PREDIABETES AND THE NEED FOR CARDIOVASCULAR RISK ASSESSMENT IN AVIATION

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ABSTRACT
Obesity, the disease of the twenty-first century, has a range of serious consequences to health. These are related in part to abnormal glucose levels, resulting in inflammatory and atherogenic response, hypertension and abnormal lipid profile. This increases the risk of cardiovascular disease significantly besides developing diabetes later. Hyperglycaemia is diagnosed with impaired fasting glucose and/or impaired glucose tolerance or elevated glycated haemoglobin (HbA1c). The Royal Australian College of General Practitioners (RACGP) guidelines for diagnosis using oral glucose tolerance test (or HbA1c) recognise the importance of extending diagnosis beyond simply identifying diabetes. This is relevant in view of the risk of composite cardiovascular events, coronary heart disease, stroke, and all-cause mortality associated with abnormal blood glucose. Since the pilot population mirrors this morbidity, the aviation regulator has an obligation to consider the impact in terms of aviation safety. Furthermore, although primary care literature predominantly focuses on the importance of diagnosing diabetes, from a regulator's perspective there are incapacitation risks originating outside that narrow diagnosis. They arise once the control of glucose has begun to deteriorate. This article considers the regulatory importance of pilots and controllers who present with hyperglycaemia, or what is sometimes termed “prediabetes”. This includes the evidence for the risk assessment to help minimise the likelihood of an adverse event due to atherosclerotic cardiovascular disease among those holding aviation medical certificates, in turn promoting aviation safety.

The impact of hyperglycaemia is not trivial and should not be minimised. To quote: “By the time a typical obese middle-aged subject is diagnosed with type 2 diabetes, he has already accrued significant cardiovascular risk in terms of hypertension, endothelial dysfunction, coagulopathy, atherogenic lipid profile and circulating pro-inflammatory adipocytokines” [1]. The endothelial dysfunction and inflammatory response, aggravated by stress responses, lead to vascular injury and associated plaque formation. Such atherosclerotic lesion is susceptible to “sudden expansion from acute thrombus formation, forming a nidus for platelet thrombosis, haemorrhage of atherosclerotic plaque microvessels, and rupture of the fibrous cap” [2]. It is known that about twenty per cent of newly diagnosed diabetics already have evidence of cardiovascular disease (CVD) [1]. “In other words, the ticking clock for vascular disease begins well before diagnosis of diabetes” [3].

The challenge therefore rests in making the diagnosis. It is known that the population with prediabetes remains asymptomatic during a prolonged phase before type 2 diabetes manifests. Prediabetics demonstrate an atherogenic pattern of risk factors several years prior to diagnosed diabetes, “possibly caused by obesity, hyperglycaemia, and especially hyperinsulinemia” [4]. Such vascular damage is preventable, hence needs to be identified and monitored. Prediabetes is the term used for individuals with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) [5, 6], or elevated glycated haemoglobin

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BACKGROUND

The rising levels of obesity, diabetes and CVD among the Australian population [13, 14]. Dunstan et al. in their landmark AusDiab study proposed that those overweight be screened for prediabetes and diabetes using a stepped approach of fasting plasma glucose measurement followed by a 75g oral glucose tolerance test [15]. This is also the recommended practice by the Royal Australian College of General Practitioners (RACGP) where equivocal values of fasting (5.5-6.9 mmol/L) or random blood glucose (5.5-11 mmol/L) warrant an oral glucose tolerance test (OGTT) [16]. Such an approach recognises the importance of extending diagnosis beyond simply identifying diabetes.

Pilots and air traffic controllers are likely to be at similar risk of CVD and diabetes as the population pool they come from. Hence the aviation regulators, including the Civil Aviation Safety Authority (CASA), have risk assessment protocols which go beyond diagnosing hyperglycaemia in isolation, and include risk assessment for CVD. For example, the CASA timetable for periodic medical examination requires estimation of fasting blood glucose and if this is 5.5 mmol/L or above, an OGTT [17]. This enables the diagnosis prediabetes or diabetes to be made, and thus informs the risk estimation for CVD.

The rationale behind CASA’s clinical practice guidelines for initial assessment of hyperglycaemia, with focus on cardiovascular morbidity is reviewed in this article [18].

HYPERGLYCAEMIA – IFG AND IGT – AND THE BURDEN OF MORBIDITY

As a regulator, following an expert guideline becomes problematic when there is divergence of guidance. Concerning prediabetes, there are five different definitions. The World Health Organisation defines IFG as fasting plasma glucose of 6.1-6.9 mmol/L and IGT as 2-hour plasma glucose between 7.8 to 11.0 mmol/L after 75g glucose load [5]. The American Diabetes Association (ADA) defines prediabetes as raised glycated haemoglobin (HbA1c) of 5.7 to 6.4% (39-47 mmol/mol) [7] while an International Expert Committee (IEC) criterion is elevated HbA1c of 6.0-6.4% (42-47 mmol/mol) [8]. In the absence of consensus on the definition, the prevalence of prediabetes will inevitably vary between different definitions [19]. Thus, it is important to understand that since these definitions have “different sensitivities, specificities, and morbidity and mortality hazard ratios”, “the choice of which test and threshold to use to identify people with intermediate hyperglycaemia will depend on the specific needs and goals of the screening programme.” [20]. CASA follows the RACGP guidelines for screening for prediabetes or diabetes [11].

WHAT MATTERS MOST – IGT OR IFG?

The AusDiab study had shown an approximately 30 percent and 20 percent increased risk of cardiovascular mortality with one standard deviation increase in fasting and 2-hour plasma glucose values, respectively [21, 22]. The DECODE study found a strong association between 2-hour glucose with mortality due to CVD than fasting glucose concentration [23]. Tominaga et al. reported that unlike IGT, IFG is not considered an independent risk factor for CVD [24]. Some meta-analyses have reported conflicting associations whether IFG or IGT was more strongly associated with CVD [25, 26]. The pathophysiological difference between IFG and IGT is that while the former reflects reduced hepatic insulin sensitivity, impaired first-phase insulin secretion, and normal/near-normal muscle insulin sensitivity, the latter has nearly normal hepatic insulin sensitivity and marked reduced peripheral insulin sensitivity combined with defective late insulin secretion [27, 28, 29].

Santaguida et al. summarised that hyperglycaemia, reflected by IFG or IGT, is a risk factor for fatal and nonfatal CVD (Table 1). They reported that IGT is a greater risk factor for CVD than IFG since the former is a physiological stress response to non-physiological glucose loading, in turn “exposing a degree of metabolic dysregulation that would not be apparent on the basis of fasting glucose levels alone” [30].
The risk of composite cardiovascular events, coronary heart disease, stroke, and all-cause mortality increases with IFG or IGT [31]. Abdul-Ghani et al. surmised that “IGT was an independent risk predictor for cardiovascular morbidity and mortality and for total mortality”. They reported that “the multivariate adjusted HR (95% CI) was 1.49 (0.95–2.34) for CHD (coronary heart disease) incidence, 2.34 (1.42–3.85) for CVD mortality, and 1.65 (1.13–2.40) for all-cause mortality”. This was not confounded by the subsequent development of overt diabetes” [27]. Hence 2-hour glucose value has strong association with insulin resistance, in turn having an independent effect on cardiovascular risk [32].

An indicator of glucose tolerance usually not taken into consideration is the one-hour post load glycaemia value of an oral glucose tolerance test. This value depends on the insulin sensitivity in skeletal muscles and beta-cell function. One-hour post load recorded glycaemia values of more than 8.6 mmol/L have 16.7% incidence rate of type 2 diabetes over five years [33] and have strong association with predictors for future adverse cardiovascular events [21]. Though it may help identify those more susceptible to atherosclerotic changes, it is not yet an acceptable diagnostic measure for prediabetes.

Another possible indicator, HbA1c, offers average levels of blood glucose over past three months, with higher reproducibility than fasting values. But HbA1c values between 5.7% and 6.4% (39-46 mmol/mol) have lower sensitivity to identify prediabetics as compared with IFG and IGT [34, 35]. HbA1c has low concordance with IFG and IGT to diagnose prediabetes. Possible explanation of this discordance is that factors affecting glycation rate, such as oxidative stress, determine the HbA1c values [36]. Increased body weight is associated with increased oxidative stress, as are reportedly higher HbA1c values found among obese. Hence HbA1c among obese may be higher instead of the true concentration of the blood glucose [10]. There is marginal difference in optimal HbA1c cut-off points for different age groups, with young and middle-aged at 5.6% (38 mmol/mol) compared with 5.7% (39 mmol/mol) for the elderly [10, 37]. A prospective study over a decade did not find increase in all-cause mortality among those with HbA1c levels in the prediabetic range [38]. Thus, CASA does not recommend HbA1c for diagnosis of prediabetes [18].

In summary, all indicators of hyperglycaemia reflect increase event rates for cardiovascular disease. It is appropriate therefore that these factors are included in aviation risk assessment.

**IMPLICATIONS FOR AVIATION MEDICAL CERTIFICATE HOLDERS - AIM AT MINIMISING THE LOSS OF TRAINED MANPOWER**

Recent data suggests that 63% Australians are overweight or obese, with rising trend from 39% of people aged 18–24 to 74% for those aged 65–74 [13]. The AusDiab study found that 17.4% of men and 15.4% of women had either IGT or IFG. There is 5.8% and 10.6% prevalence of IFG and IGT, respectively, with former being more prevalent in men (8.1% v 3.4% in women) and latter among women (11.9% v 9.2% in men) [15].

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**Table 1: Risk estimates for cardiovascular disease among those with abnormal glucose tolerance test (Modified from Santaguida et al. [30])**

<table>
<thead>
<tr>
<th></th>
<th>Impaired Fasting Glucose (IFG) (95% CI* in parentheses)</th>
<th>Impaired Glucose Tolerance (IGT) (95% CI in parentheses)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a. Risk for non-fatal CVD outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) Annualised risk estimates for any nonfatal CVD event</td>
<td>0.63 – 9.68</td>
<td>11.58 – 12.39</td>
</tr>
<tr>
<td>(ii) Unadjusted annualised relative risk</td>
<td>1.24 (1.08 – 1.43) to 1.41 (1.17 – 1.69)</td>
<td>2.43 (1.44 – 4.10) to 2.46 (1.46 – 4.12)</td>
</tr>
<tr>
<td>(iii) Attributable risk in the exposed group</td>
<td>0% - 32.9%</td>
<td>52.8% - 52.9%</td>
</tr>
<tr>
<td><strong>b. Risk for fatal CVD outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) Annualised risk per 100 persons in the exposed groups</td>
<td>01.10 – 1.54</td>
<td>01.06 – 0.76</td>
</tr>
<tr>
<td>(ii) Unadjusted annualised relative risk</td>
<td>1.32 (1.04 – 1.72) to 1.67 (1.23 – 2.26) to 3.08 (1.47 – 6.47)</td>
<td></td>
</tr>
<tr>
<td>(iii) Attributable risk in the exposed group</td>
<td>11.8% - 39.5%</td>
<td>24.8% - 67.3%</td>
</tr>
<tr>
<td><strong>c. Risk for mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(i) Annualised risk per 100 persons in the exposed groups</td>
<td>0.56 – 1.39</td>
<td>0.09 – 2.44</td>
</tr>
<tr>
<td>(ii) Unadjusted annualised relative risk</td>
<td>1.18 (1.03 – 1.35) to 1.45 (1.27 – 1.66)</td>
<td>1.36 (1.12 – 1.66) to 3.18 (1.79 – 5.63)</td>
</tr>
<tr>
<td>(iii) Attributable risk in the exposed group</td>
<td>13.9% - 61.2%</td>
<td>0% - 67.2%</td>
</tr>
</tbody>
</table>

*CI = Confidence Interval*
CVD is the leading cause of ill-health among Australians [13]: (a) coronary heart disease at 13% was the leading cause of death in 2013; (b) coronary heart disease, at 10% of deaths among those below 75 years of age, was the leading cause of premature death in 2011–2013; and (c) an estimated 3.6% adults had been diagnosed with coronary heart disease in 2014–15. Elsewhere, Valenti et al. in a prospective study among asymptomatic individuals without known coronary heart disease and coronary artery calcium score of 0 at baseline found an increased risk of mortality among diabetics (Hazard Ratio 2.53, 95% CI 1.74–3.69) after nearly 15 years of follow up [39]. Evidently atherosclerosis is the precipitating factor in cardiovascular disease, with obesity and hyperglycaemia being the commonest risk factors. Thus, it is not difficult to discern the likely implications for increasing morbidity pattern among pilots and air traffic controllers, who are from the same population pool.

Australian applicants for class 1 and 3 medical certificates undergo special periodic examination, including test for blood glucose [17]. CASA’s decision matrix for the investigation of abnormal glucose and raised BMI, follows RACGP guidelines [16, 18, 40, 41]. Conceptually, it is also consistent with International Civil Aviation Organisation (ICAO) [42] guidelines. Table 2 provides a comparison with similar jurisdictions.

Once prediabetes is diagnosed among the aviation medical certificate holders, CASA recommends that the subsequent follow up is by undertaking a blood test for HbA1c, as recommended by RACGP [40]. This permits ongoing screening for diabetes and calculation of CVD risk [17, 18].

WHERE TO NEXT?
Recent work by the Auckland group has demonstrated the validity of a multifactorial risk tool for cardiovascular risk assessment [43]. This includes HbA1c levels and will provide risk assessments for diabetics and pre-diabetics, as well as those with declared cardiovascular disease, e.g. post myocardial infarction. It is likely that the data from this study will impact the practicalities of considering this particular risk, and process changes will be needed.

It is important to distinguish aeromedical decision making from clinical management of diseases and disabilities, such as those individuals with pre-diabetes or diabetes. In the course of a risk assessment, the identification of a medical problem is followed by a referral to the relevant treating doctor. As with other regulatory authorities, CASA relies upon the relevant regulations to define

<table>
<thead>
<tr>
<th>Aviation Authority</th>
<th>Diagnosis to be established</th>
<th>Tests to establish the diagnosis</th>
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<tbody>
<tr>
<td>ICAO</td>
<td>Diabetes</td>
<td>Oral glucose tolerance test (OGTT)</td>
</tr>
<tr>
<td>CASA</td>
<td>Abnormal glucose metabolism and cardiac risk</td>
<td>Fasting plasma glucose, OGTT, Cardiac risk index</td>
</tr>
<tr>
<td>Federal Aviation Authority (FAA)</td>
<td>Diabetes</td>
<td>Supporting Laboratory findings</td>
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<td>Civil Aviation Authority, UK</td>
<td>Abnormal metabolism</td>
<td>Tests to establish abnormal glucose metabolism</td>
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<td>European Aviation Safety Authority</td>
<td>Diabetes</td>
<td>OGTT</td>
</tr>
<tr>
<td>Transport Canada</td>
<td>Diabetes</td>
<td>Fasting plasma glucose, or HbA1c, or OGTT, or random plasma glucose</td>
</tr>
<tr>
<td>Civil Aviation Authority, New Zealand</td>
<td>Abnormal glucose metabolism</td>
<td>Acceptable biochemical criteria</td>
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</table>
the acceptable level of risk. This is also in line with ICAO’s amendment 173 to Annex 1 (health promotion amendment – standard 1.2.4.3) as extracted below:

1.2.4.3 The Licensing Authority shall implement appropriate aviation-related health promotion for licence holders subject to a Medical Assessment to reduce future medical risks to flight safety.

Note 1.— Standard 1.2.4.2 indicates how appropriate topics for health promotion activities may be determined.

Note 2.— Guidance on the subject is contained in the Manual of Civil Aviation Medicine (Doc 8984).

Note 3.— Guidance on the relationship between the Licensing Authority and the implementation of Medical Assessment for licence holders is contained in the Manual of Procedures for Establishment and Management of a State’s Personnel Licensing System (Doc 9379).

CONCLUSION

CASA’s assessment protocol evaluates the risk of abnormal glucose metabolism, which is associated with a markedly higher morbidity and mortality due to CVD. Besides the clinical imperatives to “reduce premature death, improve quality of life, and lessen individual and economic burdens of associated morbidities, decreased work productivity, and high cost of medical care” [2], this promotes aviation safety by evidence based risk assessment to minimise the likelihood of functional incapacity or in-flight incapacitation among those holding aviation medical certificates due to atherosclerotic CVD.

REFERENCES


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