The Supervisory Committee for Gregory S. Hyland Certifies that this is the approved version of the following Capstone:

Diabetes Mellitus in U.S. Aviators

Committee:

James M. Vanderploeg, M.D.

LaDale St. Clair, M.D.

Randal Reinertson, Ph.D.

Dean, Graduate School

Diabetes Mellitus in U.S. Aviators

by

Gregory Scott Hyland, M.D

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Diabetes Mellitus in U.S. Aviators

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Supervisor: James M. Vanderploeg

Introduction: This project summarizes current information on the risks associated with diabetes mellitus and its medical management amongst aviation personnel. Methods: A literature review was accomplished looking at aviators with diabetes mellitus along with a literature review of the common medications used to treat type 2 diabetes. Results: Several aeromedical agencies do allow pilots with diabetes to operate aircraft, even if they require medical management to include oral or injectable medications for good control of their disease. In general, however, pilots with type 1 diabetes are restricted to non-military, non-transport duties and pilots with type 2 diabetes are more common. The risk for sudden incapacitation is the greatest concern and is increased for a number of medications commonly used to treat diabetes. Discussion: Each aeromedical agency sets it own standards regarding waiver requirements and the information presented in this project represents a general summary of these requirements.

Type 2 diabetes is becoming increasingly prevalent in the aviation community and aeromedical examiners need to be aware of current clinical practice guidelines to ensure that aviators with diabetes remain at low risk for developing sudden incapacitation.

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Chapter 1: Introduction

It is well known that diabetes mellitus is a very prevalent disease in the United States (U.S.) and in many parts of the world. Based on current data from the Centers for Disease Control and Prevention the prevalence of diabetes in the U.S. continues to rise (NDFS 2005). As the prevalence of diabetes increases in the general population, the likelihood that it will adversely affect the aviation community also increases. In recent years civil aviation regulations have been updated to allow selected pilots with diabetes to continue to be medically certified to operate specific aircraft, even if they require medical management to include oral or injectable medications for good control of their disease (FAA 2008). In general, however, civil airline transport, civil commercial and military pilots are not allowed to fly with type 1 diabetes or type 2 diabetes requiring insulin. With the last comprehensive literature review for aviators with diabetes being completed several years ago, current information summarizing the risks associated with diabetes mellitus and its medical management amongst aviation personnel is lacking. For these reasons this project will primarily discuss type 2 diabetes, not requiring insulin, and its medical management.

The relative severity of disease in an aviator and its potential impact on safe aviation performance are considerations in determining whether or not an airman should be given a medical certification to perform flying duties (Corrigan 2008). Currently there is a dichotomy in that maintaining tight glycemic control can increase the risk of a hypoglycemic events while not maintaining tight control will likely result in a higher

likelihood of serious long-term complications (Rayman 2006). It is hoped that the results of this capstone project will culminate in the publication of a Clinical Practice Guideline (CPG) that will be useful for Aviation Medical Examiners (AMEs) and other health care providers who treat aviators and other occupational health workers who are at risk for developing type 2 diabetes. It is also hoped that increased awareness and education among aeromedical examiners and other occupational health physicians will help modify the behavior of aircrew members and therefore result in improving individual health as well as in creating a safer aviation environment.

Chapter 2: Background

In the U.S., there are estimated to be over 20.8 million Americans (7% of the U.S. population) with diabetes mellitus (NDFS 2005). Approximately 14.6 million people have been diagnosed with diabetes mellitus and 6.2 million remain undiagnosed. In addition, approximately 41 million Americans have pre-diabetes mellitus, a condition that may progress to clinical diabetes if not detected and treated early. Hyperglycemia not sufficient to meet the diagnostic criteria for diabetes is categorized as either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Several studies have shown that people with pre-diabetes can take positive action to prevent or delay the development of frank diabetes mellitus. For individuals born in the year 2000, the estimated lifetime risk for developing diabetes is 33% for males and 39% for females (Robard 2007). During the time period from 1980-2004, age-adjusted prevalence rates for diabetes increased by 76% for white men, 65% for white women, 68% for black men, and 37% for

black women (Robard 2007). Other racial/ethnic populations also appear to be disproportionately affected by diabetes. The increase in the prevalence of diabetes during the past 20 years for individuals 20 years or older is likely due to an increase in the prevalence of type 2 diabetes. This increase may be due to an increase in the prevalence of obesity over the same time period. The latest data from the National Center for Health Statistics show that more than 60 million Americans 20 years or older are obese (NDFS 2005). Among individuals with known diabetes, unfavorable upward trends of being obese increased by 15.2% during the time period from 1994-2003 (NDFS 2005).

Diabetes mellitus is an endocrine disorder in which the level of glucose in the blood is higher than normal. It is primarily described as belonging to one of four classifications, with the vast majority of cases falling into two categories: type 1 and type 2. Diabetes mellitus can also occur during pregnancy and in this case is classified as gestational diabetes mellitus. Other specific types of diabetes include genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), endocrinopathies, drug or chemical induced (such as the treatment of AIDS or after organ transplantation), infections, uncommon forms of immune-mediated diabetes, and other genetic syndromes that are sometimes associated with diabetes (Robard 2007). Gestational diabetes and other types of diabetes will not be discussed in further detail in this review.

In all cases of diabetes the elevation in blood glucose is due to the improper production and/or use of insulin by the body. Insulin is a hormone secreted by the pancreas to regulate blood glucose levels. In diabetes, insulin secretion either becomes

deficient secondary to destruction of the pancreatic β-cells or insulin resistance occurs (ADA 2006). Several pathogenic processes are involved in the development of diabetes and range from autoimmune destruction of the pancreatic β-cells with consequent insulin deficiency to abnormalities that result in resistance to insulin action (ADA 2006). Regardless of the process involved, both type 1 and type 2 diabetes result in hyperglycemia. Symptoms of hyperglycemia include polyuria, polydipsia, weight loss with or without polyphagia, and blurred vision. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hypersomolar syndrome along with severe hypoglycemia that is associated with some medical treatment options.

The progression of type 2 diabetes mellitus typically begins with weight gain with excess visceral fat. Between 1980 and 2002, the prevalence of obesity doubled in adults aged 20 years or older (Flegal 2002). Recent data show that more than 60 million Americans aged 20 years or older are now obese. Among individuals with diabetes, upward trends in age-adjusted rates of being overweight or obese were also observed over the last decade (Robard 2007). During that time, age-adjusted rates of obesity increased from 34.9% to 50.1% and being overweight or obese increased from 69.7% to 80.6%. Obesity subsequently can lead to insulin resistance, impaired glucose tolerance, impaired fasting glucose, and finally type 2 diabetes. Most patients with type 2 diabetes are obese and obesity itself causes some degree of insulin resistance. In addition, some patients who are not obese by traditional criteria may have an increased percentage of body fat distributed mostly in the abdomen. As the number of individuals with risk

factors for type 2 diabetes mellitus including obesity continue to rise, all aspects of society are at increased risk from both the direct and indirect adverse effects.

The risk for death among individuals with diabetes mellitus is almost twice that of individuals without diabetes of similar age. Adults aged 65 to 74 years have the highest prevalence of diabetes mellitus (approximately 12 times the prevalence of that seen in adults younger than 45 years. Reasons for the increasing prevalence of type 2 diabetes include aging of the population and the increasing prevalence of obesity (Robard 2007).

RACIAL/ETHNIC CONSIDERATIONS

Type 2 diabetes mellitus is thought to be a multi-factorial disease with the genetics of individuals playing a major role in individual susceptibility. Racial and ethnic groups including African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans and Native Hawaiians or Other Pacific Islanders are at particularly high risk for type 2 diabetes and its complications. Racial and ethnic groups known to be at higher risk should be evaluated more closely during periodic medical evaluations and screening should be conducted as recommended by current clinical guidelines. According to the U.S. Department of Health & Human Services in 2005 the overall age-adjusted total rate for clinically diagnosed diabetes (prevalence) was 54 per 1,000 of the population. The 2005 rates per 1,000 for selected racial and ethnic populations were as follows: Asians, 47; non-Hispanic whites, 49; Hispanics, 73; non-Hispanic blacks, 84; and American Indians or Alaska Natives, 101 (Progress Review 2006). The above data is for diabetes in general and includes both type 1 and type 2.

According to the CDC National Diabetes Fact Sheet for the U.S. in 2005, type 2 diabetes accounts for about 90% to 95% of all diagnosed cases of diabetes. Based on these numbers the prevalence of type 2 diabetes in these racial and ethnic populations is likely to be similar in number.

The prevalence of diabetes (including type 1 and type 2) among racial and ethnic groups aged 20 years or older is 8.7% of all non-Hispanic whites, and 13.3% of all non-Hispanic blacks. After adjusting for population age differences, non-Hispanic blacks are 1.8 times as likely to have diabetes as non-Hispanic whites. After adjusting for population age differences, Mexican Americans are 1.7 times as likely to have diabetes and residents of Puerto Rico are 1.8 times as likely. Sufficient data is not available to derive estimates of the total prevalence of diabetes for other Hispanic/Latino groups (NDFS 2005). Taking into account population age differences, American Indians and Alaska Natives are 2.2 times as likely to have diabetes. For Asian Americans and Pacific Islanders the total prevalence of diabetes is not available. In Hawaii however, Asians, Native Hawaiians, and other Pacific islanders aged 20 years or older are more than 2 times as likely to have diagnosed diabetes after adjusting for population age differences.

In 2003-2005, the 3-year average age-adjusted rate of new cases of diabetes (incidence) among adults aged 18 to 84 years was 7.4 per 1,000 of the population, compared with 5.5 per 1,000 in for 1997-1999. For selected racial and ethnic populations, the rates per 1,000 in 2005 were as follows: for non-Hispanic whites, 6.6; for Asians, 9.1; for Hispanics, 9.8; and for non-Hispanic blacks, 10.4. The above data is for diabetes in general and includes both type 1 and type 2.

CAUSES

Type 1 diabetes mellitus accounts for only 5-10% of all diabetes mellitus cases. It is caused by an absolute deficiency of insulin secretion due to a cellular-mediated autoimmune destruction of the pancreatic β-cells (ADA 2006). This destruction has been associated with several different viruses including congenital rubella, coxsackievirus B, cytomegalovirus, adenovirus, and mumps. Markers of β-cell destruction include islet cell autoantibodies as well as a number of other autoantibodies and the rate of β-cell destruction varies. Individuals at increased risk can often be identified by evidence of an autoimmune pathologic process and by genetic markers.

Type 2 diabetes mellitus accounts for 90-95% of all diabetes mellitus cases. It is caused by a combination of metabolic disorders including insulin resistance in muscle and adipose tissue, a progressive decline in insulin secretion, unrestrained glucose production, and other hormonal deficiencies (ADA 2006). Most affected individuals are obese and have variable degrees of insulin resistance. Other risk factors include increasing age and a sedentary lifestyle. Type 2 diabetes occurs more frequently in individuals with hypertension or dyslipidemia and is associated with a strong genetic predisposition. This type of diabetes frequently goes undiagnosed for many years because the hyperglycemia develops gradually and is often not severe enough for the individual to notice any of the classic symptoms of diabetes. According to the CDC National Diabetes Fact Sheet for the U.S. in 2005, type 2 diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity.

Some patients cannot be clearly classified as to having either type 1 or type 2 diabetes and clinical presentation varies considerably in both types of diabetes. In some individuals adequate glycemic control can be achieved with weight reduction, exercise, and/or oral glucose-lowering agents. Other individuals have some residual insulin secretion but require exogenous insulin for adequate glycemic control. Still other individuals with extensive β-cell destruction require insulin for survival. Disease progression also varies considerably with some patients having a late onset and slow progression of disease while other patients may progress rapidly to ketoacidosis.

Pre-diabetes is also a concern because of the relatively high risk for development of diabetes in individuals with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)). These individuals have glucose levels that are too high to be considered normal even though they do not meet the criteria for diabetes. IFG is defined as having a fasting plasma glucose (FPG) of 100-125 mg/dl. IGT is defined as having a 2 hour postload glucose via oral glucose tolerance test (OGTT) of 140-199 mg/dl (ADA 2007). Individuals with IFG or IGT may have normal or near normal glycated hemoglobin (HbA1C) levels.

Values greater than those listed for pre-diabetes provide a provisional diagnosis of diabetes which must be confirmed on a subsequent day. Confirmation may be made by either of three specific criteria as listed in Table 1 (ADA 2007). Even though the OGTT is more sensitive and specific than the fasting plasma glucose, it is poorly reproducible and is not recommended for routine clinical use by the ADA. It may however be required in the evaluation of patients with IFG or when diabetes is still suspected when

the fasting plasma glucose in normal because approximately 30% of people with diabetes may be missed by using the fasting plasma glucose alone (WHO/IDF 2006). In these cases the HbA1C value may be normal or near normal. For this reason, the use of the HbA1C for the diagnosis of diabetes is not recommended. Screening for type 2 diabetes should be considered in individuals at 3-year intervals beginning at age 45, especially in those who are overweight (ADA 2007).

Table 1. Criteria for the Diagnosis of Diabetes Mellitus (either #1, 2, or 3 must be met)

1. Symptoms of diabetes plus casual plasma glucose concentration $\geq$200 mg/dl. Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
2. Fasting plasma glucose $\geq$126 mg/dl. Fasting is defined as no caloric intake for at least 8 h.*
3. Two hour postload glucose $\geq$200 mg/dl during an oral glucose tolerance test. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

*In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.

CONSEQUENCES

Diabetes mellitus can cause both macrovascular and microvascular disease secondary to elevated blood glucose levels (ADA 2007). The main complications include atherosclerotic cardiovascular disease, nephropathy leading to renal failure, retinopathy with potential loss of vision, peripheral neuropathy with risk of foot ulcers, peripheral artery disease, cerebrovascular disease, and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction.

Diabetes has become one of the leading causes of death in the U.S. with death certificates often listing it as a secondary cause of death. Generally, diseases of the coronary arteries, peripheral arteries, and carotid vessels are considered to be macrovascular in nature while nephropathy and retinopathy are considered to be microvascular in nature.

Cardiovascular disease is the major cause of morbidity and mortality for individuals with diabetes. It is estimated that 65% of deaths in people with diabetes are due to heart disease and stroke (Kanaya 2002). Of the deaths due to cardiovascular diseases (excluding cerebrovascular diseases), it is estimated that approximately 16% are due to diabetes (Kanaya 2002). Studies have shown that reducing cardiovascular risk factors help in preventing or slowing CVD. These risk factors include hypertension, dyslipidemia, and tobacco use.

Diabetic nephropathy occurs in 20-40% of patients with diabetes and is the single leading cause of end-stage renal disease (ESRD) (ADA 2007). Microalbuminuria in the range of 30-299 μg/mg creatinine has been shown to be the earliest stage of diabetic nephropathy in type 1 diabetes and a marker for development of nephropathy in type 2 diabetes. This is also a marker of increased risk of CVD. Patients who progress to macroalbuminuria are also likely to progress to ESRD. Intensive diabetes management has been shown to delay the onset of microalbuminuria and the progression to macroalbuminuria in patients with diabetes.

Diabetic retinopathy is a vascular complication of type 1 and type 2 diabetes and its prevalence is strongly related to the duration of diabetes. Diabetic retinopathy is estimated to be the most frequent cause of blindness in adults and other disorders

(including glaucoma and cataracts) may occur earlier in people with diabetes. Intensive diabetes management has been shown to prevent and/or delay the onset of diabetic retinopathy in large prospective randomized studies (ADA 2007).

Diabetic neuropathies occur in individuals with diabetes and are heterogeneous with diverse clinical manifestations. Most common among the neuropathies are chronic sensorimotor distal symmetric polyneuropathy and automonic neuropathy. Specific treatment for diabetic neuropathies is not available other than improving glycemic control. Effective symptomatic treatments are also available.

ECONOMIC IMPACT OF DISEASE

According to the American Diabetes Association, the total economic costs of diabetes in the U.S. in 2007 are estimated to exceed $174 billion dollars (ADA 2008). This estimate includes $116 billion in excess medical expenditures and $58 billion in reduced national productivity. Medical costs also include $27 billion for care to directly treat diabetes, $58 billion to treat the portion of diabetes-related chronic complications, and $31 billion in excess general medical costs. The burden of diabetes is imposed on all sectors of society with higher insurance premiums, reduced earnings, and reduced overall quality of life (ADA 2008).

AEROMEDICAL CONCERNS

The main aeromedical concerns in relation to diabetes are the acute effects of hypoglycemia as well as the more chronic medical complications that can occur in the presence of elevated blood glucose levels. Medical complications may include

degradations of sensory, motor, and cognitive (information processing) functioning which may lead to an aircraft mishap. Other aeromedical concerns are related to the treatment of diabetes with injectable or oral medications which can directly cause the lowering of blood glucose levels leading to hypoglycemia which may also cause degradations of sensory, motor, and cognitive (information processing) functioning. In general, the risks of sudden incapacitation are of greater concern to the aeromedical agencies in setting allowable limits for an aviator to perform flying duties. These have typically been quoted to not be greater than 1% of the risk for the general population (Mitchell 2004). Another significant risk in relation to diabetes has been identified to be the occurrence of hypoglycemia secondary to the use of insulin or oral medications. The FAA is the only agency in the U.S. that has allowed type 1 diabetics, under strict guidelines, to continue flying in non-commercial settings (FAA 2009). It also allows most oral medications to be used but has some restrictions when the aviator is concurrently on a beta-blockers which can mask tachycardia that would normally occur during a hypoglycemia episode. With the increased potential for sudden incapacitation due to hypoglycemia, the FAA has allowed less strenuous control of blood glucose levels for pilots on oral medications or insulin. This however increases the potential for long-term complications associated with poor glucose control and may increase the risk for aviation mishaps.

Because of the potential for sudden incapacitation related to the occurrence of hypoglycemia secondary to insulin use, most aeromedical authorities have not allowed flyers with type 1 diabetes to continue flying (Stienkraus 2003). Aviators with diabetes

in the U.S. are also not allowed to fly civilian or military aircraft without a waiver given by the appropriate regulating agency (Stienkraus 2003). As part of the waiver process, an understanding of the pathophysiology and course of disease is necessary for the approving authorities in order to understand all of the aeromedical concerns that would be involved in ensuring flying safety. An additional concern that the aeromedical community will be increasingly faced with is the problem of how to manage aviation personnel with elevated blood glucose levels who are controlling their diabetes and pre-diabetes by diet and exercise alone. Aviation Medical Examiners currently may issue medical certificates to airmen with pre-diabetes or diet-controlled diabetes who are not on medication as long as their laboratory values are within FAA standards (FAA 2009).

Chapter 3: Data

Data for this review came from a number of literature reviews. Primary sources for review included Ovid Medline and PubMed databases for relevant journal articles. Bibliographies were also reviewed to find reference articles not otherwise identified. Other additional sources of information included a number of textbooks on both aviation and diabetes.

LITERATURE REVIEW

A literature review was conducted using Ovid Medline and PubMed databases for articles relating aviation and type 2 diabetes mellitus from January 1, 1998 to Mar 1, 2008. Specific search terms included "aviation, aerospace, aircraft, air crew, and

aircrew" along with "diabetes and type 2 diabetes mellitus." Limits were placed on only those publications using the English language and human subjects. Additional literature searches were conducted by review of article references and including a number of additional search terms in the above reviews.

A second literature review was conducted using the Ovid Medline and PubMed databases for articles relating to the treatment of type 2 diabetes using each of the various classes of oral medications. Limits were placed on only those publications using the English language and human subsets. Search terms included "meta-analysis, type 2 diabetes mellitus, and treatment." Drugs were limited to oral forms currently available in the U.S. and approved by the FDA for the treatment of type 2 diabetes mellitus.

Chapter 4: Results

DIABETES AND AVIATION

Search results relating aviation and type 2 diabetes were relatively limited. Of the articles found by the literature review, only one article was found which specifically addressed the occurrence of type 2 diabetes mellitus in aviation personnel. This was a review article published by Steinkraus, et. al. in October, 2003. This article primarily summarized data from the USAF Aeromedical Consult Service (ACS) at Brooks AFB, TX and the other aeromedical agencies in North America including the U.S. Navy, U.S. Army, the Federal Aviation Administration (FAA) and the Canadian Forces. In this review article, the authors conducted a literature review on type 2 diabetes mellitus along with obesity and the metabolic syndrome and discuss the pathophysiology and course of

type 2 diabetes mellitus. The authors also reviewed medical charts from the U.S. Air Force Aeromedical Consult Service (ACS) for aviators with type 2 diabetes mellitus between 1975 and 2000. Of 70 charts reviewed, over 95% were for type 2 diabetes mellitus. Waiver considerations were also reviewed for flyers with type 2 diabetes mellitus for each of the aeromedical agencies in the United States and Canada.

According to Steinkraus, et. al., 2003, the FAA has the most experience with allowing aviators with diabetes mellitus to perform flying duties with a waiver. Of 4,855 aviators with diabetes, a total of 8% (355 individuals) were identified as having type 1 diabetes and a total of 92% (4,500 individuals) were identified as having type 2 diabetes. Of the aviators with diabetes, 90% were issued a waiver to continue flying duties. The most common reason for denial of waivers for diabetes was inadequate control. The second most common reason for denial of waivers was secondary complications. In the U.S. Air Force, 37 flyers were identified as having adult onset type 2 diabetes controlled by diet. The total number of waivers given was 40% with the majority of waivers having been granted for diet-controlled type 2 diabetes and a limited number of waivers have been granted for a few flyers on oral hypoglycemic medications. In the U.S. Air Force, waivers have not been given for flyers on insulin. In the Army, 15 individuals have been identified as having type 2 diabetes at the time of the review article and 13% of those had been given a waiver. Of those, two aviators have been followed on metformin and no individuals with type 1 diabetes have been waived. In the Navy, 223 flyers had type 2 diabetes and 46% had received waivers.

Since the review article was published in 2003 there has been relatively limited information published regarding diabetes mellitus in aviators. One general review article was published by the Flight Safety Foundation (FSF) in 2005 and is found on their internet site (FSF 2005). This article provides a general review of diabetes mellitus (types 1 and 2) in relation to aviation, as well as some general information on pre-diabetes.

Lastly, a few articles were published in Aviation, Space, and Environmental Medicine from the Israeli Aeromedical Center regarding the use of insulin for the treatment of type 1 diabetes mellitus in Israeli aviators. These include a short communication by Grossman, et.al., 2005 and a research article by Carter, et.al., 2005. Both articles suggest that safe flying can be achieved by accomplishment of blood glucose awareness training. A commentary was also published in the same journal by Heller and Nicholson in the UK, which took the opposing viewpoint in that even in applying the most stringent clinical criteria, blood glucose awareness training cannot guarantee that a hypoglycemic episode can be prevented (Heller 2006). A fourth article was found which discussed pre-diabetes in relation to cases reviewed at the FAA Civil Aerospace Medical Institute (CAMI) (Files 2006).

MEDICATIONS

Search results relating medication (with primary emphasis on medications other than insulin) and type 2 diabetes were more readily available and review of these results is summarized below by drug class. Of the drugs currently recommended for treatment,

the following drug classes were reviewed for potential adverse reactions or complications. Each of these drug classes can be used as monotherapy and several are available for combination use. In general, combination therapy is not approved for civil transport, commercial and military aviators. Because of the large number of possible combinations of drug classes and the increased likelihood for side effects, specific adverse reactions or complications of the combination therapies will not be discussed in this article.

Biguanides

Metformin primarily acts to reduce hepatic glucose production in the presence of insulin but does not require functioning pancreatic β-cells for reduction of hyperglycemia (Gardner 2007). It also is associated with less hypoglycemia than sulfonylurea therapy and overall weight loss. The major nonglycemic effect of metformin is either weight stability or modest weight loss (Nathan 2009). Use of phenformin was discontinued in the U.S. because of its association with the development of lactic acidosis. This was a primary concern in patients with coexisting liver or kidney disease. The primary action of metformin is on the liver where it reduces hepatic gluconeogenesis by activating adenosine monophosphate-activated protein kinase. Metformin has been shown to decrease mortality rates in type 2 diabetes and is considered a first-line agent (Rispin 2009).

Adverse effects of metformin frequently include gastrointestinal distress (anorexia, abdominal pain, nausea, vomiting, and diarrhea) which occur in up to 20% of

patients (Gardner 2007). These effects are dose-related and tend to occur at onset of therapy. These effects are also often transient and can be minimized with titration of therapy and consumption of food with medication dosing. In 3 to 5% of patients, therapy may have to be discontinued because of persistent diarrheal discomfort (Gardner 2007). Hypoglycemia does not occur with therapeutic doses of metformin.

Metformin should not be used in patients with renal impairment and are at increased risk for lactic acidosis since lactic acidosis has been reported as a side effect, although it is relatively uncommon. Current guidelines recommend that metformin should not be used in patients with chronic or acute renal insufficiency and should be discontinued when creatinine levels reach 1.4 mg per dL in women or 1.5 mg per dL in men (Salpeter 2003). Metformin should also be avoided in patients with hepatic dysfunction, congestive heart failure, metabolic acidosis, dehydration and alcoholism (Robard 2007). In patients with acute illness or those undergoing radiocontrast studies or surgery, metformin should be temporarily withheld.

Thiazolidinediones

Thiazolidinediones are known to exert direct effects on the liver and sensitize peripheral tissues to insulin. These drugs also act as receptor agonists and regulate the release of adipokines from adipocytes through activation of peroxisome proliferator-activated receptors (PPARs) which are found predominantly in adipocytes and macrophages (Gardner 2007). Troglitazone has been withdrawn from clinical use in the U.S. because of drug-associated fatal liver failure. The two thiazolidinediones that are

currently available in the U.S. are rosiglitazone and pioglitazone. Unlike troglitazone, rosilitazone and pioglitazone have not caused drug-induced hepatotoxicity. Both of these drugs are effective when used as monotherapy and in combination with sulfonylureas or metformin.

Adverse effects of thiazolidinediones include weight gain, edema, and anemia (Gardner 2007). The occurrence of peripheral fractures in women has also been reported. Weight gain occurs when the drug is combined with a sulfonylurea or insulin. Edema occurs in about 3 to 4% of patients receiving a thiazolinedione as monotherapy and may result in congestive heart failure, although this occurs more frequently in patients receiving concomitant insulin therapy. These drugs should not be used in diabetic patients with moderate or severe congestive heart failure (New York Heart Association class III and IV). This class of drugs does not cause hypoglycemia. Macular edema is a rare side effect which occurs more often in patients with peripheral edema and resolves or improves once the drug is discontinued. Anemia occurs in 4% of patients but this effect may be due to a dilutional effect of increased plasma volume (Gardner 2007). The FDA has recommended that periodic measurement of hepatic function is recommended in patients treated with thiazolidinediones. These drugs are contraindicated in individuals with known hepatic dysfunction or known liver disease.

Secretagogues

This drug class includes the sulfonylureas and the glinides (meglitinides). Sulfonylureas lower blood glucose by binding to sulfonylurea receptors on pancreatic β-

cells and subsequently stimulate insulin secretion (Robard 2007). Sulfonylurea agents are metabolized by the liver and cleared by the kidney and should be used cautiously in patients with either hepatic or renal impairment (Gardner 2007). Currently approved sulfonylureas include first-generation drugs (tolbutamide, tolazamide, acetoheamide, and chlorpropamide) and second-generation drugs (glyburide, glipizide, and glimepiride). Sulfonylurea therapy is associated with two common adverse effects which are weight gain and hypoglycemia. Hypoglycemia is of significant concern in those individuals who have irregular meal schedules (Inzucchi 2002).

First generation sulfonylureas all have been reported to have some side effects. Tolbutamide has been reported rarely to cause prolonged hypoglycemia mainly in patients receiving certain drugs (e.g., warfarin, phenylbutazone, or sulfonamides) that compete with sulfonylureas for hepatic oxidation. Talazamide has maximal hypoglycemic effect occurring between the fourth and fourteenth hours. Large doses should be divided to minimize hypoglycemic effects. Acetohexamide and chlorpropamide are now rarely used. Chlorpropamide has a prolonged biologic effect and severe hypoglycemia can occur, especially in the elderly. Other side effects include alcohol-induced flushing and hyponatremia.

Second generation sulfonylureas should be used with caution in patients with cardiovascular disease as well as in elderly patients (Gardner 2007). Glyburide has few adverse effects other than its potential for causing hypoglycemia, especially in patients over 65 years of age. Glipizide therapy is contraindicated in patients who have hepatic impairment who would be at high risk for hypoglycemia. It does have a shorter half-life

and may be preferable to glyuride in the treatment of the elderly patient. Glimepiride has a long duration of effect allowing once-daily administration.

Meglitinides have a similar mechanism of action to the sulfonylureas but have a shorter metabolic half-life. These agents stimulate insulin secretion for a period that lasts between 1 to 2 hours and decrease the risk of hypoclycemia during the late postprandial phase (Robard 2007). Meglitinides are metabilized by the liver and cleared by the kidney and should also be used with caution in patients with either hepatic or renal impairment. Repaglinide is currently approved and is a meglitinide analog. Hypoglycemia is the main side effect of repaglinide and when compared with glyburide it appears to cause less hypoglycemia. Nateglinide is also in this class of medications and like repaglinide, causes a brief rapid pulse of insulin. Its main side effects include hypoglycemia and weight gain (Gardner 2007). One disadvantage of this drug category is the frequent dosing schedule with meals (Inzucchi 2002).

α-Glucosidase Inhibitors

This drug class provides postprandial glucose control by decreasing the absorption of carbohydrates from the gastrointestinal tract by acting as competitive inhibitors of the intestinal brush border α-glucosidase inhibitors. Currently approved drugs include acarbose and miglitol (Gardner 2007). Adverse effects of α-glucosidase inhibitors include flatulence, diarrhea, and abdominal discomfort. Titration of drug dose may lessen these adverse effects. Flatulence is caused by undigested carbohydrate reaching the lower bowel and occurs in 20-30% of patients. Troublesome diarrhea occurs

in 3% of cases. When used as monotherapy, there is no risk of hypoglycemia. Concentrations of the α-glucosidase inhibitors have been shown to increase when renal dysfunction is present and use in patients with serum creatinine levels more than 2.0 mg per dL is not recommended (Luna et al 2001).

GLP-1 Agonists

This drug class includes exenatide and liraglutide which are glucagon-like peptide 1 (GLP-1) receptor analogs resistant to dipeptidyl-peptidase 4 (DPP 4) degradation. Exenatide is FDA approved while liraglutide is currently under review (Gardner 2007). These drugs exert their effects by promoting insulin production, reducing glucose production, and creating a feeling of fullness. Potential side effects include nausea and vomiting, diarrhea, and dizziness and occur in 30-45% of treated patients (Nathan 2009). Acute pancreatitis can also occur but this is relatively rare. Both agonists are only available in subcutaneous formulations at this time. Exenatide lowers blood glucose levels and stimulates modest weight loss. This may be due to slowing gastric emptying and producing satiety as mentioned above. The use of exenatide is not recommended in patients with severe renal disease (creatinine clearance < 30 mL per minute) (Ripsin 2009). One potential advantage of GLP-1 is that it does not cause hypoglycemia.

Dipeptidyl-Peptidase 4 Inhibitors

This drug class act in part by slowing the inactivation of incretin hormones (glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide, which subsequently increases the concentrations of these hormones which are abnormally

low in type 2 diabetics (Gardner 2007). Incretin hormones stimulate glucose-dependent insulin secretion, decrease glucagon secretion, slow gastric emptying, and decrease appetitie. Sitagliptin has been approved for use in the U.S. while vildagliptin is currently under review by the FDA. Several other DPP 4 inhibitiors are currently in late-stage development and include saxagliptin, alogliptin, and denagliptin. These drugs have few adverse reactions but include nausea and vomiting. Dosage should be adjusted in patients with renal impairment. Treatment with sitagliptin as monotherapy has no effect on body weight.

Chapter 5: Discussion

Known risk factors for developing type 2 diabetes mellitus include obesity as well as increasing age (WebMD 2008). Since U.S. aviators are subject to these risk factors and especially since older commercial pilots are now being allowed to continue to fly up until age 65, it is likely that the prevalence of type 2 diabetes is also increasing in this select population (FAA 2008). Individuals with type 2 diabetes are at increased risk for incapacitation secondary to a number of factors including both acute and chronic complications. Acute complications include diabetic ketoacidosis, hyperglycemic crisis, and hypoglycemic changes including mental status changes and visual disturbances. Chronic complications include increased cardiovascular disease, end-stage renal disease, neuropathic complications and blindness. In addition, individuals undergoing treatment with medications are also at increased risk for incapacitation secondary to hypoglycemia and other common side effects. Adverse health effects secondary to type 2 diabetes or its

treatment among aviators can have a significant effect on their personal safety as well as on public safety in general. Quantification of these risks is important and can fill the information gap that is currently present in the aerospace medicine literature.

MEDICATION RISKS

In regards to type 2 diabetes mellitus in aviators, primary prevention efforts are best suited to be applied towards those individuals who have elevated risks and can be reviewed during annual flight physicals as well as during periodic counseling sessions aimed at improving population health. Once an aviator has been diagnosed to have type 2 diabetes, secondary and tertiary prevention efforts should be applied in the disease management process. Pharmaceutical approaches are primarily used in those individuals who have been identified to have type 2 diabetes. Many medications can cause side effects that place individuals and aviators at increased risk for sudden incapacitation as well as at risk for subtle degradation of sensory, motor, and informational processing functions. The primary drugs used to treat type 2 diabetes as monotherapy and their major adverse effects include the following:

- Metformin: Reduces glucose production in the liver and has some effect in decreasing peripheral insulin resistance. It may cause lactic acidosis in some individuals and has been associated with gastrointestinal side effects, B12 deficiency, and decreases in hemoglobin and hematocrit. Metformin is contraindicated in those individuals with renal insufficiency.

- Thiazolidinediones: Reduce peripheral insulin resistance in skeletal muscle and adipose tissue and are associated with small decreases in hemoglobin and hematocrit, an increase in anemia, and edema and may result in congestive heart failure.
- Sulfonylureas: Increase β cell insulin production independent of blood glucose levels and have the potential for causing hypoglycemia.
- Meglitinides: Stimulate insulin secretion similar to the sulfonylureas for a period that lasts between 1 to 2 hours and their main side effects include hypoglycemia and weight gain.
- α-Glucosidase Inhibitors: Decrease the absorption of carbohydrates from the gastrointestinal tract by acting as competitive inhibitors. Adverse effects include flatulence, diarrhea, and abdominal discomfort.
- Dipeptidyl-Peptidase 4 Inhibitors: Act in part by slowing the inactivation of incretin hormones which subsequently increases their concentrations. These drugs have few adverse reactions.

Metformin is currently recommended as first line therapy for the treatment of type 2 diabetes mellitus and should be started in a newly diagnosed patient at the same time as lifestyle intervention recommendations (ADA 2007). Metformin is generally considered safe when used as monotherapy and in therapeutic doses does not cause hypoglycemia (Luna 2001). This permits its description as a "euglycemic" or "antihyperglycemic" drug rather than an oral hypoglycemic agent (Gardner 2007). One large study that looked at the use of metformin was the UK Prospective Diabetes Study (UKPDS 1998). In this

study the occurrence of major hypoglycemic episodes among overweight patients with type 2 diabetes mellitus treated with intensive metformin therapy (2550 mg/day) were 0.7% on diet therapy and 0% on metformin. The occurrence of any hypoglycemic episodes were 0.7% on diet therapy and 4.2% on metformin. Hypoglycemic episodes in patients on diet therapy were described as reactive hypoglycemic attacks either after meals or after termination of glucose infusions in post-op patients. What constitutes "any hypoglycemic episode" was not specifically defined for the patients treated with metformin. Other smaller studies show the rates of hypoglycemia for metformin to be either zero or comparable to the prevalence in diet-treated patients. Lactic acidosis has also been reported as a side effect for metformin. One large systematic review by Salpeter, et al (2003) has shown that pooled data from 176 comparative trials and cohort studies totaling 35,619 patient-years revealed no cases of fatal or non-fatal lactic acidosis in any medication group (Bolen 2007). Several additional studies showed little or no elevated risk for lactic acidosis in metformin recipients.

A recent systematic review was completed that compared the effectiveness and safety of oral medications for type 2 diabetes (Bolen 2007). This review excluded first generation sulfonylureas because they are rarely used now that second-generation agents are available. This study found that older agents such as second-generation sulfonylureas and metformin have similar or superior effects on glycemic control, lipids, and other intermediate end points as compared with new more expensive agents such as thiazolidinediones, α-glucosidase inhibitors, and meglitinides. This study also found no definitive evidence about the comparative effectiveness of oral diabetes agents on all-

cause mortality, cardiovascular mortality or morbidity, peripheral arterial disease, neuropathy, retinopathy, or nephropathy. It was observed that several studies consistently demonstrated that hypoglycemic episodes are more frequent in adults receiving second-generation sulfonylureas (especially glyburide) than in those receiving metformin or thiazolidinediones, thiazolidinediones were associated with greater risk for heart failure, and metformin was associated with greater risk for gastrointestinal problems compared with other oral agents. Lastly, it was shown that lactic acidosis was no more common in metformin recipients without comorbid conditions than in recipients of other oral diabetes agents.

In another recent review emerging therapies for type 2 diabetes were compared to established treatments with regard to efficacy and tolerability (Campbell 2008). This study showed that the more recently developed antidiabetic drugs including dipeptidyl-peptidase 4 inhibitors have been shown in clinical trials to produce glucose-lowering effects similar to those of established agents.

PREVENTION CONSIDERATIONS

Individual lifestyle choices are also known risk factors and include high-fat, high-calorie diets, sedentary lifestyles, and obesity. These risk factors can be addressed by prevention efforts to prevent or delay the onset of type 2 diabetes mellitus and its subsequent complications. Primary prevention includes those efforts that are aimed at preventing the development of type 2 diabetes and include diet, exercise and weight control. Secondary prevention includes those efforts that are aimed at early disease

detection which allows for the interventions to prevent progression of the disease and the emergence of symptoms. Tertiary prevention includes those efforts that are aimed at reducing the negative impact of an already established disease by restoring function and reducing disease-related complications. Several studies have highlighted the potential for interventions which reduce progression from subjects with impaired glucose tolerance to type 2 diabetes. One study was the Diabetes Prevention Program which was completed in 1999. This study showed that over three years, lifestyle interventions of diet and exercise reduced the risk of progression by 58% while the oral hypoglycemic drug, metformin, reduced the risk by 31% (Diabetes Prevention 1999). A more recent study by the Diabetes Prevention Program showed that lifestyle changes or treatment with metformin both reduced the incidence of diabetes in persons at high risk (Knowler 2002). In this study the lifestyle intervention reduced the incidence of type 2 diabetes by 58 percent and metformin by 31 percent as compared with placebo.

The NCEP ATP III defined the metabolic syndrome as a cluster of criteria that increase the risk of developing diabetes and therefore, coronary artery disease (CAD) (NCEP 2001). Possessing more than 3 of the criteria listed in Table 2 qualifies a patient as having the metabolic syndrome. CHD appears to be more prevalent in those with the metabolic syndrome than in non-diabetic patients, but less prevalent than in diabetics. Controlling the metabolic syndrome is considered an important prevention of CHD.

The concept of diabetes as a major cardiovascular risk factor is not a new topic. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) reports that the risk of CHD is similar in diabetic subjects without pre-existing

vascular disease as in non-diabetic subjects with known vascular disease. Glycemic control alone will not eliminate the excess risk of CHD in diabetic subjects. The NCEP

Table 2. NCEP ATP III Risk Factors.

Risk Factor	Defining Level
Waist circumference Men Women	 ≥ 40 inches ≥ 35 inches
Triglycerides	≥ 150 mg/dL
HDL-C Men Women	 < 40 mg/dL < 50 mg/dL
Blood Pressure	≥130 mm Hg systolic or ≥ 85 mm Hg diastolic
Fasting glucose	≥110 mg/dL

ATP III therefore recommends for the diabetic population lowering the LDL to below 100 mg/dL, the total cholesterol below 200 mg/dL, and the HDL above 40 mg/dL. In addition, treatment of overweight patients with type 2 diabetes mellitus has been shown to decrease the incidence of myocardial infarction by 39% and all-cause mortality by 34% (Holman 2008).

WAIVER REQUIREMENTS

There is limited evidence for a direct relationship between individuals with diabetes and the occurrence of aviation accidents. The highest risk has been stated to be

due to the occurrence of hypoglycemia which is a side effect of some medications commonly used to treat diabetes. Symptoms of hypoglycemia include excess perspiration, shakiness, nervousness or feeling anxious, dizziness and/or light-headedness, sleepiness, confusion, difficulty speaking, and weakness. Because these symptoms and the possibility for sudden incapacitation exists in individuals taking medications or combinations of medications which can cause hypoglycemia, U.S. aeromedical regulating agencies still place significant restrictions on aviators requiring these medications for control of their disease (FSF 2005).

Waiver considerations for type 2 diabetes mellitus vary among the different U.S. aeromedical agencies and have been described in previous literature (Steinkraus 2003). In recent years, civil aviation authorities have become increasingly likely to issue medical certificates to applicants whose diabetes is controlled with oral medications (usually monotherapy) that do not have the potential for significant hypoglycemia. Listed below are the three classes of airman medical certificates for the FAA, identifying the categories of airmen certificates applicable to each class.

- First-Class: Airline Transport Pilot
- Second-Class: Commercial Pilot; Flight Engineer; Flight Navigator; or Air Traffic Control Tower Operator
- Third-Class: Private Pilot, Recreational Pilot, or Student Pilot

In general, medical certificates given to First-Class are more restrictive than those given Second-Class, etc.

Diabetes mellitus (type 1 or type 2) which requires insulin or an oral hypoglycemic medication is disqualifying for all three classes of airman medical certificates for the FAA. Diabetes controlled with diet and exercise and pre-diabetes are not specifically disqualifying by the FAA as long as the airman is able to safely perform aviation duties. In addition, there must also be no evidence of an associated disqualifying cardiovascular, neurological, renal, or ophthalmological disease as evident by history of clinical findings (FAA 2008). Diabetes not requiring insulin controlled with medications may be given a waiver (special issuance medical certification) to perform flying duties. In some cases, the FAA may also give a special issuance medical certification of insulin-treated applicants for third-class medical certification. Consideration will be given only to those individuals who have been clinically stable on their current treatment regimen for a period of 6 months or more. Consideration is not being given for first- or second-class certification (FAA 2009).

One concern that should also be considered in any discussion of type 2 diabetes is that the incidence tends to increase in older populations. In terms of aviation safety, pilots may be at increasing risk due to a number of factors—one of which to consider is an increase in current age limits which allows older pilots to fly commercial aircraft. In November 2006, the International Civil Aviation Organization (ICAO) implemented an amendment to the international Standards and Recommended Practices which included a relaxation of the upper age limit of 60 years to 65 years of age. Some restrictions apply and require that they work in a multi-crew cockpit where the other pilot is under 60 years of age (Cornell 2007). This amendment gives ICAO contracting states the opportunity to

relax their age restrictions and also requires countries with an upper age limit less than 65 to allow pilots from contracting states to fly into their airspace. The FAA has recently updated their standards to reflect the ICAO standards with the Fair Treatment of Experienced Pilots Act that was signed into law on December 13, 2007 (FAA 2008). The main concern with changing the upper age limits centers around the question of whether a pilot's safety performance changes significantly during the process of aging. The Aerospace Medical Association published a position statement in 2004 which reviewed the relationship between pilot age and safety performance. Currently there is insufficient medical evidence to restrict pilot certification on age alone (AMA 2004).

Chapter 6: Summary

The intent of this capstone project was to perform an in-depth literature review of one of the most common endocrine diseases in the U.S. today. The impact of this disease on the country is considerable with an estimated annual cost for 2007 of more than $174 billion. In addition, risk factors for type 2 diabetes include age and obesity, both of which have been increasing over the previous two decades and are expected to continue to increase. From an occupational health standpoint, this paper has attempted to show that U.S. aviators, who have similar risk factors as the general population are also at increased risk for developing type 2 diabetes. Because of flight safety concerns, U.S. aviators are restricted from operating commercial or military aircraft if they have type 1 diabetes or type 2 diabetes that requires the use of insulin. Restrictions are also placed on the use of multiple medications in maintaining adequate control of the disease. For these

reasons waiver requirements are briefly discussed but vary among the different aeromedical agencies.

A number of different medications may be used in the treatment of type 2 diabetes. Most of the aeromedical agencies restrict the use of medications to oral forms and usually limit treatment to monotherapy because combination therapy tends to increase the risk for side effects and specifically hypoglycemia for some medications. Current treatment guidelines recommend Metformin as first line therapy in conjunction to diet and exercise. Metformin has some risk for adverse reactions but these are relatively low. More significantly, the risk for hypoglycemia is very low as compared to several of the other oral medications. The use of Metformin therefore is generally in agreement with the requirements of the U.S. aeromedical agencies but specific requirements of each agency may vary. Each of the oral medications described in this paper in general have relatively low risks for incapacitation and may be waiverable by the various aeromedical agencies.

The development of an evidence-based clinical practice guideline is seen as a way to deliver state of the art care, based on randomized clinical trials when available. A current clinical practice guideline for the appropriate management of diabetes for use by the U.S. aeromedial agencies is not currently available. This paper seeks to fill that gap by the creation of such a clinical practice guideline that could be used for most patients with elevated blood sugar levels as well as aviators in which flying safety is of critical importance. This clinical practice guideline will be submitted to the American Society of Aerospace Medicine Specialists and the Aerospace Medical Association. It is hoped that

it will be adopted for use and be made available to civilian aviation medical examiners, military flight surgeons, and by any healthcare provider that might be responsible for the care of aviators with type 2 diabetes mellitus. As new medical information becomes available, the clinical practice guideline will need to be modified and updated as appropriate. It is believed that this clinical practice guideline will benefit not only the aerospace community directly but also the civilian community indirectly by minimizing the small but possible risk associated with aviators flying with type 2 diabetes and its medical management.

Appendix

CLINICAL PRACTICE GUIDELINE: DIABETES IN U.S. AVIATORS*

I. OVERVIEW

Diabetes mellitus is very prevalent in many parts of the world and based on current data the prevalence of diabetes in the U.S. continues to rise (NDFS 2005). Diabetes mellitus is an endocrine disorder in which the level of glucose in the blood is higher than normal. It is primarily described as belonging to one of two classifications, type 1 and type 2, with the vast majority of cases falling into these two broad categories. There are currently estimated to be over 20.8 million Americans (7% of the U.S. population) with diabetes mellitus. Approximately 14.6 million people have been diagnosed with diabetes mellitus and 6.2 million remain undiagnosed. Hyperglycemia not sufficient to meet the diagnostic criteria for diabetes is categorized as either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Individuals with IFG or IGT are considered to be pre-diabetic. Approximately 41 million Americans have pre-diabetes mellitus, a condition that may progress to clinical diabetes if not detected and treated early.

- Type 1: Absolute insulin deficiency related to pancreatic beta cell destruction. In general these folks are younger, thinner and have a family history of autoimmune diseases. This is rare, <1% of the US population.

- Type 2: This is what was traditionally called adult onset diabetes. It is seen in 6-7% of the US population. There is usually a strong family history. It is caused by insulin resistance and/or relative insulin deficiency.
- Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT): Intermediate metabolic states between normal glucose homeostasis and diabetes. These are also referred to as pre-diabetes.

As the prevalence of diabetes increases in the general population, the likelihood that it will adversely affect the aviation community also increases. In general, commercial and military pilots have not been allowed to fly with diabetes requiring insulin or oral medications which have a high risk of sudden incapacitation. In recent years, civil aviation regulations have been updated to allow selected pilots with diabetes to continue to be medically certified to operate specific commercial aircraft, even if they require medical management to include oral or injectable medications for good control of their disease (FAA 2008). The relative severity of disease in an aviator and its potential impact on safe aviation performance are considerations in determining whether or not an airman should be given a medical certification to perform flying duties (Corrigan 2008).

In all cases of diabetes the elevation in blood glucose is due to the improper production and/or use of insulin by the body. Insulin is a hormone secreted by the pancreas to regulate blood glucose levels. In diabetes, insulin secretion either becomes deficient secondary to destruction of the pancreatic β-cells or insulin resistance occurs (ADA 2007). Several pathogenic processes are involved in the development of diabetes and range from autoimmune destruction of the pancreatic β-cells with consequent insulin

deficiency to abnormalities that result in resistance to insulin action. Regardless of the process involved, both type 1 and type 2 diabetes results in hyperglycemia. Symptoms of hyperglycemia include polyuria, polydipsia, weight loss with or without polyphagia, and blurred vision.

Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome, and may include mental status changes and visual disturbances. Chronic complications include increased cardiovascular disease, end-stage renal disease, neuropathic complications and blindness. In addition, individuals undergoing treatment with insulin or oral medications are also at increased risk for incapacitation secondary to hypoglycemia and other common side effects. Currently there is a dichotomy in that maintaining tight glycemic control can increase the risk of a hypoglycemic events while not maintaining tight control will likely result in a higher likelihood of serious long-term complications (Rayman 2006). Adverse health effects secondary to diabetes or its treatment among aviators can have a significant effect on their personal safety as well as on public safety in general.

Some patients cannot be clearly classified as to having either type 1 or type 2 diabetes and clinical presentation varies considerably in both types of diabetes. This is true in adults, adolescents, and children. In some individuals adequate glycemic control can be achieved with weight reduction, exercise, and/or oral glucose-lowering agents. Other individuals have some residual insulin secretion but require exogenous insulin for adequate glycemic control. Still other individuals with extensive β-cell destruction require insulin for survival. Disease progression also varies considerably with some

patients having a late onset and slow progression of disease while other patients may progress rapidly to ketoacidosis.

Prediabetes is also a concern because of the relatively high risk for development of diabetes in individuals with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG). These individuals have glucose levels that are too high to be considered normal even though they do not meet current criteria for diabetes. IGT is defined as having a 2 hr postload glucose (via oral glucose tolerance test) of 140-199 mg/dl. IFG is defined as having a fasting plasma glucose (FPG) of 100-125 mg/dl. Values greater than these provide a provisional diagnosis of diabetes which must be confirmed on a subsequent day. Confirmation may be made by either of three specific criteria as listed in Table 1 (ADA 2007).

Table 1. Criteria for the Diagnosis of Diabetes Mellitus (either #1, 2, or 3 must be met)

1. Symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dl. Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
2. FPG ≥126 mg/dl. Fasting is defined as no caloric intake for at least 8 h.*
3. 2-h postload glucose ≥200 mg/dl during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

*In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.

Many individuals with IGT are euglycemic in their daily lives while individuals with IFG or IGT may have normal or near normal glycated hemoglobin levels.

Diabetes mellitus can cause both macrovascular and microvascular disease secondary to elevated blood glucose levels (ADA 2007). The main complications include atherosclerotic cardiovascular disease, nephropathy leading to renal failure, retinopathy with potential loss of vision, peripheral neuropathy with risk of foot ulcers, peripheral artery disease, cerebrovascular disease, and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Diabetes has become one of the leading causes of death in the U.S. with death certificates often listing it as a secondary cause of death. Generally, diseases of the coronary arteries, peripheral arteries, and carotid vessels are considered to be macrovascular in nature while nephropathy and retinopathy are microvascular in nature.

II. AEROMEDICAL CONCERNS

There is limited evidence for a direct relationship between individuals with diabetes and the occurrence of aviation accidents. The highest risk has been stated to be due to the occurrence of hypoglycemia which is a side effect of some medications commonly used to treat diabetes. Hypoglycemia can be very disabling, causing autonomic symptoms of sweating, tremor, palpitations, and weakness, and neurologic symptoms of double vision, slurred speech, irritability, confusion, and even coma. Prolonged hyperglycemia is an additional concern as it can cause polyuria, dehydration, nausea, fatigue, and changes in visual acuity.

The primary drugs used to treat type 2 diabetes as monotherapy and their major adverse effects are the following:

- Metformin: reduces glucose production in the liver and has some effect in decreasing peripheral insulin resistance. It may cause lactic acidosis in some individuals and has been associated with gastrointestinal side effects, B12 deficiency, and decreases in hemoglobin and hematocrit.
- Thiazolidinediones: reduce peripheral insulin resistance in skeletal muscle and adipose tissue and are associated with small decreases in hemoglobin and hematocrit, an increase in anemia, and edema.
- Sulfonylureas: increase β cell insulin production independent of blood glucose levels and have the potential for causing hypoglycemia.
- Meglitinides: stimulate insulin secretion similar to the sulfonylureas for a period that lasts between 1 to 2 hours and their main side effects include hypoglycemia and weight gain.
- α-Glucosidase inhibitors: decrease the absorption of carbohydrates from the gastrointestinal tract by acting as competitive inhibitors. Adverse effects inhibitors include flatulence, diarrhea, and abdominal discomfort.
- Dipeptidyl-peptidase 4 inhibitors: act in part by slowing the inactivation of incretin hormones which subsequently increases their concentrations. These drugs have few adverse reactions.

Because the possibility for sudden incapacitation exists in individuals taking some medications or combinations of medications, U.S. aeromedical regulating agencies still place significant restrictions on aviators requiring medications for control of their disease (FSF 2005). Most of the aeromedical agencies restrict the use of medications to oral

forms and usually limit treatment to monotherapy because combination therapy tends to increase the risk for hypoglycemia. Current treatment guidelines recommend metformin as first line therapy in conjunction to diet and exercise. Metformin has some risk for adverse reactions but these are relatively low. More significantly, the risk for hypoglycemia is very low as compared to several of the other oral medications. The use of metformin therefore is generally in agreement with the requirements of the U.S. aeromedical agencies but specific requirements of each agency may vary. Each of the oral medications described in this paper in general have relatively low risks for incapacitation and may be waiverable by the various aeromedical agencies.

The aeromedical community will be increasingly faced with the problem of how to manage aviation personnel on flying status with elevated blood glucose levels found in individuals with pre-diabetes and diabetes mellitus. Diabetes is presently the sixth leading cause of death in the U.S., with about 50% of those with diabetes dying from coronary artery disease (ROBARD 2007). Aviation Medical Examiners may issue medical certificates to airmen with pre-diabetes or diet-controlled diabetes who are not on medication as long as their laboratory values are within FAA standards. Current clinical practice guidelines will help AME's in making aeromedical determinations for airmen with pre-diabetes or type 2 diabetes mellitus.

Pharmaceutical approaches are primarily used in those individuals who have type 2 diabetes mellitus. Many medications can cause side effects that place individuals, and more specifically aviators, at increased risk for sudden incapacitation as well as at risk for subtle degradation of sensory, motor and informational processing functions. The use of

injectable agents such as insulin or oral hypoglycemic agents is not compatible with USAF aviation.

Metformin is currently recommended as first line therapy for the treatment of type 2 diabetes mellitus and should be started in a newly diagnosed patient at the same time as lifestyle intervention recommendations (ADA 2007). Metformin is generally considered safe when used as monotherapy and in therapeutic doses does not cause hypoglycemia (Luna 2001). This permits its description as a "euglycemic" or "antihyperglycemic" drug rather than an oral hypoglycemic agent (Gardner 2007). One large study that looked at the use of metformin was the UK Prospective Diabetes Study (UKPDS 1998). In this study the occurrence of major hypoglycemic episodes among overweight patients with type 2 diabetes mellitus treated with intensive metformin therapy (2550 mg/day) were 0.7% on diet therapy and 0% on metformin. The occurrence of any hypoglycemic episodes were 0.7% on diet therapy and 4.2% on metformin. Other smaller studies show the rates of hypoglycemia for metformin to be either zero or comparable to the prevalence in diet-treated patients. Lactic acidosis has also been reported as a side effect for metformin. One large systematic review by Salpeter, et.al., 2003 has shown that pooled data from 176 comparative trials and cohort studies totaling 35,619 patient-years revealed no cases of fatal or non-fatal lactic acidosis in any medication group (Bolen 2007). Several additional studies showed little or no elevated risk for lactic acidosis in metformin recipients. Current guidelines recommend that metformin should not be used in patients with chronic or acute renal insufficiency and should be discontinued when creatinine levels reach 1.4 mg per dL in women or 1.5 mg per dL in men.

In regards to type 2 diabetes mellitus in aviators, primary prevention efforts are best suited to be applied towards aviators who have elevated risks and can be emphasized during annual flight physicals as well as during periodic counseling sessions aimed at population health efforts. Once an aviator has been diagnosed to have type 2 diabetes, secondary and tertiary prevention efforts should be applied in the disease management process. Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are not disqualifying diagnoses per current aviation guidelines.

However, the Diabetes Prevention Program (n=3234) study demonstrated that without intervention, eleven cases out of 100 person-years with IFG or IGT go on to develop type 2 diabetes within a 3 year period (DPPRG 2002). However, of those who receive lifestyle modification (diet and exercise), only 5 go on to develop type 2 diabetes. This is a 58% relative reduction in the incidence of diabetes. Prevention of the development of type 2 diabetes in the aviator with IFG or IGT is an important concept when looking at their long-term health, and at their future flying career. Aviators that have the diagnosis of IFG or IGT should be strongly counseled to undergo the appropriate lifestyle modifications. Suggested lifestyle interventions include weight loss of 10-15% bodyweight, consultation with a dietician for weight loss, and a monitored exercise program. The control population in the prevention study was given a pamphlet that listed the exercise and weight loss goals, but did not provide more intensive counseling or guidance.

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) defined the metabolic syndrome as a cluster of criteria that increase the risk of

developing diabetes and therefore, coronary heart disease (CHD) (NCEP 2001). Possessing 3 or more of the criteria listed in Table 2 qualifies a patient as having the metabolic syndrome. CHD appears to be more prevalent in those with the metabolic syndrome than in non-diabetic patients, but less prevalent than in diabetics. Controlling the metabolic syndrome is considered an important prevention of CHD.

Table 2. NCEP ATP III Risk Factors.

Risk Factor	**Defining Level**
Waist circumference Men Women	 ≥ 40 inches ≥ 35 inches
Triglycerides	≥ 150 mg/dL
HDL-C Men Women	 < 40 mg/dL < 50 mg/dL
Blood Pressure	≥130 mm Hg systolic or ≥ 85 mm Hg diastolic
Fasting glucose	≥110 mg/dL

The concept of diabetes as a major cardiovascular risk factor is not a new topic. The NECP ATP III reports that the risk of CHD is similar in diabetic subjects without pre-existing vascular disease as in non-diabetic subjects with known vascular disease. Glycemic control alone will not eliminate the excess risk of CHD in diabetic subjects. The NCEP ATP III therefore recommends for the diabetic population lowering the LDL

to below 100 mg/dL, the total cholesterol below 200 mg/dL, and the HDL above 40 mg/dL. In addition, treatment of overweight patients with type 2 diabetes mellitus has been shown to decrease the incidence of myocardial infarction by 39% and all-cause mortality by 34% (Holman 2008).

III. WAIVER CONSIDERATIONS

Waiver considerations for diabetes and pre-diabetes are as follows:

- Type 1 diabetes mellitus: Generally, a waiver will not be considered.
- Type 2 diabetes mellitus: A waiver should be considered if there is evidence of good control on diet alone or with meformin.
- Impaired Fasting Glucose and/or Impaired Glucose Tolerance: No waiver is required since it is not a disqualifying diagnosis.

Good control is defined as:

- Fasting glucose level < 126 (report quarterly data points)
- Hgb A1C less than < 7% (report quarterly data points)
- No diabetes related complications that interfere with safety of flight / mission completion.

In addition, the following are recommended annually to meet NCEP ATP III guidelines:

- Lipid panel
- Waist circumference
- Blood pressure

The following information should be included in the aeromedical summary:

- Evidence of diabetic counseling which includes diabetic education, consultation with a dietician, lifestyle modification for diet and exercise, modification of cardiac risk factors, monitoring of glucose levels as appropriate, attention to complications, etc.

- Complete history: focus on dietary, familial, and risk factors
- Complete physical exam including vitals and blood pressure: focus on evidence of diabetic complications
- BUN/Creatinine
- Fasting lipid panel
- HbA1C
- Urine: check albumin / creatinine ratio in random, spot collection (microalbuminuria). Also check for ketones, protein and sediment
- Ophthalmology evaluation to look for evidence of retinopathy
- Screening ECG

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*This Clinical Practice Guideline was developed for the Aerospace Medical Association by their constituent organization, the American Society of Aerospace Medicine Specialists, with permission by its CPG manager Dr. Daniel L. Van Syoc.

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Vita

Dr. Gregory S. Hyland is currently a medical officer in the United States Air Force and is enrolled in the Air Force's Residency in Aerospace Medicine (RAM) program at Brooks City-Base in San Antonio, Texas. He was born on July 6, 1963 in Monroe, Michigan and graduated from Willow Run High School in Ypsilanti, Michigan in 1981. He then attended Michigan Technological University in Houghton, Michigan and graduated with a Bachelor of Science degree in Chemistry in 1986. He joined the U.S. Air Force and became a Minuteman III Missile Launch Officer in Grand Forks, North Dakota. While stationed there he completed a Master of Science degree in Biochemistry and Molecular Biology in 1993. He then became an Air Force ROTC Instructor at Syracuse University where he was stationed until 1996. At that time he was accepted into the University of Michigan Medical School in Ann Arbor, Michigan. After initial medical training he became a military flight surgeon by attending the Aerospace Medicine Primary course in San Antonio, Texas. He then was stationed at Buckley AFB in Denver, Colorado. After three years he completed a one year remote tour of duty at Osan Air Base, Republic of South Korea and subsequently was stationed at Eglin AFB, Florida. He was recently accepted into the RAM program and is currently enrolled in the Master of Public Health Program at the University of Texas Medical Branch, Galveston, Texas.

Permanent address: 3810 Maiden Way, Converse, TX 78109

This dissertation was typed by Gregory S. Hyland.