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Diabetes mellitus and its effects on pilot performance and flight safety: A review

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EXECUTIVE SUMMARY

Diabetes mellitus is a disease with a wide spectrum of severity and many potential complications if inadequately treated. These include the risk of hypoglycaemia, ketoacidotic coma, cardiovascular disease, and kidney, eye and neural disease. The prevalence of diabetes is increasing both in Australia and around the world, and is increasing the costs associated with medical care. In Australia, 7.4% of the population have diabetes, and 16% have impaired glucose metabolism. In 1995, the health care costs associated with diabetes in Australia were estimated to be $1 billion.

Historically, diabetic pilots have been permanently disqualified from flying duties. This policy was based on the increased risk of sudden incapacitation in-flight due to hypoglycaemia and cardiovascular disease in diabetics. In recent decades, a shift in worldwide aeromedical policy has occurred. This has resulted in diabetic pilots in several countries, including the United States and Australia, being granted limited flying certification. These pilots are required to satisfy a number of stringent medical criteria to achieve this certification.

Aeromedical policy must be based on an appropriate risk management strategy, taking into account all relevant issues. Australian guidelines for the certification of diabetic pilots are designed to limit certification to all but the most well-controlled, motivated, and well supervised diabetic with no disease-related complications. Strict adherence to this policy by those involved in the certification process should ensure the continued safety of all involved in the aviation industry. Ongoing evaluation of the policy and research into the aviation safety outcomes of diabetic pilots is recommended.

INTRODUCTION

Diabetes mellitus is a complex disease with a wide spectrum of severity. It is also a disease with an increasing prevalence in modern society. Some authors have likened it to an epidemic, with more than 170 million people worldwide suffering from diabetes (98). In the US, 7.3% of the adult population have diabetes (74). Diabetes is the seventh leading cause of death in both Australia and the US, and is the tenth leading cause of chronic illness in the US in the 45 to 64 years age group (54). Diabetes affects 1 in 10 adults over 65 years in the US (54). Australia has one of the highest recorded prevalences of diabetes among developed countries, with 7.4% of the population having diabetes (28). This represents a three-fold increase over a 20 year period. Sixteen percent of Australian adults have impaired glucose metabolism, which is a strong risk factor for full diabetes and cardiovascular disease (28,32). Significantly, only half of those who have diabetes have been diagnosed (28,54,63,74).

Worldwide, the prevalence of diabetes is increasing (10,51,54,74,76,92,98). Experts now predict that by 2010 the number of people with diabetes will have increased by 50%, with the biggest increases in developing countries such as Asia and South America (98,108). By the year 2010, the number of people with diabetes in Australia is expected to be 33% more than in the year 2000 (108). It is estimated that by 2025, 300 million people worldwide will suffer from diabetes (108).

Diabetes places an enormous strain on healthcare systems and budgets (10,55,74,78,91,97). Diabetes is the most common endocrine problem encountered in medical practice (16). In 1995, the total minimum cost of diabetes in Australia was estimated at $1 billion (10). In 1997, the direct and indirect health costs associated with diabetes in the US were estimated at US$98 billion (74).

Until relatively recently, the task of completing a review of diabetes and pilots would not have been possible. Historically, the diabetic pilot has been an oxymoron. A person applying to become either a military or civil pilot who was found to be diabetic on initial medical screening was rejected, and any pilot who developed diabetes was generally permanently disqualified. That situation has changed in recent years, and there is now a small but potentially growing group of diabetic pilots. This is still a controversial development in aviation, with much ongoing discussion.

The purpose of this report is to review diabetes mellitus in terms of its effects on pilot performance and flight safety.

The review will first examine in detail the clinical syndrome of diabetes, in terms of its metabolic basis, diagnosis, classification, causes, complications and treatment. Then, the implications of diabetes in the aviation environment, in terms of pilot performance and flight safety, will be discussed in conjunction with a review of the limited available literature on the diabetic pilot. Finally, the issues involved in the aeromedical certification of the diabetic pilot will be considered at length.

1 DIABETES MELLITUS

1.1 The metabolic basis of diabetes

Put simply, diabetes can be defined as an excess of sugar in the blood. It reflects an underlying problem with carbohydrate metabolism (14). In order to understand the syndrome of diabetes, and how it causes morbidity and mortality in sufferers, it is beneficial to have an understanding of the normal process of metabolic control of blood sugar, and why this is important to normal functioning of the body's systems.

Maintenance of adequate fuel supplies for working tissues and an ideal body weight involve careful control of the process of metabolism. The fuel for most body processes is glucose, taken in the form of complex carbohydrate in the food that we eat. Indeed, glucose is the major energy source for the brain (38). The glucose liberated as a result of the digestion process is then taken up by the blood for delivery to the end-organs for which it acts as a fuel source.

Under normal circumstances, the human body maintains relatively tight control of the blood sugar level, in order to prevent the adverse consequences of either too little or too much blood sugar. The human body has, over the generations, adapted to periodic eating with periods of fasting in between. As such, various hormones are produced at different times in order to lower the blood glucose level and promote glucose storage after eating, and to increase blood glucose levels and liberate glucose from storage sites during periods of fasting between meals. In this way, maintenance of normal carbohydrate metabolism can be achieved through the coordinated interaction of glucose and the various controlling hormones (27).

One of the key regulating hormones for the control of blood glucose is insulin. Insulin is a complex molecule, produced in the β (beta)-cells of the Islets of Langerhans in the pancreas (1,34,44,96). These islets comprise only about 3% of the pancreatic mass, but their importance in metabolic control is much more significant. The islets comprise not only β-cells but also other cells which produce different hormones necessary for metabolic control (such as glucagon, which works in the opposite way to insulin).

Insulin is secreted by the β-cells of the pancreas, initially as a precursor hormone known as proinsulin. This molecule is then hydrolysed to yield the active insulin hormone and a metabolically inactive C-peptide fragment. Cleavage of the proinsulin molecule into insulin and C-peptide occurs in the β-cell (16). The level of C-peptide can be used as an indicator of endogenously secreted insulin (16).

After eating, blood glucose levels rise. This in turn triggers the release of insulin from the pancreatic β-cells. Insulin has several major target tissues, namely the liver, skeletal muscle and fatty tissue (1). The liver has an important role to play in glucose control, acting as both a storage depot and a producer of glucose. It takes up glucose when there is an abundant supply in the blood, storing it in the form of glycogen, and reducing its own production of glucose. When the blood glucose level is low, as in the fasting state, it releases glucose into the circulation. This glucose is derived from the breakdown of internal glycogen stores and an increased endogenous production of glucose (27). There is emerging evidence that the kidneys also play a role in glucose metabolism (70,97).

Insulin's role in the metabolic control of glucose is to reduce an excess level of glucose in the blood to the normal range. It does this through several modes of action. First, it facilitates the transport and uptake of glucose from the blood into

skeletal muscle and fat cells. Second, it suppresses the endogenous production and release of glucose from significant storage deposits in the liver. Third, insulin increases the rate of synthesis of glycogen in the liver.

In the fed state, the effects of insulin predominate, whereas in the fasting state, other hormones that promote glucose release into the blood stream predominate and insulin levels are significantly decreased. The net effect of this whole complex regulatory process is that blood glucose levels tend to be controlled within a fairly tight range.

Considerable controversy still surrounds the precise mechanism of action of insulin, especially at the molecular level (1,49,71,86). Some researchers are directing their attention to the role of insulin receptors in order to provide clues as to the pathogenesis of diabetes (49).

Diabetes mellitus thus represents a failure of this metabolic control process. It can be characterised by hyperglycaemia (high blood glucose) in the fasting state, accompanied by an exaggerated post-eating increase in blood glucose level (27).

1.2 Diagnosis of diabetes

The diagnosis of diabetes is either made when a patient presents with symptoms of diabetes or when there is an incidental finding of hyperglycaemia (high blood glucose) or glycosuria (elevated glucose in the urine) during a routine medical examination. The diagnostic criteria for diabetes are based on World Health Organisation (WHO) guidelines, shown in Table 1 (98).

Table 1. WHO diagnostic criteria for diabetes mellitus

	Fasting Blood Glucose	Two-hour post-glucose load
Diabetes mellitus	$\geq$ 7.0 mmol/L	$\geq$ 11.1 mmol/L
Impaired glucose tolerance	< 7.0 mmol/L	$\geq$ 7.8 and <11.1 mmol/L
Impaired fasting glucose	$\geq$ 6.1 and < 7.0 mmol/L	< 7.8 mmol/L

The standard glucose tolerance test involves the administration of an oral 75 g glucose load, with the blood glucose level then being determined two hours later.

The presenting symptoms of diabetes can be varied and multiple. Typically they consist of excessive thirst (polydipsia), increased urination (polyuria), loss of weight, fatigue, tiredness, and persistent infections (1,2,34,44,73,75). Occasionally, neuropsychological symptoms such as depression, anxiety, forgetfulness and panic may also be seen (47,54). Rarely, the life-threatening consequences of diabetes, such as hypoglycaemia or ketoacidotic coma may be the initial presenting symptoms.

1.3 Classification of diabetes

There have been several classifications of diabetes in use over the years. The current classification is discussed here. In 1936, two distinct types of diabetes were first described (34,37). These two types are distinct in terms of genetic and metabolic features, and are now universally known as type 1 and type 2 diabetes mellitus (2,63).

1.3.1 Precursor states

As shown in Table 1, the WHO guidelines also define two precursor or pre-diabetes states: impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). In Australia, 10.6% of the population aged 25 or more years and older have IGT, while 5.8% have IFG (28). Impaired glucose tolerance is defined as hyperglycaemia with glucose values intermediate between the normal range and that of diabetes following a glucose load (108). It affects approximately 200 million people worldwide (108). Impaired fasting glucose is defined as an elevated blood glucose level after fasting, with a normal glucose level two hours after an oral glucose load (108).

These precursor states are important, since they represent an increased risk of developing diabetes in the future (108). 7% of sufferers with impaired glucose metabolism will progress to full diabetes per year. Approximately 40% of people with IGT progress to full diabetes mellitus over a five to ten year period (108). These precursor states also have an increased risk of some diabetic complications, especially cardiovascular disease (31,108).

1.3.2 Type 1 diabetes

Type 1 diabetes mellitus (previously known as insulin-dependent diabetes mellitus or IDDM) accounts for approximately 10% of diabetes, and is marked by a decreased ability to produce insulin (1,28,34,44,73). It is the most life-threatening form of diabetes. Type 1 diabetics are more prone to coma, caused by poor glycaemic control and a phenomenon known as ketoacidosis (1,2,34,73).

The onset of type 1 diabetes is usually in children and adolescents (1,16). However, there is a bimodal curve for the age of onset in type 1 diabetes – the first peak is seen in early adolescence, close to puberty, and the second peak occurs in the fifth decade. Adults developing type 1 diabetes tend to have a longer duration of symptoms prior to diagnosis than adolescents, and also tend to have better preservation of residual beta cell function (46). Type 1 diabetes demonstrates interesting geographic variation—in the UK, type 1 diabetes is more frequent in Scotland than in other parts of the UK, while it is 35 times more common in Finland than in Japan (44).

1.3.3 Type 2 diabetes

Type 2 diabetes mellitus (previously known as non-insulin-dependent diabetes mellitus or NIDDM) accounts for 90% of total diabetes, and is increasing in prevalence worldwide (1,8,10,28,34,44,55,98,101). The onset of this form of diabetes is typically in adulthood. It is usually characterised by obesity, insulin resistance, insulin secretory dysfunction and overproduction of glucose in the liver (1,16,27,34,44,58,63,69,92,105). Type 2 diabetics are less prone to coma.

The prevalence of type 2 diabetes increases with age, inactivity and body weight. Since 1981, the prevalence of type 2 diabetes in Australia has more than doubled,

with the total number of cases increasing three times (28). In Australia, 20% of the population in the over 60 years age group have type 2 diabetes (28). In the US, the prevalence of type 2 diabetes in women in the 45 to 54 years age group is 4.3%, rising to 8.9% in the 65 to 74 years age group (44).

Obesity is a key risk factor for the development of type 2 diabetes. Some authors have described the rise in type 2 diabetes as an epidemic, due to the increasing level of obesity in modern society (36). In Australia, approximately 30% of the adult population is obese. In the US, obesity has increased by 70% in adults aged 18 to 29, and type 2 diabetes has increased by 70% in adults aged 30 to 39. Young adults therefore represent the fastest growing adult group for both type 2 diabetes and obesity (36). It is estimated that by 2020, 250 million people worldwide will suffer from type 2 diabetes (92).

1.4 The cause of diabetes

In general terms, type 1 diabetes is a total insulin deficiency caused by the autoimmune destruction of pancreatic islet β-cells (16,34,44). While the genetic causes of type 1 diabetes in humans are not well understood, it is known that certain genes within the major histocompatibility complex of humans contribute to the development of type 1 diabetes.

A pathogenetic model of the cause of type 1 diabetes has been described (16,29). According to this model, there are six stages in the development of type 1 diabetes. First, there is an inherent genetic susceptibility to type 1 diabetes, the basis of which still requires further understanding (1,16,65). Second, a triggering agent is introduced. This trigger may be environmental, and there is evidence that some drugs and viral infectious agents (such as the Coxsackie virus or rubella virus) are able to trigger the onset of type 1 diabetes in a genetically susceptible individual. About 20% of persons born with a congenital rubella infection will develop diabetes later in life (29).

The third stage occurs when the triggering agent leads to activation of the autoimmunity process in genetically susceptible individuals. White blood cells known as lymphocytes invade the pancreas and begin to destroy the islet cell mass. Antibodies that react with islet cells can be detected in patients up to 10 years before the onset of type 1 diabetes (16). This lymphocytic invasion of the pancreatic islet cells is known as insulitis, and results in progressive beta cell destruction (16,29). This then results in the fourth stage, where there is progressive loss of glucose-stimulated insulin secretion.

The fifth stage occurs when approximately 90% of the pancreatic beta cell mass is destroyed, and overt clinical type 1 diabetes becomes apparent with signs and symptoms of poor glucose control (16). During this stage, there is still some residual insulin secretion from the remaining 10% of the pancreatic beta cells. Inflammation within the pancreas is also still usually present, and this tends to correlate well with residual beta cell function. The sixth stage occurs when there is complete beta cell destruction, and all insulin secretory capacity is eliminated. This process can take up to nine years (29).

Type 2 diabetes is a very heterogeneous disease with a complex multifactorial pathogenesis. Genetic factors are also involved, but these are less well understood (32,81,98,101). The genetic influence is well illustrated by studies in identical twins, which demonstrate a more than 90% concordance for type 2 diabetes (34,98). There thus appears to be a strong polygenic cause for type 2 diabetes, although the precise genes responsible have not yet been identified (32).

Environmental influences on the development of type 2 diabetes such as age, diet, increasing body weight and physical inactivity are well understood (32). Lifestyle and overeating tend to be the dominant associated factors with the onset of type 2 diabetes (1,2,34,44,98). Typical type 2 diabetes sufferers tend to be obese. As seen previously, the prevalence of both obesity and type 2 diabetes is increasing.

Type 2 diabetes is associated with the presence of insulin resistance (9,23,32,48,59,93,98). Insulin resistance, which plays a major role in the development of type 2 diabetes, can be defined as the effects of insulin being less than expected (48,50,98). Target cells such as liver and muscle are resistant to the effects of insulin, leading to impaired glucose uptake and disposal, accelerated endogenous glucose production and impaired fatty acid metabolism (23,48,90,98). Fasting hyperglycaemia occurs as a consequence of this insulin resistance. Insulin levels may be high in the face of persistent hyperglycaemia, which worsens after eating due to the poor overall insulin response (44). Such insulin resistance is strongly linked with obesity and inactivity.

Type 2 diabetes is also associated with various insulin secretory problems, due to different levels of beta cell dysfunction (33,98,102,105). The problems with impaired beta cell function in type 2 diabetes are not well understood. Although autoimmune destruction of beta cells does not occur, there is evidence based on post-mortem studies of a reduction in beta cell mass over time in type 2 diabetes (1,2).

1.5 Complications of diabetes

Diabetes is a significant disease, which can produce a multitude of acute and chronic complications, as well as increasing the risk of other disease processes such as heart disease, stroke, amputation and death (8,41,104). Untreated diabetes is life-threatening. Indeed, most diabetics tend to die from complications of diabetes and the disease shortens life expectancy by an average of 5 to 10 years (8).

1.5.1 Acute complications

Acute complications are generally a result of either inadequate or excessive control of blood glucose. Hypoglycaemia is a significant and life-threatening complication of an excess of insulin. It is the major complication of insulin therapy. As such, it is much more commonly seen in type 1 diabetic patients. Hypoglycaemic episodes are common in type 1 diabetes, with asymptomatic episodes of moderate hypoglycaemia occurring at frequencies up to twice per week (22,26,82).

Untreated, hypoglycaemia can prove fatal. Symptoms and signs of hypoglycaemia are widespread, and include sweating, shakiness, anxiety, palpitations, weakness, tremor, hunger, faintness, increased heart rate, double vision, headaches, irritability, confusion, motor incoordination, and, in serious forms, convulsions and coma (1,2,34,73,75). Treatment of hypoglycaemia involves giving the patient a sugar load, to improve the blood glucose level and therefore central nervous system function. Many of the symptoms of hypoglycaemia are due to the widespread effects of various hormones attempting to increase blood glucose levels. Other symptoms are due to central nervous system dysfunction caused by inadequate fuel supplies being delivered to the brain.

In contrast, poor blood glucose control that is secondary to an insufficient level of insulin in a type 1 diabetic results in persistent hyperglycaemia which can then lead to a condition known as diabetic ketoacidosis (1,2,34,75) This is also life-threatening if not treated adequately and promptly as it can develop into a

ketoacidotic coma. Patients may present with dehydration, shortness of breath, and altered mental states, including unconsciousness and coma. They have generally been suffering in the days prior to the ketoacidotic event with all the symptoms of elevated blood sugar including frequent urination, thirst, weight loss, nausea, vomiting, anorexia and occasionally abdominal pain. Treatment involves lowering the blood sugar level, and many different insulin regimes have been used for this successfully. Often an event such as emotional stress, an infection, trauma or a cardiovascular event may precipitate poor glucose control and ketoacidosis.

There are some acute visual symptoms that can occur in association with poor diabetic control. Transient visual acuity changes and sudden changes in refraction in diabetics were first reported in 1925 (46). These changes are attributed to osmotic fluctuations caused by hyperglycaemia and a resulting change in the shape of the lens. Transient 'sugar cataracts' have also been reported as occurring early in the course of diabetes (46).

Diabetes can also cause some acute neurocognitive impairment. Researchers have found that during a visual reaction time test, complex cognitive processing required significantly longer response latencies during hypoglycaemia. Their findings indicate that complex decision-making skills are disrupted during hypoglycaemia. They also reported that performance changes during hyperglycaemia were more subtle, but trended towards poorer performance. In overall terms, it appears that some cognitive skills are particularly sensitive to acute blood glucose fluctuations (38).

1.5.2 Chronic complications

The chronic complications of diabetes reveal themselves in most major organs and tissue groups of the body. The most significant chronic complication of diabetes is vascular damage, involving both small and large blood vessels, as a consequence of the effect of diabetes on accelerated atherogenesis (formation of degenerative lesions in blood vessel walls).

Macroangiopathic damage (large blood vessel disease) to the heart and major blood vessels can lead to cardiovascular disease making diabetes a significant risk factor in the development of heart disease, hypertension and stroke (1,2,34,44,62,73,75,98). The risk of cardiovascular disease in patients with type 2 diabetes is two to four times greater than in non-diabetics. Type 2 diabetes of early onset in young adults (18 to 44 years) is associated with a more aggressive form of disease from a cardiovascular viewpoint. Such patients have a higher risk of cardiovascular disease than age-matched controls, with 14 times the risk of a heart attack (36).

Accelerated atherogenesis produces both microangiopathic and macroangiopathic damage to many organs. In the kidney, this damage results in the development of diabetic nephropathy (kidney damage secondary to diabetes), which may lead to kidney failure in extreme cases. The small blood vessels of the retina in the eyes are also sensitive to the effects of persistent hyperglycaemia, and the microangiopathic damage associated with this level of poor metabolic control can result in diabetic retinopathy. This is a leading cause of blindness in adults, leading to various degrees of retinal damage which may be permanent. Diabetic retinopathy can lead to partial or complete loss of visual function. It has been shown that by 20 years after diagnosis, almost all type 1 diabetics and more than 60% of type 2 diabetics have some degree of diabetic retinopathy (52).

Peripheral vascular disease can also occur more commonly in diabetics. This is due to atherosclerosis (degenerative plaque formation) in the peripheral blood vessels. This can result in slow healing, persistent foot ulcers, and poor peripheral blood supply. It is this process that results in the increased susceptibility to some infections and the higher risk of limb amputation in the diabetic patient.

Furthermore, diabetes can lead to damage to peripheral nerves resulting in a condition known as peripheral neuropathy. Diabetic neuropathy is a common disabling condition associated with diabetes (1,34,44,73,75). It can increase the degree of morbidity and reduce the sufferer's quality of life to a significant extent. It can result in ulcers and pressure sores on weight-bearing areas, sexual dysfunction, gastrointestinal disturbance and increases the risk of amputation (2,8).

1.6 Treatment of diabetes mellitus

Not surprisingly, a complex disease like diabetes can sometimes involve complex treatment. The goals of diabetic treatment in general terms are the control of blood glucose levels and the prevention of long-term complications.

Diet is an extremely important component of treatment. This involves ensuring the correct caloric intake to meet the body's energy needs, appropriate timing of meals, the appropriate proportion of carbohydrates in the total caloric content, and the correct types of food (slowly digested and absorbed foods are recommended).

In type 1 diabetes, insulin replacement therapy is required (1,2,34,44,75,95,100). There are several regimes available for this, as well as various forms of injectable insulin (with different durations of action, and derived from different sources, such as beef, pork or synthetic human insulin). Interestingly, in 10% to 25% of type 1 diabetes sufferers, a remission after initial diagnosis will occur with reduced or no insulin being required to maintain normal blood glucose levels. The duration of this so-called 'honeymoon' period is often less than 18 months, after which insulin therapy is again required (16).

Self-monitoring of blood glucose levels is now a standard part of a diabetic management and treatment strategy. This is especially true for type 1 diabetics, who may need to tailor their insulin therapy to their blood glucose monitoring results.

Glycosylated haemoglobin, or HbA1c, can be used as a measure of the quality of blood glucose control, at least from a retrospective point of view. HbA1c gives a measure of how well blood glucose has been controlled in the preceding months. The level of HbA1c reflects the average exposure of a red blood cell to glucose over its life span (approximately 120 days). In normal individuals, glycosylated haemoglobin may constitute 5% to 8% of the total haemoglobin, whereas in poorly controlled diabetics it may be as high as 20%. With good control, the level of HbA1c will decrease and approach that of a non-diabetic. As such, HbA1c measurements are useful in giving an overall assessment of the quality of metabolic control (1,34,44).

HbA1c of less than 7.2% and average blood glucose levels in the range of 8 to 8.5 mmol/L are considered appropriate treatment goals (26). The results of the work of the Diabetes Control and Complications Research Group showed quite clearly that intensive therapy with tight control effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy and neuropathy in type 1 diabetic patients. However, this tight control had some adverse consequences—the research showed a two to three times greater risk of hypoglycaemia in these patients

(44,57,100). Furthermore, in more than a third of cases, no warning symptoms were experienced prior to a severe hypoglycaemic event (100).

Since lifestyle factors are of such key importance in the development of type 2 diabetes, most of the treatment strategies initially focus on these factors (1,11,12,18,20,25,34,44,53,59,73,75,79,91,101,105). A study in Finland showed that making lifestyle changes in terms of diet and exercise reduced the risk of diabetes by 58%, with a near zero incidence four to five years later (101). The effect of lifestyle intervention in terms of proper eating habits and regular exercise on reducing the incidence of type 2 diabetes has been shown in several studies (25,101,105). Weight loss and exercise have been shown to be more effective than some oral hypoglycaemic drugs (25).

Various oral hypoglycaemic agents have been developed and used in the treatment of type 2 diabetes (1,6,9,44,59,60,73,75). In general terms, these drugs can be grouped into broad categories—the sulphonylureas (examples include chlorpropramide, glypizide), the biguanides (such as metformin), the thiazolidinediones (such as rosiglitazone) and other drugs such as acarbose and even salicylate (19,50). All of these drugs work in different ways, have different types and degrees of side-effects, and varying levels of efficacy. A comprehensive review of all available oral hypoglycaemic agents is beyond the scope of this paper. However, a few general points can be made.

The sulphonylurea class is effective in most type 2 diabetics and was the first category of hypoglycaemic agents. They work by increasing the release of insulin from the pancreas. Hypoglycaemia is their biggest side-effect, which limits their ability to ensure tight glycaemic control (35,43,85).

Metformin is the only biguanide drug available now. It can effectively lower blood glucose in type 2 diabetes. The actual mechanism of action of metformin remains unknown, but it appears to inhibit glucose release from the liver (23). Its main advantage is that it does not have the same risk of hypoglycaemia as the sulphonylurea class. It also appears to favourably affect cholesterol and lipid metabolism (23,60). Metformin has been shown to reduce the incidence of type 2 diabetes in high-risk people by as much as 31% (25). It does have its side-effects however. Metformin is associated with vitamin B_{12} deficiency, which is a potentially serious side-effect (4).

The thiazolidinediones, or glitazones, appear to decrease insulin resistance (8,89). Early examples of this drug class were associated with significant liver damage, leading to their withdrawal from the market. Newer examples such as rosiglitazone are still approved for diabetic use. These drugs tend to also enhance vascular function and improve lipid imbalances.

There are several other issues to note in terms of overall diabetic treatment and management. The occasional neuropsychological symptoms such as depression and forgetfulness may have implications for compliance of patients with treatment (47,54). Fat hypertrophy at injection sites can create an artificial depot for insulin, leading to lower than expected insulin levels and erratic insulin release, and thus correspondingly inadequate treatment (26). Since type 1 diabetes is an autoimmune disease, various immunosuppressive agents have been used to try to induce remissions. Some of these have been successful, but there does not appear to be a lasting and persistent response in the long term beyond one year (34).

2 AEROMEDICAL IMPLICATIONS OF DIABETES MELLITUS

2.1 Overview

Flying an aircraft is a complex task. Pilots require a high level of cognitive functioning and psychomotor skill to ensure the safe and efficient operation of the aircraft. Diabetes is a disease with a wide spectrum of severity and its treatment has some potentially adverse consequences. Thus, there are significant aeromedical implications associated with diabetes in the flight environment.

The biggest risk is that of sudden incapacitation of the pilot in-flight. Such an event can seriously jeopardise flight safety and endanger the lives of not only the pilot and passengers, but also those on the ground should the aircraft crash. The development of hypoglycaemia in a diabetic pilot is the complication of greatest concern (34). This can lead to impaired decision-making, disorientation, poor performance at cognitive skills, confusion and unconsciousness (2,34,38,44,75). A diabetic pilot on insulin or one of the sulphonylurea class of oral agents has some risk of hypoglycaemia, as seen previously. If the aim of the treating medical staff is to ensure tight control to prevent diabetic complications, then the pilot has up to three times the risk of a hypoglycaemic event. If such an event occurs in-flight, the results could be catastrophic.

Hyperglycaemia, either through poor control or a deliberate attempt to prevent in-flight hypoglycaemia, can also pose problems to a pilot. Longer term it can increase the risk of serious complications, some of which are of themselves disqualifying for flight. It can also cause short-term problems such as visual impairment, refractive changes, and poor performance of cognitive tasks (38,46). There is also a risk of ketoacidosis occurring, which may progress to coma if untreated. These issues represent a hazard to the safe conduct of the flight.

The complications of diabetes may limit the ability of a pilot to satisfy the regulatory authorities as to their ongoing fitness to fly. For instance, diabetic neuropathies may interfere with the pilot's ability to manipulate the controls of the aircraft safely. Cardiovascular disease or renal disease secondary to diabetes and/or poor diabetic control may also lead to loss of flying privileges. Similarly, the visual complications of diabetes such as retinopathy may also render them unfit to fly.

The effect of the aviation environment on the natural history of diabetes and its chronic complications remain to be fully evaluated (61). However, a case report was published in 1995 where flight in a pressurised aircraft cabin made a diabetic retinal complication in a passenger worse (24). Insulin resistance has even been seen in astronauts, which is a process thought to be secondary to the loss of body protein from skeletal muscle in the absence of the normal gravitational loading (94).

The modern aviation environment imposes additional logistic problems on the diabetic pilot. Flying, especially commercial flight operations, often involves fatigue, irregular daily schedules, and eating away from home (99). In addition, transmeridian flight adds another dimension to insulin treatment schedules. In-flight monitoring of glucose levels, if required by the flight duration or by the regulatory authorities, represents another layer of workload for the pilot to contend with, and can be distracting in terms of situational awareness and orientation. Furthermore, diabetes represents an additional problem to consider and deal with in a post-crash survival setting.

The aviation medicine literature contains a number of reports of in-flight incapacitation of pilots. While most cases of such incapacitation have been attributed to gastrointestinal causes (42,56), some cases where diabetes was responsible for the incapacitation have been reported (13,66,83,84). In a number of these cases, the diabetes was symptomatic, but no formal diagnosis had yet been made.

One case was described of a navigator who had flown with diabetic symptoms for a two month period, before becoming incapacitated in the air during a mission and then going on to die some two days later in hospital (84). In another example, the pilot in command of an aircraft which crashed on approach to land in bad weather was found at post-mortem examination to have most probably died of heart failure in-flight. The pilot had been on medication (not defined) for both coronary artery disease and diabetes (13).

It must be noted, that in most of these cases, diabetes had not been diagnosed at the time of the accident, and that the treatment of diabetes and the ability to achieve good glycaemic control have both improved substantially since these accidents occurred.

In a survey of 15 insulin-taking glider pilots, one pilot admitted landing due to diabetic reasons. One had had a landing accident before being diagnosed, and stated that his undiagnosed condition had hindered his thinking and decision-making. All took some form of carbohydrate with them while flying. Three had noticed a hypoglycaemic event in the previous week, three more within the previous month, and all within the previous five years. All considered themselves to be fit and safe-to-fly gliders. However, one had retinitis sufficient to almost ban him from driving a car. One had also suffered a heart attack. The author of this study suggested that the problems faced by diabetic recreational glider pilots are manageable, and that there is no evidence that flying gliders represents a greater hazard than driving on a highway. The author stated that insulin-requiring glider pilots who satisfy the current driving rules (used as the basis for glider pilot medical certification in the UK) should be allowed to fly gliders solo (88).

It is worth examining briefly the issue of diabetic drivers. Are they more at risk of an accident than non-diabetics? The research is somewhat equivocal. Some reports suggest that type 1 diabetic drivers are more likely to have accidents than type 2 drivers (21,26). Other studies report different results. In a study of type 1 diabetic drivers, 103 had symptoms of hypoglycaemia while driving during the previous year. Twelve reported hypoglycaemia as having caused an accident. The authors found that in overall terms, diabetic drivers treated with insulin and under adequate medical supervision have no more accidents that non-diabetic drivers (23% versus 25%). The authors suggest that diabetic drivers may be more careful drivers as they are aware of the risks involved. However, this study was based on the results of a self-reported questionnaire, and the data must therefore be interpreted with caution (95).

2.2 Aeromedical certification of diabetic pilots

In view of all the potentially adverse consequences of diabetes, especially the risk of hypoglycaemia and loss of consciousness, the historical approach to the certification of the diabetic pilot was generally one of permanent disqualification from flying duties (14,73). There are many reports in the aviation medicine literature of permanent disqualifications of civil and military pilots due to diabetes (5,7,14,16,39,45,61,67,103,107). In a study examining medical disqualification in USAF aircrew, diabetes was the fourth most frequent reason for disqualification

(107). In the civil aviation setting, diabetes has been found to be the third most common reason for disqualification, accounting for approximately 10% of disqualifications (14). However, some diabetics have been waivered to return to flying, usually if they are type 2 diabetics treated by diet and exercise alone (5,16,61).

In the last 20 or so years, the standard approach to the aeromedical certification of pilots with diabetes has changed from one of permanent disqualification to one of fitness to fly, subject to certain relatively stringent conditions being met. This shift in aeromedical policy did not occur without controversy, and indeed this controversy still continues. The reasons for the policy shift are numerous. In 1984, the American Diabetes Association published a position paper stating that any person with diabetes should be eligible for employment if they are qualified for the particular job. This position was restated in a recent publication in 2004, where they emphasized that people should be individually considered for employment based on the job requirements and their particular diabetic condition, history and treatment requirements (3).

Diabetes continues to have significant implications for an individual's employment, especially in terms of job choice and entry into safety-sensitive areas. Many reports have shown that unemployment and diabetes are closely related (30,40,55,64,68,87). Nine per cent of diabetic patients have had to change their jobs because of their disease (87).

Years of lobbying by vested interest groups ultimately led to a change in the aeromedical policy of the US Federal Aviation Administration (FAA). As a consequence, some diabetics controlled by oral hypoglycaemic agents were granted permission to fly in 1986; in 1992, insulin-requiring air traffic controllers were certified for duty; and in the late 1990s, some insulin-dependent diabetics were granted aviation medical certificates, but only at Class 3 private pilot level (73). Current FAA guidelines are very stringent, and require close medical supervision, good glycaemic control and no diabetic complications. The certification protocols for both type 1 and type 2 diabetes are complex.

While the numbers of insulin-requiring diabetic pilots remains small, their numbers worldwide are increasing. One study shows that diabetes occurs in 3% of airline pilots in the 45 to 64 years age group and 22% in the 65 to 74 years age group (77). Another study revealed that there were 234 diabetic inquiries in response to an aviation medicine advisory service, 16% of which were for type 1 diabetes (80). Out of a total of 2071 Japan Airlines pilots, 92 were found to have either impaired glucose tolerance or type 2 diabetes (99).

Aeromedical certification is a process of risk identification and management, with policy ideally based on robust scientific evidence (13,17,44). Furthermore, aeromedical standards should realistically and practically reflect the requirements for safe and efficient operation of the aircraft, especially in terms of the probability of in-flight incapacitation of the aircrew (13,17). The application of aeromedical standards should help to ensure the overall safety of the aviation system by only allowing medically and psychologically fit pilots to fly.

However, a 'blanket' approach to aeromedical certification may not be appropriate, as it could unfairly disqualify a number of pilots who may represent no additional hazard to flight safety. This is an idea encapsulated in the policies of the International Civil Aviation Organization (ICAO), whose ICAO standard 1.2.4.8 is also known as the 'flexibility standard' (72). Under this standard, ICAO signatory nations (such as Australia) are able to take into account accredited medical conclusion, operational limitations, and experience and qualifications of the pilot in

order to reach a decision regarding aeromedical certification. This approach underscores the inability of aeromedical policy to cover every aeromedical situation for every pilot.

It must also be recognised that aeromedical standards need to be continually reappraised in light of the results of ongoing medical research and improving treatment outcomes. Aeromedical policies need to be sufficiently flexible in order to take these developments into account and thereby remain evidence-based, justifiable and legally defensible.

On that basis, it is fair to say, as some authors have, that not all diabetics can be considered as fit to fly. However, by the same token, it may be unfair to universally disqualify all diabetics from flying duties on a permanent basis, as was the historical case (14,34). This is consistent with the stated employment policy of the American Diabetes Association, although some authors still oppose this view (3,15).

The issue therefore is how to allow diabetic pilots to fly while maintaining the overall safety and integrity of the aviation transportation system. Regulators have addressed this issue by imposing stringent requirements on diabetic pilots that must be satisfied before they are allowed to fly. The underlying reasoning is that if the pilot is able to satisfy these conditions, then the risks of an adverse diabetic-related event will be minimised, as only the truly fit and well-controlled diabetics will be flying. This is consistent with the ICAO flexibility standard.

Clearly, if the diabetic pilot has significant complications or a markedly increased risk of incapacitation in-flight, the aeromedical decision to disqualify them is straightforward and justifiable. As an example, in a study examining possible re-certification of heart transplant recipient pilots, it was found that in those pilots with pre-transplant type 1 diabetes, the risk of sudden death in the following 12 months was much higher. The authors concluded that the presence of type 1 diabetes in a pilot receiving a heart transplant should be a disqualifying condition, since the risks of adverse consequences were considered to be too high (68).

For more typical diabetics, the decision-making approach requires a careful consideration of all the attendant issues. A thorough understanding of diabetes is mandatory for an informed decision to be reached. For instance, while type 1 diabetics have an increased risk of hypoglycaemia due to the requirement to take insulin, it is known that type 2 diabetics controlled by diet and exercise alone have almost no more risk of hypoglycaemia than non-diabetics. Furthermore, there is some evidence that type 1 diabetic pilots with some residual endogenous insulin secretion have a reduced risk of hypoglycaemia (34).

The weight of scientific opinion therefore is that diabetic pilots can be considered fit to fly if they can satisfy strict criteria that mitigate all the attendant risks of diabetes in the flight environment. These criteria include a blood glucose level in the normal range, evidence of good glycaemic control, absence of diabetic complications, regular blood glucose monitoring and ongoing medical surveillance (14,34,99).

There is however an important potential ethical dilemma, as noted by some authors, in terms of the trade-off between tight control of blood glucose and an increased risk of hypoglycaemia, particularly in type 1 diabetics (34). Put simply, to allow a pilot to fly with less strict glycaemic control, in order to minimise the risk of in-flight hypoglycaemia, exposes the pilot to an increased risk of long-term chronic diabetic complications as a direct consequence of the lack of tight control. This is contrary to the current accepted practice of good diabetic management.

It is important to note that there are no recent published reports in the scientific literature evaluating the aviation safety outcomes of diabetic pilots compared with non-diabetic pilots. Such an analysis, especially in terms of the accident and incident rates among diabetic and non-diabetic pilots, would be extremely useful to aeromedical policy-makers. It is to be hoped that in coming years, with increasing numbers of diabetic pilots, such an objective analysis will be carried out.

2.2.1 Australian regulations

Current Civil Aviation Safety Authority (CASA) regulations are quite stringent when it comes to aeromedical certification of diabetic pilots. According to Civil Aviation Safety Regulation 67 (Tables 67.150, 67.155 and 67.160) a pilot may receive class 1 (commercial pilot) certification if the diabetes is satisfactorily controlled without an anti-diabetic drug, and class 2 (private pilot) and class 3 (air traffic controller) certification even with an oral anti-diabetic drug if the drug is approved by CASA and there is on-going medical supervision and control.

In general, CASA's aeromedical policy requires evidence of good diabetic control and the absence of long-term complications of the disease before granting certification to fly. Multiple specialist reports must be provided by the applicant to demonstrate that they are well controlled and not suffering from complications. Furthermore, there are strict guidelines as to what a diabetic pilot must accomplish during flight to maintain safe flight, in terms of in-flight blood glucose monitoring (with a glucometer equipped with a memory chip) and the requirement to take a source of glucose with them during the flight. There are also restrictions on what class of licence can be held by a diabetic pilot, depending on what sort of diabetes they suffer from and what sort of treatment regime they are on.

To summarise the CASA policy, diabetes controlled by diet alone may be certified to Class 1, 2 or 3 standard if they have evidence of good blood glucose control (HbA1c less than 7.5%), no evidence of diabetic complications and satisfactory specialist medical reports. Diabetics controlled by diet and an oral hypoglycaemic drug may be certified to Class 2 or 3 standard only if they have evidence of good blood glucose control, no side-effects from the drug, no episodes of symptomatic hypoglycaemia in the preceding twelve months, no evidence of diabetic complications and satisfactory specialist medical reports. Diabetics controlled with insulin do not satisfy the certification criteria. However, CASA policy gives the aviation medicine staff at CASA the discretion to grant certification at Class 2 level, as or with co-pilot and in Australian airspace only, provided they can satisfy the same criteria as above, but with serial HbA1c measurements of less than 7.5% at two-monthly intervals over the preceding six months, and no episodes of hypoglycaemia requiring intervention from others.

This policy gives sufficient flexibility to the issue of diabetic pilot certification, which is consistent with the ICAO flexibility standard. It also imposes sufficiently stringent criteria to minimise the risk of a poorly controlled diabetic with a greater than acceptable risk of sudden or subtle in-flight incapacitation becoming certified to fly. However, the medical surveillance requirements of all involved in the process (CASA, the designated aviation medical examiner, and the pilot) are demanding, complex and time-consuming. In order for the policy to work, and for the integrity of the aeromedical certification process and the safety of the aviation industry to be maintained, strict adherence to it by all involved must be considered mandatory.

3 CONCLUSIONS

Diabetes is a serious, potentially life-threatening disease. It has an increased risk of incapacitation and performance impairment due to hypoglycaemia and ketoacidosis, and the long-term chronic complications affect many body organs, including the cardiovascular system, kidneys, nerves and eyes. The aeromedical certification of the diabetic pilot represents a delicate balancing act, between the rights of the individual and the need to protect public safety. A shift in aeromedical policy has led to the adoption of medical standards for diabetic pilots that would have been unthinkable a few decades ago. The strict criteria and medical surveillance requirements imposed on the diabetic pilot under the new policies are designed to ensure that only well-controlled, motivated, fit diabetics with ongoing medical supervision and no diabetic complications will be granted certification and be allowed to fly.

Clearly what is crucial is that the aviation regulator must enforce its own policies, by ensuring adherence to the requirements by diabetic pilots and maintaining a close supervision of their medical status. Failure to do this amounts to an abrogation of a legislated responsibility. Aeromedical certification authorities must also continually review and evaluate their policies, so that they reflect the latest opinion and developments in the medical and scientific understanding of diabetes and its management. Regular analysis of the aviation safety outcomes of diabetic pilots, in terms of incidents and accidents in comparison with the non-diabetic pilot population, must also be conducted. Such activities will help to refine and update their aeromedical risk management approach to the issue of diabetic pilot certification. In this way, all potential risks to flight safety can be adequately identified and managed, thus ensuring the continued safety of all those who travel by air.

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