG, IGT: Yes   □   No   □

Confirmed By;   Documentation   □   Treatment_____

                                    Signs and Symptoms   □ _____

                                    Random Venous Blood Glucose □

                                    OGTT   □

                                    Venous Blood Glucose Pre _____   2 hr Post ___

Discovered Type 1 Diabetes: Yes   □   No   □

                                    Signs and Symptoms   □ _____

                                    Blood Results   □

                                    Blood Glucose Level □ _____

                                    Blood Gas Analysis   □ _____

Discovered Type 2 Diabetes, IFG, IGT: Yes   □   No   □

                                    Signs and Symptoms   □ _____

                                    Random Venous Blood Glucose □ 1st _____ 2nd _____

                                    OGTT   □

                                    Venous Blood Glucose Pre _____   2 hr Post ___

Medical History:

Microvascular Complication: Nephropathy □

                                    Retinopathy   □

                                    Neuropathy   □

Macrovascular Complication: Coronary Heart Disease _____

                                    Peripheral Vascular Disease _____

                                    Cerebrovascular Disease _____

Risk Factors;   Hypertension □

                                    Obesity   □

                                    Hyperlipidaemia □

                                    Microalbuminuria □

Exclusion Criteria: _____

Appendix 9:

Flow Chart of Population Screening for Known and New Altered Glucose States   .

Unselected Sample of 1237 Hospital Medical
Admissions between June 2005 - December 2006

Ineligible Patients: $n = 739$
< 18 years: $n = 2$
Acromegaly: $n = 5$
Cushing's Disease: $n = 11$
Phaeochromocytoma: n = 2
Known Normal Glucose Tolerance or
Screen Failure: $n = 719$

Eligible Participants $n = 498$

Subjects Screened for Altered Glucose
States
$n = 228$

Known Altered Glucose States
$n = 270$

Screened Type 1 Diabetes: $n = $ **6**

- Physiological Signs & Symptoms
- Venous Blood Glucose
- Blood Gas Analysis
- Ketoacoidosis

Screened Type 2 Diabetes, IFG, IGT
$n = 222$

Type 1 Diabetes: $n = 26$
Type 2 Diabetes: $n = 204$
Impaired Glucose Tolerance: $n = 40$

Overt Type 2 Diabetes
- 2 x Random Blood Glucose levels
  > 11.1mmols
$n = 6$

Maturity Onset Diabetes of the Young
(included in type 2 diabetes data)
$n = 1$

Subjects Screened with OGTT
$n = 215$

Type 2 Diabetes: $n = $ 53
IGT: $n = 84$
IFG + IGT: $n = 1$
 (included in IGT data)
Normal: $n = 78$

159