Diabetes Mellitus Type 2 in Aviators: A Preventable Disease

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Introduction: The current epidemic of obesity and resultant diabetes mellitus type 2 (DMT2) is a tsunami that will impact healthcare worldwide and lap over into aerospace medicine. Metabolic syndrome (MBS) is the major link between obesity and DMT2. ***Methods:*** A review of U.S. Air Force Aeromedical Consult Service (ACS) records was accomplished looking at aviators with a diagnosis of DMT2. Case reports of three flyers with DMT2 are presented and discussed. Other aeromedical agencies were contacted regarding their experiences and this information was summarized. A literature review on DMT2, obesity, and metabolic syndrome was accomplished. ***Results:*** Of 70 charts for flyers identified with diabetes mellitus at the ACS between 1975 and 2000, over 95% were for DMT2. The mean body mass index for these aviators was 26.2. Currently, all services grant restricted waivers for some aviators with DMT2, none in high performance, single-seat aircraft. The FAA is currently allowing most flyers with stable DMT2 to operate aircraft in all categories with specific restrictions. ***Discussion:*** Obesity and metabolic syndrome are becoming increasingly prevalent in the aviation community. Aggressive actions to limit weight gain and identify those at risk for developing DMT2 must be considered for all populations.

Keywords: diabetes mellitus type 2, obesity, metabolic syndrome, insulin resistance.

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THE CURRENT EPIDEMIC of obesity and resultant diabetes mellitus type 2 (DMT2) is a tsunami that will impact all healthcare worldwide and lap over into aerospace medicine (**Fig. 1**) (54). It is estimated that presently, in the U.S., there are over 16 million people with DMT2, of which only about one-half to two-thirds have been diagnosed (33). The 2001 Behavioral Risk Factor Surveillance System, developed by the Centers for Disease Control and Prevention, found the prevalence of diabetes had increased from 7.3% in 2000 to 7.9% in 2001 (34). In 2000, it was estimated that over 151 million people worldwide had been diagnosed with diabetes mellitus (DM). These numbers will continue to grow, with over 221 million having been diagnosed with DM by 2010. These numbers do not account for those who have not been diagnosed (estimated at 30–50% of actual DM cases) and those with impaired glucose tolerance syndromes. DM is presently the sixth leading cause of death in the U.S., with about 50% of those with DM dying from coronary heart disease (9). By 2050, the World Health Organization (WHO) estimates that cardiovascular disease, of which DMT2 is a major contributor, will be the number one cause of death worldwide. Reasons for the increasing prevalence of DMT2 include aging of the population and, more importantly, the increasing prevalence of obesity in developed and developing countries. This impending metabolic disaster mandates that the aeromedical community understand current approaches to the prevention and recognition of this disease.

Metabolic syndrome (also insulin resistance syndrome, dysmetabolic syndrome, syndrome X, Reaven syndrome, pluri-metabolic syndrome, Chaos syndrome, diabesity) is the current term for a constellation of metabolic and physiologic abnormalities defined variously by the National Cholesterol Education Program (from the National Heart, Lung, and Blood Institute), the WHO, and the ICD-9-CM.* The three authorities agree that metabolic syndrome (MBS) includes excess abdominal adipose tissue, hypertension, hypertriglyceridemia, low HDL-cholesterol, and elevated fasting glucose. Insulin resistance, hyperuricemia, and hypercoagulability are also included by the WHO and ICD-9-CM. MBS is part of a spectrum of metabolic abnormalities that, if not interrupted, can lead to the development of DMT2 and its complications. Visceral abdominal fat (VAT) appears to be key to this process. Supporting this connection are numerous studies demonstrating direct biochemical and pathophysiologic links between excess VAT, abnormalities in insulin regulation, and disordered glucose metabolism (50).

The aeromedical community is and will be increasingly faced with the problem of how to deal with overweight flyers. Being overweight [defined as a body mass index (BMI= kilograms of body weight per meter squared body height) of 25–29.9] or obese (BMI $\geq$ 30) is rapidly becoming one of the most common medical

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* Supplemental data are available on-line at www.ingentaselect.com/vl=1151019/cl=61/nw=1/rpsv/cw/asma/00956562/contp1-1.htm (Table A).

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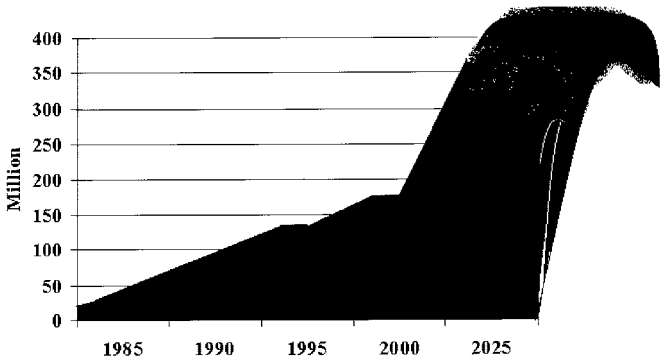

Fig. 1. Trend line for number of people (in millions) diagnosed with diabetes mellitus worldwide (WHO/NCD).

problems among Americans. Per the 1999 National Health and Nutrition Examination Survey (NHANES) and NHANES II data, 61% of American adults were either overweight or obese. The number of obese adults has nearly doubled since 1980 to an estimated 27% of the U.S. population (10). The 2001 Behavioral Risk Factor Surveillance System found the prevalence of obesity had increased from 19.8% in 2000 to 20.9% (34). It is estimated that deaths due to causes related to obesity account for approximately 300,000 deaths per year and for direct healthcare costs of nearly 4.3–10% of the healthcare budget (1,35,46,52). The ill effects of excess VAT are a continuum beginning with MBS, leading to impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and finally, DMT2. The concept of "diabesity" has been created to emphasize this connection (54). A recent study by Robbins et al. documented the cost of excess weight gain among active duty U.S. Air Force personnel. They found that for 1997, approximately 20% of the U.S. Air Force population exceeded maximum allowable weight for height standards. Total excess body-weight attributable costs (direct and indirect) were estimated at $22.8 million/yr. They also calculated that attributable lost workdays were approximately 28,351/yr (39).

In this paper, we will present three cases of flyers modeling various levels of progression from MBS to IGT and then DMT2. We will present U.S. and Canadian aeromedical agencies' current experiences with DMT2 in flyers. We will then discuss some current ideas about the pathophysiology of DMT2, MBS, and obesity. Additionally, we will review the waiver implications of MBS and DMT2 in aviators and present some prevention recommendations.

METHODS

The reference list for the review was compiled after a Medline search, review of U.S. Air Force School of Aerospace Medicine (USAFSAM) library resources, review of primary source documents, and use of Internet resources such as the Google search engine. Key words for searches included, but were not limited to: diabetes mellitus, diabetes mellitus type 2, adult onset diabetes, non-insulin dependent diabetes, metabolic syndrome, Reaven's syndrome, pluri-metabolic syndrome, insulin resistance, insulin resistance syndrome, Chaos syndrome, obesity, overweight, adipose, body fat, body composition, central obesity, visceral adipose tissue, visceral fat, aviation, flyers, aviators, aerospace, aeromedical, pilots, and weight gain. The information on other aeromedical agency experiences was obtained using published documents from those agencies, as well as communication with each agency via telephone, e-mail, and written communication.

Three Typical Case Reports from the ACS Files

Case reports were generated using records from the files of the U.S. Air Force Aeromedical Consult Service (ACS) at Brooks AFB, TX. An exemption was applied for and granted from the USAFSAM Institutional Review Board for use of the data from these files. Identifying information was removed from the cases described.

Case 1: Senior Officer A, a 35-yr-old active duty U.S. Air Force male pilot, was seen at the ACS in 1967. He presented for evaluation of incomplete right bundle branch block (RBBB), diagnosed on a routine flight physical exam. This eventually progressed to a complete RBBB. On his first evaluation, Senior Officer A was without cardiac or diabetic symptoms. His cardiac and metabolic evaluation was unremarkable and he was granted an unrestricted waiver for return to flying. Over the next 24 yr, he underwent nine follow-up exams at the ACS. There was no family history of diabetes mellitus. Physical exams were noted as being normal except for "labile hypertension" in 1977 and, in 1991, a 5-d BP check showed an average reading of 142/92. His BMI increased from 25.4 to 30.3 from 1967 to 1991. Measured body fat percentages (using neck, waist, and upper arm circumference calculations (11,25) showed a steady rise from 14% to 25%. Laboratory results showed no glucosuria, proteinuria, or ketonuria. Over the years, his fasting blood glucose (FBG) went from 98 to 143 mg $\cdot$ dl^{-1}. In 1991, his glucose tolerance test (GTT) 2-h level was 185 mg $\cdot$ dl^{-1}. Lipid measurements also demonstrated gradual increases in total cholesterol from 215 to 260 mg $\cdot$ dl^{-1}; HDLs were low, usually in the low 30s or high 20s. Triglycerides were usually above 250 mg $\cdot$ dl^{-1}. His complete blood count, thyroid tests, liver panels, and electrolytes were normal. Diagnoses included the RBBB, labile hypertension, and excess body fat. At his last evaluation in 1991, he was diagnosed with diet-controlled diabetes mellitus. By this time, he had been retired for almost 4 yr. Except for his first evaluation, he was recommended for waiver for unrestricted pilot duties at all ACS visits. Treatment recommendations typically consisted of diet, exercise, and avoidance of tobacco products.

Case 2: Senior Officer B was a 50-yr-old active duty U.S. Air Force single-seat jet pilot initially evaluated in 1982 at the ACS for a history of elevated cardiac risk index identified under the Tactical Air Command Risk Factor Identification Program. He had no cardiac or diabetic symptoms. There was a history of several abnormal fasting blood glucose levels in the past with normal 2-h GTTs. Family history was positive for both parents and one of four sisters being diabetic. His father had died of a myocardial infarction in his 60s and his

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mother had died of a stroke at age 59. Initial ACS evaluation included full cardiac work-up (with angiography), and complete metabolic evaluations. His physical was remarkable for overweight with a BMI of 27.4. Angiography showed left anterior descending coronary intimal roughening and right coronary artery ectasia. A FBG was 153 mg · dl^{-1}. Fasting lipids revealed a total cholesterol of 172 mg · dl^{-1} with an HDL of 33 mg · dl^{-1} and triglyceride of 294 mg · dl^{-1}. No GTT was performed. His diagnoses included coronary artery intimal roughening on cardiac catheterization, fasting hyperglycemia, and mild hypertriglyceridemia. Waiver was recommended for continuation of unrestricted pilot duties, and this was granted. Treatment recommendations included weight loss, diet, exercise, daily aspirin, avoidance of tobacco, and follow-up in 1 yr. He returned for re-evaluation 2 yr later after an abnormal thallium stress test. There were no cardiac or diabetic symptoms noted. FBG levels in the intervening period were consistently elevated with values ranging from 130 to 204 mg · dl^{-1}. ACS evaluation included repeat thallium and exercise testing, as well as metabolic screening. Physical exam continued to show an elevated BMI of 27. Thallium and exercise testing were interpreted as borderline and normal, respectively. A FBG was 133 mg · dl^{-1} and repeat was 109 mg · dl^{-1}. Diagnoses were essentially unchanged and an unrestricted pilot waiver was again recommended and granted. Treatment recommendations were unchanged. At his last ACS evaluation in 1991, Senior Officer B was retired and without symptoms of heart disease or diabetes. Physical exam showed a BMI of 29. Repeat cardiac studies did not show progression of disease. His labs, however, showed FBG levels above 160 mg · dl^{-1}. Lipids remained abnormal with low HDLs. He was diagnosed with adult-onset diabetes mellitus and referred to an endocrinologist.

Case 3: Senior Officer C was evaluated three times over a period of 19 yr beginning when he was 44 yr old and a rotary wing senior pilot with the U.S. Army. He was initially referred in 1976 for the USAFSAM Cardiovascular Disease Follow-up Study. He had a history of elevated cholesterol. He had no history of cardiac or diabetic symptoms or diagnoses. Family history was positive for his father having had his first heart attack at age 60 and dying of one at age 69. Physical exam showed a BMI of 24. Body composition studies using the 40K technique (15,17) revealed a body fat percent of 24. Laboratory testing was normal. Cardiac catheterization showed a 20% occlusion of the left main artery. Diagnoses included coronary atherosclerosis and obesity. Waiver was not recommended. Close follow-up of cardiac risk factors was recommended, along with weight loss, diet, and abstention from tobacco. Senior Officer C subsequently retired and was followed up in 1988 at the ACS. At that point, he was 56 yr old and had no symptoms of heart disease or diabetes. He was on no medications. Physical showed a substantial weight gain with BMI of 32.4. Labs showed FBGs of 236 and 244 mg · dl^{-1}. Lipid testing showed a total cholesterol of 242 mg · dl^{-1}, HDL of 25 mg · dl^{-1}, and triglycerides of 171 mg · dl^{-1}. Non-invasive cardiac testing did not indicate progression of disease. Diagnoses included coronary atherosclerosis, diabetes mellitus, and obesity. Recommendations included weight loss, diet, exercise, and follow-up with his personal physician for the diabetes. On his last visit to the ACS in 1995, Senior Officer C was reporting a stable anginal symptom pattern, nocturia four to six times per night, occasional paroxysmal nocturnal dyspnea, and two-pillow orthopnea. He was taking Hytrin, allopurinol, Glucotrol, and aspirin. In the interim, he had been diagnosed with gouty arthritis and renal lithiasis. Physical showed his BMI at 31.6 and a III/VI systolic murmur. Labs showed a FBG of 151 mg · dl^{-1}, normal chemistries, a total cholesterol of 224 mg · dl^{-1}, HDL at 37 mg · dl^{-1}, triglyceride of 97 mg · dl^{-1}, and calculated LDL of 171 mg · dl^{-1}. Thyroid functions were normal. Urinalysis was normal. Coronary catheterization demonstrated severe three-vessel coronary artery disease (CAD). Diagnoses included severe CAD requiring surgical intervention, atrial fibrillation with slow ventricular response, angina, DMT2, gouty arthritis, dyslipoproteinemia, and obesity. Recommendations included surgical intervention for his severe CAD, appropriate cardiac risk factor interventions per his cardiologist, weight loss, diet, and reduction of LDL to < 100 mg · dl^{-1}.

In the first case (Senior Officer A), we see a demonstration of the relationship between obesity and DMT2. The elevation of the BMI followed by the appearance of frank DM is classic. In the case of Senior Officer B, there was a delay in diagnosing diabetes or further addressing the elevated FBGs during his active duty evaluations. No GTTs were performed during any of his evaluations. The elevated FBGs were not a new phenomenon and the elevated body fat had been present for years. In the last case (Senior Officer C), there is a clear pattern of increased weight and progression to diabetes along with acceleration of coronary disease. These cases show several themes. All met current National Cholesterol Education Program criteria for MBS at some point. There was a clear progression of weight gain and glucose levels. In the last two cases, coronary disease was diagnosed in the fifth and sixth decades. Finally, the recommended therapies were unsuccessful in preventing the appearance of diabetes mellitus in all cases. **Table I** lists some biometric and lab values for each case chronologically.

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RESULTS

Summary of Aeromedical Experience from the ACS and Other Agencies

A 1994 U.S. Army report estimated that the U.S. Army aviation community could expect about 21 new cases of DM and impaired glucose tolerance (IGT) each year. They expected that 78.4% and 10.9%, respectively, would not be granted waivers based on inability to achieve control with diet and exercise, or existence of concurrent disease. They noted that most cases were being seen in aviators over age 35 and recommended appropriate screening measures (30). Others have noted a similar increase in incidence and prevalence of DMT2 with age in aviators (26). **Table II** summarizes current

TABLE I. LIST OF USAF ACS CASE BIOMETRICS AND LAB STUDIES.

Case	Age	BMI	FBS	GTT	TChol mg · dl^{-1}	HDL mg · dl^{-1}	TG mg · dl^{-1}	Percent Body Fat
A	35	25.4	98	Negative	215	N/A*	94	19
	47	28	103	Not Done	205	54	119	25.95
	59	30.3	143	Positive	299	42	228	25
B	50	27.4	153	Not Done	172	33	294	28.87
	52	28	133	Not Done	143	33	132	Not Done
	56	29	170	Not Done	164	30	126	28.75
C	44	24.3	105	Negative	183	N/A	80	24
	56	32.4	244	Positive	242	25	171	36.2
	1991	31.6	151	—	224	37	81	29.3

*Not Available

aeromedical agency information on flyers with DM. The following paragraphs outline some specific findings from each aeromedical agency.

A record review of all patients diagnosed with diabetes mellitus (ICD9: 250.0) seen at the ACS at Brooks AFB since 1975 was accomplished. Of 70 records reviewed, 68 were patients with DMT2 (including adult onset, diet controlled, and non-insulin dependent diabetes). U.S. Air Force flyers were patients in 39 of the 70 cases. Of those, 62% had BMIs over 26 and the mean BMI was 26.5. All were male and 90% were over age 35. There were three cases with flyers who were not overweight (or were losing weight) and who had rapid resolution of their diabetes with diet and exercise. This raises the question of whether these cases were in the early stages of DM type I (DMT1). Lower weight and weight loss are more commonly seen in either DMT1 or atypical cases (such as chemically induced DM). The honeymoon period for insulin dependent DM may take months to resolve with patients being initially misdiagnosed as "chemical" or non-insulin dependent diabetes (8). Without these atypical cases in the case series, the average BMI would increase to over 27. Waivers have not been granted for flyers on insulin, and limited waivers (non-single seat) have been granted for a few flyers on oral hypoglycemics. The majority of waivers reviewed were for diet-controlled DMT2. Per the U.S. Air Force Safety Center, there have been no mishaps identified where DM was found to be a causal factor.

In the Navy, flyers with DMT2 are not allowed to fly single-seat aircraft. There is no record of DM related mishaps. Metformin is an insulin-sensitizing biguanide that does not stimulate insulin production, and thus does not cause hypoglycemia. It has been waived for use in the Navy for Class 2 and 3 aviators.

The Army tends to have the oldest military aviators, with many working for the Department of Army Civilians and others working as contractors. Over the last 10 yr there has been a distinct increase in average weight for aviators in the Army (average 10 lb). Interestingly, there has also been an increase in average height for the same aviator group. A number of flyers have been returned to duty with a diagnosis of IGT (diet controlled). A number of Air Traffic Control members have been returned to duty with DMT2 on oral hypoglycemics. Two aviators have been followed with DMT2 on Metformin. These were described as special cases with the individuals in critical specialties who were close to retiring. No individuals with type 1 DM have been waived.

For the FAA, the most common reason for denial of waivers for aviators with DM is inadequate control. The second most common reason is secondary complications. Of those with DMT2, approximately 1500 or 30% were not on medication (diet-controlled). There has been at least one case where abnormal glucose levels may have played a role in pilot error leading to an aircraft mishap (7). However, no reliable estimates can be made regarding near-misses, poor landings, or loss of situational awareness related to abnormal plasma glucose levels in flight. Specifically, there is no good information on the frequency of hypoglycemia or related aircraft mishaps in aviators with DMT2 or glucose intolerance.

The Canadian Forces do not grant waivers but may return diabetic aircrew to flying duties on a case-by-case basis with an operational flying restriction if appropriate. The CF aircrew database indicates 15 pilots and navigators with DMT2 (personal communication). Pilots diagnosed with DMT2 are generally restricted to flying "with or as copilot" unless fully controlled by diet and exercise alone. Metformin is typically used as a first-line medication to which rosiglitazone and acar-

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TABLE II. SUMMARY OF EXPERIENCE WITH DM IN AEROMEDICAL AGENCIES.

	Aeromedical Agency				
	Air Force	Navy	Army	FAA	Canadian Forces
DMT1	2/39 (5%)	28/251 (11%)	0	355	1
DMT2	37/39 (95%)	223/251 (89%)	15 (currently)	4500 (92%)	15
Waivers	40%	46%	13%	90%	Case by case
Mishaps w/DM as a factor	None	None	None	Possibly 1 (NTSB decision pending)	None

abose may be added. The addition of a sulfonylurea imposes a requirement for an operational flying restriction.

Administrative program actions for overweight military members are problematic, as they are for many medical prevention programs (27). Potential adverse administrative outcomes may stimulate members to try to maintain appropriate fitness standards. Some members may follow unhealthy programs to maintain prescribed weights. Higher rates of eating disorders and use of non-prescribed diet supplements may result. There may be a reluctance to follow through on identifying overweight individuals due to perceived adverse administrative outcomes for members or the member's unit. Evidence points to significant variability in how flyers are measured (e.g., U.S. Army experience), with the benefit of the doubt often stretched considerably. Unfortunately, as outlined in this paper, the longer individuals take to identify and address their overweight status, the higher the likelihood of developing problems such as MBS and DM.

DISCUSSION

Understanding the pathophysiology and course of DMT2 requires an understanding of the role of insulin resistance (IR) and VAT. A cluster of metabolic disorders was described by Reaven in 1988 and has been expanded on since (38). MBS classically consists of hypertension, central (visceral) obesity, hyperinsulinemia, dyslipidemia (low HDL, small LDL particles, and high triglycerides), hyperuricemia, and a prothrombotic state (elevated levels of plasminogen activator-1). MBS has been associated with endocrine diagnoses such as polycystic ovary syndrome and acromegaly. Importantly, MBS has been closely correlated with a high risk for cardiovascular disease.

Most experts feel that DMT2 is a multi-factorial disease. Genetics play a major role in the susceptibility to developing DMT2. This is seen especially with the tendency for some racial groups to develop DMT2, including Native Americans, African-Americans, Pacific Islanders, Hispanic groups, and Asian groups. Lifestyle influences are also directly linked as risk factors for the development of DMT2 and include high-fat, high-calorie diets, sedentary lifestyle, and the development of obesity. DMT2 involves three metabolic abnormalities: peripheral insulin resistance (mostly skeletal muscle and adipose tissue), insulin secretory dysfunction (pancreatic β cell), and increased hepatic glucose production. Insulin resistance develops as the result of genetic and acquired factors. Supporting a genetic risk component is strong evidence that in non-diabetic relatives of those with Type II DM, there is a higher prevalence of IR (18,48). Support for acquired risk factors for IR comes from numerous studies linking obesity and sedentary lifestyle with higher IR rates (24).

Insulin resistance, almost universal in the obese and the elderly, does not necessarily lead to hyperglycemia. β cell functional decline is a prerequisite. By the time fasting hyperglycemia is evident, β cell function has declined by approximately 50% (4,20). The proposed mechanism for β cell decline is a β cell gene defect, probably in combination with other factors. The cytokine tumor necrosis factor α is possibly one such factor (14). Plasma free fatty acids (FFAs) released from adipocytes after lipolysis of triglycerides are another. Elevations in FFAs have been associated with obesity and contribute to the development of insulin resistance. FFAs may be responsible for up to 50% of the insulin resistance seen in DMT2 (4). FFAs are essential for β cell function in the normal state, but chronically elevated levels are toxic (36). Once β cell dysfunction develops, hyperglycemia appears. Hyperglycemia desensitizes β cells and impairs insulin secretion in response to insulin secretogogues, including glucose itself. This is referred to as glucotoxicity, which contributes to further β cell decline. β cell dysfunction is also accompanied by the development of amyloid fibrils containing islet amyloid polypeptide. Amyloid deposition is associated with declining β cell mass and further impairment of β cell function, thus worsening hyperglycemia (20).

Adipose tissue, traditionally considered a simple depot for fat energy, has become a major focus of research. It is becoming apparent that this tissue is quite active metabolically. Evidence that adipose cells, specifically visceral adipose cells, are intimately involved in various energy management feedback loops, has stimulated a search for modifiable factors in the development and pathophysiology of obesity (53). The "adipostat" concept suggests a feedback mechanism between brain, fat, and other tissues. Adipokines such as leptin, resistin, adiponectin, and anti-tumor necrosis factor α are being studied as potential adipose-derived messengers that may play parts in pathogenic processes identified in MBS. Adipose tissue appears to be a critical component of a toxic regulatory cascade leading to hypertension, atherosclerosis, and other endothelial disease processes. There is a clear relationship between increasing BMI or waist circumference (and thus VAT) and levels of IR. Present evidence points to a gradual progression of higher levels of visceral fat leading to IR (especially in those more genetically susceptible), initial increased pancreatic β cell hypertrophy, and insulin production with maintenance of normoglycemia, followed by waning β cell function, the appearance of hyperglycemia, and clinical DMT2 (**Fig. 2**). An important concept is that IGT is a precursor to DMT2 and may exist for years before DMT2 becomes established. Impaired fasting glucose (IFG) occurs later in the progression toward DMT2 than IGT.

Intensive research is ongoing utilizing innovative genetic techniques (transgenic mice, knockout mice, gene mapping) to identify the specific substances involved in the various metabolic processes within adipocytes. Leptin, and more recently ghrelin, have been under intense study as potential agents to assist with weight loss. Other agents are being investigated for their ability to ameliorate complications related to MBS and DMT2 (6,12,13,40,42,43). The list of mediators and substances involved in what is a complex set of feedback loops has also continued to grow.**

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** Supplemental data are available on-line at www.ingentaselect.com/vl=1151019/cl=61/nw=1/rpsv/cw/asma/00956562/contp1-1.htm (Table B).

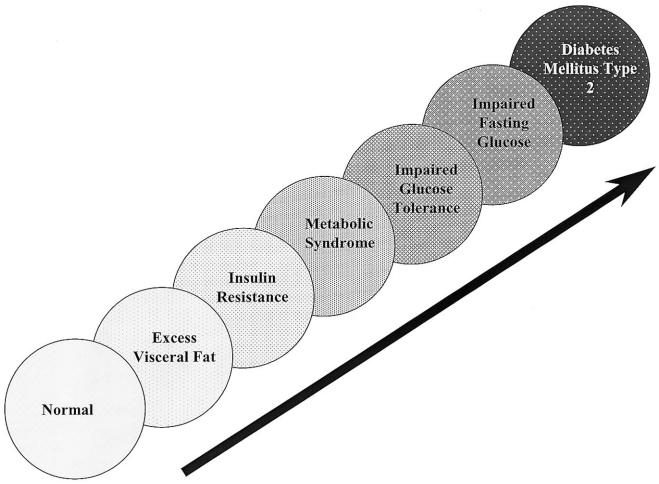

Fig. 2. Progression of disease: normal to diabetes mellitus type 2.

Patient Issues

The cases presented here demonstrated a progression of disease from MBS to IGT or IFG to DMT2 followed by the appearance of secondary complications in two of three. Physicians or patients do not always appreciate this progression. In the aeromedical world, IGT or IFG is often viewed as a relatively benign state addressable with diet and exercise advice. It is clear, however, that patients with MBS are at higher risk for macrovascular complications (threefold increase in risk for coronary disease and stroke) (19). Those with frank diabetes add microvascular risk (renal, retinal, and autonomic disease). MBS is not uncommon. Recent evidence points to an age-adjusted prevalence of MBS of 23.7% in the U.S. population (16). At any point until the appearance of frank DM, there is the potential to stop the progression. The results from the Diabetes Prevention Program confirm that progression to diabetes can be slowed with appropriate diet and exercise therapies. Reduction of the VAT mass is the key. The higher the VAT mass, the higher the risk and the harder it is to return the individual to a normal state. Unfortunately, non-medical and non-surgical approaches to weight loss, while effective, are problematic (28). Behavioral therapy alone often fails to halt the progressive accumulation of VAT. The worldwide epidemic of "diabesity" points to a need for more aggressive approaches to reduce body fat (54). Medical therapies, such as diets, medications, and psychotherapy, have all had varying levels of success. Surgical therapy, including gastroplasty and liposuction, may or may not be valid approaches. Effects of gastroplasty may go beyond simple reduction in meal size, with possible hormonal changes also being involved (12). Some evidence does point to potential positive effects of liposuction on lipids and insulin resistance, but there have been no long-term controlled studies to document their effects on the incidence of DMT2 or MBS (3). Caution is in order, however, against this seemingly direct approach to reducing BMI. One study that looked at effects of large volume liposuction found a disproportionate increase in visceral fat vs. subcutaneous fat post-surgery (31). Subcutaneous lipectomy has also been found to cause a metabolic syndrome with more intra-abdominal fat as a percent of total body fat, higher insulin, and elevated serum triglycerides in rodents (49). The cases described did not have any waiverable or available options for weight loss other than diet and exercise. Presently, liposuction, after recovery, is waiverable or a non-factor for return to flying in all aeromedical agencies.

Prevention

All evidence points to the critical need to recognize and treat IGT, IFG, and MBS to prevent or delay the onset of DMT2 and its complications. There is often a temptation to avoid diagnosing flyers with DMT2 because of career implications. This is a disservice to the individual as delayed aggressive therapy clearly speeds the onset of micro- and macrovascular complications with increased morbidity and mortality. In the military, programs designed to identify overweight members provide a ready means to motivate those who are overweight to lose that weight. Physicians must get overweight individuals to begin reduction efforts before they become obese. There is evidence that the body's homeostasis system may be programmed for weight gain, implying a need for more aggressive and specific therapies (41). If we are serious about obesity, we may have to consider more radical approaches such as stringent behavioral therapies, medication, and surgery. It may be time to loosen obesity treatment waiver restrictions. Medical and surgical approaches together may be required to reduce obesity in some individuals. This means taking a hard look at current and future obesity therapies and their aeromedical implications.

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Primary Prevention

Primary prevention efforts including exercise, low-fat diets, and avoidance of obesity should be the core of any aeromedical program in addressing these issues. These approaches have been suggested previously for MBS in the flying population, specifically in Germany. There, researchers noted that it was possible to identify flyers with higher potential for developing full-blown MBS using standard flight physical techniques (21). Obesity, especially excess VAT, is a disease. Weight gain is a surrogate marker for MBS and increased risk for development of DMT2. We must address those with BMIs above 25 and elevated VAT (central obesity) as we address flyers with elevated BPs. If these individuals cannot reduce their increased VAT levels given close monitoring, diet, and exercise, then they may need grounding while therapies that are more aggressive are implemented pending waiver.

Secondary Prevention

Secondary prevention, specifically, the identification of those with IR, MBS, IGT, and IFG is important. Numerous studies indicate that all elevations of blood glucose and insulin levels increase the risk for development of macrovascular and microvascular disease. IGT and IFG, being pre-diabetic states, are especially important to detect. This is because there is still a chance to salvage β cell function, or at least significantly prolong

β cell function and, thus, prevent or delay diabetic related complications. It may be true that β cell function declines progressively, leading to worsening of the disease and increased medication requirements. However, with intensive glycemic control, the rate of macro- and microvascular complications can be reduced to nearly that of nondiabetics.

In the Finnish Diabetes Prevention Study, patients with impaired glucose tolerance were randomly assigned to either control or intervention (increased dietary fiber, increased physical activity) groups and were followed for 3.2 yr. The risk of diabetes was reduced by 58% in the intervention group (47). In a recently published study, The Diabetes Prevention Program Research Group enrolled 3,234 nondiabetic middle-aged, overweight patients with elevated fasting and post-load glucose. They were randomized to one of three groups: placebo, metformin, or lifestyle intervention with a goal of 7% weight loss and 150 min/wk of physical activity. The incidence of diabetes was reduced by 31% and 58% in the metformin and lifestyle groups as compared with placebo (23). These results demonstrate that early, aggressive lifestyle intervention in patients with glucose intolerance can prevent or at least delay the development of overt diabetes and its associated complications.

Tertiary Prevention

Once DMT2 is diagnosed, tertiary prevention of potential complications becomes important. Numerous complications accompany DMT2. Micro- and macrovascular complications are of special concern. The pathophysiology of these vascular complications is endothelial dysfunction mediated by a blunted vasodilation response to endothelial-derived nitric oxide and excess production of vasoconstrictors (45). Treatment of DMT2 has changed based on our knowledge of the underlying pathophysiology. Diet and exercise remain the bedrock on which anyone with DMT2 should start (2). Reduction of VAT decreases IR, improves lipid status, reduces BP, and delays onset of DMT2. Exercise and increased muscle mass positively influence glucose uptake, IR, and BP. It has been shown that calorie restriction and lowered fat intake, along with increases in complex carbohydrates, all improve metabolic status (37).

Pharmaceutical Approaches

The sulfonylureas are glucose-independent insulin secretogogues and increase β cell insulin production for any level of blood glucose. They are probably most effective in leaner patients with relative insulin deficiency. Metformin reduces hepatic glucose production and has some effect in decreasing peripheral insulin resistance by enhancing skeletal muscle glucose uptake. Metformin may be an appropriate first choice in more obese patients with higher levels of insulin resistance. The thiazolidinediones reduce peripheral insulin resistance in skeletal muscle and adipose tissue (2). These agents may also positively influence lipid status, for example: pioglitizone (Actos®) has been shown to reduce triglycerides and increase high-density lipoprotein levels (5,22). Other pharmacological approaches include reducing fat absorption (orlistat), and use of weight-loss drugs (sibutramine).

Aeromedically, medications carry potential side effects with negative impacts for aviators. Sulfonylureas carry the potential for hypoglycemia, and stability of glucose levels on these medications is required by the FAA before approval for use. Metformin may rarely induce lactic acidosis in susceptible individuals. Additionally, Metformin is associated with gastrointestinal side effects including diarrhea and nausea. B_{12} deficiency and minor decreases in hemoglobin and hematocrit have been reported with Metformin as well. Orlistat and acarbose are associated with gastrointestinal side effects such as diarrhea and bloating, each potential distracters. Thiazolidinediones such as rosiglitazone (Avandia®) and pioglitizone (Actos®) are associated with small decreases in hemoglobin and hematocrit (1 g/3.3% and 2–4% respectively). Adverse reactions for both drugs include a slight increase in incidence of anemia in treated patients. Increases in median plasma volume with edema have been noted in patients taking either drug. Finally, combination therapy with other diabetic drugs may increase the risk for hypoglycemia. Sibutramine, used in weight reduction, is a centrally acting neurotransmitter re-uptake inhibitor, with attendant potential for central nervous system side effects. Insulin is associated with significant potential for hypoglycemia.

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Implications of Waiver

Because of the potential for sudden incapacitation related to hypoglycemia, most aeromedical authorities are not allowing flyers with DMT1 to continue flying. Evidence for a direct relationship between hypoglycemia and aircraft mishaps is scanty. Part of the problem is the post-mortem change in glucose levels, allowing hyperglycemia but not hypoglycemia, to be diagnosed (7). The potential for using glycosylated hemoglobin to monitor control, and to assess control post-accident, is of interest (51). One 20-yr study of Air France pilots looked at 10 cases of sudden incapacitation. Only one case was diagnosed as hypoglycemia, with most related to cardiovascular events (29). In a review of 216 fatal U.S. general aviation accidents from 1990–1998, where possible physical impairment or incapacitation was mentioned by the FAA, only one identified a pilot with probable Type 1 diabetes (insulin bottles present). Hypoglycemia was not mentioned as being causal per the report (44). The issue of whether subtle degradation of sensory, motor, and information processing function may have contributed to mishaps is still pending, but the potential certainly has to be considered in aviators taking medications with the potential to produce hypoglycemia, but not complete incapacitation.

The Canadian Forces have one pilot with DMT1 flying with an operational flying restriction to fly with or as copilot, and a geographic restriction that prohibits deployments. The FAA is the only agency in the U.S. that has allowed type 1 diabetics to continue flying in non-commercial settings, and there are strict guidelines

TABLE III. WAIVER CONSIDERATIONS FOR DMT2 IN VARIOUS AEROMEDICAL AGENCIES.

	Aeromedical Agency				
	USAF	USN	USA	FAA	CF
Diet Controlled	Yes	Yes	Yes	Yes	Yes
FBGs	<126 mg · dl^{-1}	<126 mg · dl^{-1}	<126 mg · dl^{-1}		<7.0 mmol · l^{-1} (126 mg · dl^{-1})
Postprandial Glucose			WNL		<11.0 mmol · l^{-1} (198 mg · dl^{-1})
Waiver F/U	Yearly	Yearly	Every 6 months	Yearly	Yearly
HgA1C	Quarterly	$<7.5\%$	$<7\%$ every 3–6 months	Within 2% of upper limit of normal	$<7\%$
Approved Treatments (flyers)	Diet and weight reduction	Diet and weight reduction for Class 1/2/3	Diet and weight reduction	Diet and weight reduction	Diet and weight reduction
Medications Allowed	Rare oral hypoglycemics	Above plus Metformin only for Class 2/3	Rare oral hypoglycemics	No concurrent beta blocker use for oral hypoglycemics	Metformin, rosiglitazone, acarabose, sulfonylureas
Other Follow-up Tests	24 hour urine for protein and creatinine clearance; eye exam; thyroid function testing; lipids	Eye and neurological exams; internal medicine or family medicine consult	EKG; eye exam; blood urea nitrogen and serum creatinine; urinalysis	As required per personal physician	Annual ophthalmology, renal function including microalbumin, exercise test Q 2–3 years
Weight			WNL		

and restrictions in place. Of note, most investigators feel that the risk for hypoglycemia increases with the duration of the disease, the intensity of therapy, and a history of previous hypoglycemia (32,44). Concerns about hypoglycemia and the potential for sudden incapacitation (especially in those with hypoglycemia unawareness) has led the FAA to advocate less strenuous control of blood sugars for pilots on insulin. This raises the concern for potential long-term complications associated with looser glucose control. Potential DM complications that could effect crewmembers include third cranial nerve palsies, acute cardiac events related to higher risks for atherosclerosis, visual problems related to retinopathy, or changes in the lens due to hyperglycemia. Gastroparesis and other enteropathies related to diabetic autonomic neuropathy problems could degrade mission performance. Various sensory and autonomic neuropathies may certainly affect performance capabilities, and, in deployed military settings, could result in such problems as foot ulcers and intolerance of environmental extremes. MBS-related conditions, especially hypertension and dyslipidemia, increase the risk for cardiovascular and cerebrovascular events. Medications for DMT2 could be a problem, whether it would be hypoglycemia with long-duration sulfonylureas, or the need for monitoring of liver enzymes with the thiazolidinediones. Drug interactions with medications such as the anti-malarials have not been entirely worked out.

Table III lists waiver considerations for some aeromedical agencies. Generally, flyers should have high motivation, stable glucose levels, no medication side effects (if on medication), and no evidence of end-organ complications (CAD, renal disease, peripheral vascular disease, retinopathy, neuropathy). Regular and close follow-up to ensure compliance and look for incipient complications is mandatory.

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SUMMARY

DMT2, MBS, and obesity are rapidly increasing in prevalence. Complications and costs associated with these diseases are enormous. MBS appears to be a critical link between excess VAT and the development of DMT2, CAD, and other complications. More flyers will be presenting with these diseases and associated metabolic precursors (IR, MBS, IGT, and IFG) within the aeromedical community. The case reports described illustrate a classic progression of overweight, high-risk individuals from IGT to DMT2. The appearance of macro- and microvascular disease in these high-risk settings validates the need to address metabolic abnormalities as early as possible. Waiver experience among the various aeromedical agencies varies from least restrictive (FAA) to most restrictive (U.S. Air Force and U.S. Army). There are no military agencies allowing pilots with DM to fly single-seat aircraft at this point. Aeromedical specialists must focus on the identification of, and prevention of, obesity and MBS, even if this means grounding flyers to provide aggressive VAT-lowering therapy. Additionally, the identification of those with obesity, MBS, IGT, and IFG should be viewed as a secondary prevention approach, with the aim of preventing the appearance of DMT2. Obesity, specifically excess VAT, is a disease. In view of the critical role VAT has in this progression of disease, it is time to re-assess our approach to treating obesity. Whether the choice is medical or surgical, it may be time to aggressively approach any flyer with obesity vs. taking what has been historically a more passive approach.

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TABLE A. NCEP, WHO, AND ICD-9-CM DEFINITIONS OF THE METABOLIC SYNDROME(1,2)

	Group Defining Syndrome		
	NCEP 2001	WHO 1998	ICD-9-CM 277.7
Health Factor	Any 3 of the following	IGT or DM, and/or IR plus 2 of the following	(Dysmetabolic Syndrome X)
Abdominal Obesity*	Waist circumference†	Waist to hip ratio:	Waist circumference
	Men >102 cm (>40in)	Men >0.90	Men >102 cm (>40in)
	Women >88 cm (>35in)	Women >0.85	Women >88 cm (>35in)‡
		And/or BMI > 30	
Triglycerides	>150 mg · dl^{-1}	>150 mg · dl^{-1}	>150 mg · dl^{-1}‡
HDL Cholesterol	Men <40 mg · dl^{-1}	Men <35 mg · dl^{-1}	Men <35 mg · dl^{-1}
	Women <50 mg · dl^{-1}	Women <39 mg · dl^{-1}	Women <45 mg · dl^{-1}‡
Blood Pressure	>130/85 mm Hg	>140/90 mm Hg	Hypertension‡
Fasting Glucose	>100 mg · dl^{-1}	Impaired glucose regulation or diabetes	IFG or DMT2‡
Insulin Resistance		Present	Present‡
Hyperuricemia		May be present	Present‡
Microalbuminuria		Present	Minor criteria
Polycystic Ovary Syndrome			Minor criteria
Hypercoagulability		May be present	Minor criteria
Coronary Heart Disease			Minor criteria
Vascular Endothelial Dysfunction			Minor criteria

*Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.

†Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94–102 cm (37–39 in). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

‡Major criteria for diagnosis. The CDC does not require that a given number of components be present for the diagnosis.

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TABLE B: ADIPOCYTE METABOLISM - IDENTIFIED FACTORS AND CURRENT STATUS

Factor	Current Status
Adiponectin (Acrp30/adipoQ)	Fat derived peptide; decreases insulin resistance, FFAs, TGs; increases energy expenditure.
Adipsin	Serine protease—same as human complement factor D, secreted by adipose cells—gene expression decreased in some forms of genetic and acquired obesity—may act as obesity regulating protein.
AMP activated kinase (AMPK)	Critical part of a biochemical cascade that helps regulate the energy metabolism in cells.
Free Fatty Acids (FFAs)	Increased levels implicated in insulin resistance and inflammation.
Ghrelin	An orexigenic hormone secreted primarily in the stomach and duodenum—implicated in both mealtime hunger and long-term regulation of body weight (1).
Leptin	Cytokine produced by adipose tissue; acts on CNS receptors to inhibit food intake/increase energy metabolism.
Melanocortin-4 Receptor (MCR-4)	Central neuroendocrine receptor: appears to modulate features of the MBS; involved with energy metabolism.
Peroxidase Proliferator Activated Receptors (alpha, delta, gamma) - PPARs	Ligand activated transcription factors; act at the nuclear receptor level to modify fat cell metabolism.
Resistin (FIZZ) or Adipose-Tissue Specific Factor (ADSF)	Fat derived cysteine rich adipose tissue-specific secretory factor that inhibits adipocyte differentiation; may be associated with increased insulin resistance (3).
Tumor Necrosis Factor alpha (TNF-a)	Increased in obese subjects; negative regulator of resisting gene expression (2).

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