Continuous Glucose Monitoring for In-Flight Measurement of Glucose Levels of Insulin-Treated Pilots

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INTRODUCTION: Due to the risk of hypoglycemia-related incapacitation, diabetic pilots requiring insulin are assessed as unfit according to the International Civil Aviation Organization and most national authorities. Some authorities, such as those from Canada, the United Kingdom, and the United States, permit selected insulin-treated pilots (ITDM-pilots) to fly subject to a protocol requiring pre- and in-flight capillary glucose measurements to show safe levels ($>$100–$<$300 mg · dl^{-1}). Critics of such permission question the practicability of these in-flight measurements and whether clinically desired glycemic targets can be achieved while keeping glucose levels in the safe range. Subcutaneous continuous glucose monitoring (CGM) has recently been approved by the FDA as a stand-alone method to provide accurate glucose levels and treatment decision guidance in patients. This commentary considers that use of CGM by ITDM pilots facilitates practicability and recording of in-flight glucose measurements and facilitates achievement of clinically desired glycemic targets without increasing hypoglycemia risks.

KEYWORDS: diabetes mellitus, insulin, flight, continuous glucose monitoring.

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Individuals with diabetes mellitus (DM) who are treated with insulin will often be disqualified for safety-sensitive jobs due to the hypoglycemia risk. This also applies for most ATPL and CPL certified pilots who need insulin for treatment of their Type 1 (T1) or Type 2 (T2) DM. The International Civil Aviation Organization denies certification for pilots with T1DM, but considers fit assessment for T2DM pilots on insulin via Standard 1.2.4.9.[8] Transport Canada and the U.S. Federal Aviation Administration permit the special issuance medical certification of insulin-treated applicants for first-, second-, and third-class license subject to strict requirements laid down in a protocol.

The European Aviation Safety Agency regulations deny aeromedical certification to all insulin-dependent T1 and T2DM commercial air transport pilots. In an exception to the European Aviation Safety Agency rules, the Civil Aviation Authorities of the United Kingdom, Ireland, and Austria allow all classes of insulin-treated diabetes mellitus (ITDM) pilots to fly subject to a protocol with strict entrance and operational requirements.[10] This exception and protocol are criticized by other European member states. The debate focuses on the practicality of the ITDM pilot's in-flight glucose measurements and on the critic's assumption that by pursuing sufficiently low glycemic targets to prevent macro- and microvascular diabetic complications, one might increase the in-flight hypoglycemia risk, whereas supporters reason that a target HbA1c level as recommended by the American Diabetes Association allows pilots to have safe in-flight glucose levels (100–300 mg · dl^{-1}).[13] In this context, it is considered that use of subcutaneous continuous glucose monitoring (CGM) will facilitate optimal glycemic control in active commercial ITDM pilots.

Significant progress has been made in DM management through technical and software developments in CGM. Advanced CGM methods have recently been approved by the U.S. Food and Drug Administration (FDA) as a stand-alone

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method and might be used by patients to provide instant single glucose readings, glucose trends, treatment decision guidance, and long-term glycemic control reports.[6,7] The FDA approved CGM methods to measure glucose levels in interstitial fluid. The Dexcom G5® Mobile (Dexcom, San Diego, CA, USA) measures glucose levels in interstitial fluid via a sensor inserted into a patient's abdomen. It automatically takes readings every 5 min. The device converts sensor data into glucose readings which it transmits via Bluetooth for display on a receiver or mobile app on a smart phone. The flash sensor FreeStyle Libre™ (Abbott Diabetes Care Inc., Alameda, CA, USA) has a round sensor which is placed on the upper arm with a thin filament inserted just under the skin and takes glucose readings once a minute. For monitoring, users hold a scanner/smart phone over the sensor to transmit the data.

CGM methods will briefly be discussed in terms of reliability, precision/accuracy, effectiveness, user friendliness, recording/presentation of results, and costs. Subcutaneous glucose levels depend on the physiological 10- to 20-min substrate transfer delay between blood and interstitial tissue utilization rate. First generation CGM devices could not reliably register fast glucose changes, but, after appropriate algorithm development, CGM readings are presently considered as reliable and interchangeable with blood glucose meter (BGM) data in terms of decision making.[9]

Mean absolute relative difference (MARD) is the measure of choice to assess the accuracy of CGM systems. A good precision absolute relative deviation value is considered a precondition to trust a good MARD value.[11] Both precision and accuracy of CGM systems with an advanced algorithm were documented in adult[4] and pediatric[9] patients as is shown in **Fig. 1**.

Because of the high precision and accuracy standards attained (i.e., good precision absolute relative deviation values combined with MARD values <10%), the FDA approved the Dexcom G5® Mobile and the flash sensor FreeStyle Libre™ (Abbott Diabetes Care, Inc.) as safe and effective stand-alone CGM devices for therapeutic decision making according to specific protocols taking into account glucose values, trend arrows, trend diagrams, and/or attainable warnings, as well as any discrepancy between symptoms and data.[6,7]

Although not all CGM systems are yet validated to function in the hypobaric aircraft cabin environment, there is evidence that these systems perform well in hypobaric conditions that prevail at the 5500-m (18,045-ft) altitude.[1] Some authorities require ITDM pilots to calibrate their CGM using blood glucose readings despite the fact that many BGMs are not compliant to recent ISO standards and have specific temperature and altitude limitations. BGMs based on the glucose-oxidase reaction may especially be greatly affected by low partial oxygen pressure. Therefore, some BGMs may be less reliable in flight either per se or as CGM system recalibration tools.

The effectiveness of the use of CGM is shown by an age-independent HbA1c decrease over time. Older CGM users on multiple dose injections showed a mean 0.4% decrease in HbA1c levels in the absence of severe hypoglycemic events or diabetic ketoacidosis.[12] Studies involving T1DM and insulin-treated

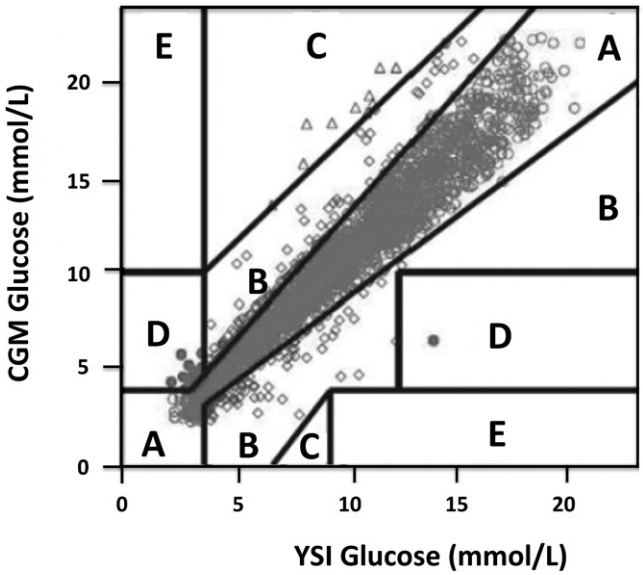

Fig. 1. Error grid obtained by comparing CGM derived glucose levels and reference glucose measurements obtained every 15 ± 5 min using arterialized venous blood (YSI). 'A' areas correspond to results (white circles) adequate for clinical decisions; 'B' areas correspond to results (white diamonds) expected to have little or no impact on clinical decisions; 'C' areas correspond to results (white triangles) with minimal impact on clinical decisions; 'D' areas correspond to results (grey circles) with possible impact on clinical decisions; 'E' areas correspond to results (none in this case) triggering dangerous therapeutic choices (Adapted from Laffel[9]).

T2DM patients showed significant HbA1c reductions along with an overall "time in range" increase.[5,12] An explanation for these findings is that tissue glucose readings help patients make more appropriate corrections by providing more relevant metabolic information than blood glucose levels, which only reflect general substrate availability. The CGM systems are user-friendly because patients are only required to apply sensors at weekly intervals as opposed to 4 to 8 meal/exercise-related finger pricks a day. The proportion of individuals using CGM is rapidly increasing. CGM technology has triggered development of new treatment strategies and user-friendly algorithms substituting trend arrows for single readings, thereby enabling patients and clinicians to make subtle insulin adjustments.[2]

CGM data may be stored within the device's memory and can securely be uploaded in digital systems (e.g., the cloud) and kept there safely to be retrieved when needed by the patient and authorized professionals. This ensures nonmodifiable results to be stored safely and accessed as needed. At the same time single-point data can be presented on a hand-held monitor along with easily interpreted glucose change curves and trend arrows. This allows forecasting and preventing possible glycemic peaks and troughs well in advance and, when applied to pilots, this translates into higher practicality of the in-flight requirements and lower hypo- and hyperglycemic risks. When continuously used, advanced devices are cost-effective as compared to repeated and frequent daily self-monitoring of blood glucose and help prevent expensive hypoglycemic events and hospitalizations in the short term, as well as resource-consuming complications in the long run.[14]

In conclusion, use of CGM by ITDM pilots would greatly improve the practicability of in-flight glycemic control and provide pilots with an effective method to share their results with aeromedical examiners and treating physicians and get timely medical advice concerning their glycemic and lifestyle management. A further step toward the use of stand-alone CGM devices among pilots should be made by submitting the various CGM systems to flight certification procedures, including specific mechanical, physical, and chemical stress tests. It is recommended to initiate scientific discussions among supranational aeromedical/operational expert panels aimed at finding harmonized solutions for the challenges of keeping insulin-dependent pilots on flying status.

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