TECHNOLOGY ADVANCES IN CONTINUOUS GLUCOSE MONITORING TO THE BENEFIT OF PILOTS ON INSULIN AND ALL AVIATION STAKEHOLDERS: ARE FLIGHT REGULATIONS WARRANTED UPDATES?

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SUMMARY

Aeromedical certificates are almost consistently denied to people with Type 1 Diabetes Mellitus (T1DM) willing to fly. Sudden incapacitation risk due to unexpected hypoglycemic events is behind that and has obviously to be avoided at any costs for the safety of both the pilot and all the other people on the aircraft and on the ground, yet certificate denial has a heavy impact on working and social life of people boasting high profile and cost professional requirements and has raised deep concern in many patient associations. Due to that they are not homogeneously issued to commercial pilots with insulin-treated (IT) Type 2 Diabetes Mellitus (T2DM) world-wide and, within Europe, UK, Austria e Ireland have allowed insulin-treated pilots to fly for the last few years according to a strict protocol requiring repeated finger pricking. This paper deals with newer subcutaneous continuous glucose sensors by describing technical and safety characteristics of the latter and thus providing the reader with as clear as possible an overview of devices based on ever improving technology. This will hopefully raise a wider and wider discussion among regulators, AMEs and all aviation stakeholders on the opportunity to exploit diagnostic advances for a legally, clinically and operationally supportable, as well as, fully safety compliant way of proceeding in the flight sector as for insulin treated pilots and the entire galaxy of flight professionals/operators.

DIABETES AND FLIGHT INTERNATIONAL FRAMEWORK

Aeromedical certificates are almost consistently denied to people with Type 1 Diabetes Mellitus (T1DM) willing to fly but are not homogeneously issued to commercial pilots with insulin-treated (IT) Type 2 Diabetes Mellitus (T2DM) world-wide. In fact, they are granted to IT-T2DM pilots by ICAO (International Civil Aviation Organization) “Flexibility Standard” 1.2.4.9 [1] - based on an estimated annual incapacitation rate of one to two per cent - and by Transport Canada and the U.S.
FAA (Federal Aviation Administration) subject to strict requirements laid down in a protocol permitting a special issuance for first-, second-, and third-class license. However, they are denied in Italy, and the majority of other European Union countries, in case of both de novo applications and license extension for newly diagnosed people. Despite being in line with EASA (European Aviation Safety Agency) rules, this has a heavy impact on working and social life of people boasting high profile and cost professional requirements and has raised deep concern in many patient associations. Among the latter, ANIAD, the Italian National Diabetic Athletes Association, has strongly protested at the national level for the last decade and acted as a tireless advocate against discrimination of its members, starting from those involved in drone steering, sport flying and LAPL aircrafts and progressively enlarging its area of interest thereafter.

An exception to European rules, however, is represented by a strict protocol utilized by UK, Ireland e Austria to allow flight to pilots with T1DM or IT-T2DM according to specific operational requirements [2] associated with glycated hemoglobin (HbA1c) and inflight self-monitoring blood glucose (SMBG) levels high enough to prevent sudden hypoglycemia-related incapacitation. Such protocol has the drawback of adopting HbA1c and SMBG levels far from best clinical practice standards currently suggested for chronic micro- and macro-vascular disease complication prevention [3] but is of course a good compromise between a fully closed and an open-minded attitude.

Sudden incapacitation due to unexpected hypoglycemic events has obviously to be avoided at any costs for the sake of both the pilot and all the other people on the aircraft and on the ground. Nevertheless timely glucose measurements involve a whole series of only apparently simple gestures so that the pilot, during pre-flight operations or during no critical phases of the flight, has to catch and hold the glucose meter, take a glucose strip out of its container and slip it into the meter’s reading cell, catch and load the fingerstick with a needle to prick his own skin, wait for a blood drop to take shape and get in contact with the strip, wait some 5 to 20 seconds depending on the device, read out the result and take note of it. All this requires the pilot the use of both hands and causes divided attention for at least 90 seconds despite being expected to keep highly focused on his task as well throughout the flight.

Luckily enough, hand-free high technology devices have become available allowing continuous glucose monitoring (CGM) in body fluids which let people know their own glucose levels by just quickly scanning a skin-attached sensor and/or directly taking a glance at a display in front of them.

**MAY GLUCOSE SENSORS HAVE AN IMPACT ON SAFE FLIGHT?**

Such technology allows bloodless continuous glucose monitoring for many days or weeks in a row, which offer a great advantage over SMBG, which by definition enables only a broken line to be drawn by connecting discrete points.

The amount of literature available has greatly increased during the last few years documenting CGM superiority in terms of improved glucose and HbA1c levels, dramatically reduced event number of, and risk for, hypoglycemia, as well as, increased time in euglycemic range [4-14]. Further positive features of CGM as compared to SMBG are tighter adherence to disease management, greater
satisfaction for diabetes care and better quality of life, as well as, reduced costs in terms of hypoglycemic events and consequent hospital admissions [15].

CGM may be performed according to procedures based on instruments differing from one another and therefore warranting specific training but all have a very interesting feature as far as aviation activities are concerned, i.e. the ability to predict glucose trends within the next few minutes based on the slope of the curve describing previous concentrations and on the change rate of the most recently measured levels. Glucose trends in fact allow the system to suggest timely actions to be taken to prevent any possible incapacitating hypoglycemic events, as well as, any disabling consequences of too high glucose levels including e.g. oversight errors or long-lasting drowsiness [6-9, 10].

**DIFFERENCES AMONG VARIOUS CGM SYSTEMS**

All CGM systems need a sensor to be applied on the skin by a micro-needle or subcutaneously through a tiny skin incision. The sensor continuously measures glucose levels just below the skin and sends data wirelessly to a display device via a transmitter.

Sensors measure glucose concentrations within the interstitial subcutaneous fluid (ISF) continuously, thus requiring no troublesome repeated finger pricking and proving an incredibly higher number of glucose values than SMBG [6]. They are classified as either real-time CGM (rtCGM) and intermittently viewed CGM (iCGM) – see Fig. 1 -, also named flash glucose monitoring (FGM) – see Fig. 2.

![Figure 1. Dexcom G6 (rtCGM). 1. The automatic applicator (one-touch applicator) simply inserts a small sensor just below the skin. 2. The sensor and transmitter: a thin sensor that continuously measures glucose levels just below the skin and sends data wirelessly to a display device via a transmitter. 3. Display device: an iOS or Android compatible smart device or a touch screen receiver that displays blood glucose data in real time.](image-url)
Figure 2. The Abbott Freestyle libre 2.0 (FGM). To read the blood glucose just select the reading option on the reader's display, pass it on the sensor applied to the arm by scanning, and read the blood glucose on the reader display.

Both systems are able to provide the above information including previous and current glucose levels plus trends but, as outlined by the 2017 International Consensus Conference on Use of Continuous Glucose Monitoring [17], rtCGMs continuously measure concentrations without any human intervention while the only FGM available at the time of submitting our paper for publication provides the needed information each time the user scans the sensor by either its specific reader or a smartphone having a dedicated App. Opposite to old FGMs (FreeStyle Libre by Abbott Diabetes Care), most utilized transcutaneous rtGCMs (Dexcom G5 by Dexcom Inc. and Medtronic Enlite by Medtronic Inc.) and implanted rtGCMs (Eversense, Senseonic Inc.) available in Italy are equipped with sound and vibration alarms for fast hypoglycemic of hyperglycemic trends. Recently FDA and EMA approved Dexcom G6 and FreeStyle Libre 2.0 sensors have been significantly improved in terms of utilization time and of personalized alarms, respectively.

A typical output printed by a woman wearing an FGM sensor is shown in Figs 3-6, showing how user-friendly and self-explaining results are provided to the user and so how easy might be for the pilot to get relevant and ready to use information on his own current and pending metabolic conditions when displayed on the screen in front of him.
Figure 3 - Tracing from Dexcom G6 rtCGM. Individual patient adjusted upper and lower desired glucose range levels are reported as yellow and red lines, respectively in the lower section of the figure. In the upper section data are shown as derived from glucose monitoring including estimated HbA1c (5.6%), average glucose levels (113 mg/dl), standard deviation (24 mg/dl), hypoglycemic risk coding (red portion of the vertical bar = minimum) and percent time in the desired range (green portion of the bar = 92%).

Figure 4 – Device individually-tailored alarm settings
Figure 5 – Graphic representation of glucose levels observed during the 24 hours. Indicate alarms activating at glucose levels which, as a precautionary measure, the user defined as low enough to get alerted in order to prevent any further decrease and obviously higher than strictly hypoglycemic levels. Interestingly, throughout the observation time, 100% glucose curve keeps within the desired range.

Figure 6. Graphic representation of glucose levels observed during the 24 hours. Only 2 alarms are present: they were activated at 05:04 and 23:39 (as shown in the lower section) with values approaching the lower desired range level which, as a precautionary measure, had been set above the hypoglycemic threshold.

WHAT’S NEW WITH SENSORS IN DIABETES MANAGEMENT
All CGM systems measure glucose in the ISF as opposed to SMBG devices providing blood glucose (BG) concentrations. ISF and blood have different dynamics [18] so that some latency exists between
the two compartments: to reach the equilibrium with BG ISF glucose takes about 30 min which have now been brought down 5-10 min by suitable algorithms in most updated systems [19,20]. All this might have some impact, yet shown to be clinically negligible, on device accuracy in case of hypoglycemia [21-24].

Sensor wearing time is 14 days for the FGM, 5 to 7 days for most rtCGMs up to 10 days to the latest G6 device [25] and 180 days for implantable Eversense [26,27]. The most relevant difference is anyway the need for SMBG-based calibration at least twice a day for all rtCGM but G6, which in fact is pre-calibrated and therefore acts as a standalone device exactly as automatically calibrated FGM. FGM sensor working electric potential is much lower than the one needed by rtCGM, which enhances signal stability [28] and employs Bluetooth Low Energy (BLE) for communication. Features of different CGM systems are reported in Table I for immediate appraisal and comparison as available at the time of paper submission within a tumultuously growing technological frame.

Table I. Features of different continuous glucose monitoring systems

<table>
<thead>
<tr>
<th>Monitoring style</th>
<th>rtCGM</th>
<th>FGM</th>
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<tbody>
<tr>
<td>Devices</td>
<td>Medtronic Enlite, Dexcom G5 and G6, Eversense</td>
<td>FreeSyle Libre, Freestyle Libre 2.0</td>
</tr>
<tr>
<td>Fluid under investigation</td>
<td>Interstitial</td>
<td>Interstitial</td>
</tr>
<tr>
<td>Calibration</td>
<td>Daily SMBG-based (not for G6, stand-alone device)</td>
<td>No, stand-alone device</td>
</tr>
<tr>
<td>Sensor wearing time</td>
<td>5-7 days; 10 days for G6, 180 days for Eversense</td>
<td>14 days</td>
</tr>
<tr>
<td>Sensor positioning</td>
<td>Transcutaneous (intradermal for Eversense)</td>
<td>Transcutaneous</td>
</tr>
<tr>
<td>Access to glucose readings</td>
<td>Continuous, reader-visualized after pressing a button</td>
<td>Intermittent, visualized when scanned by devoted reader-/smartphone</td>
</tr>
<tr>
<td>Interference by paracetamol</td>
<td>Yes only for Eversense and G5</td>
<td>No</td>
</tr>
<tr>
<td>Stand-alone insulin dose calculation</td>
<td>Yes only for G5 and G6</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypo-/hyperglycemia alarms</td>
<td>Yes</td>
<td>Yes for Libre2.0</td>
</tr>
<tr>
<td>Trend arrows</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Operating conditions</td>
<td>Electric potential</td>
<td>LEP (low electric potential)</td>
</tr>
<tr>
<td>Transmission</td>
<td>Bluetooth</td>
<td>LEB (low energy bluetooth)</td>
</tr>
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</table>

rtCGM = real time continuous glucose monitoring; FGM flash glucose monitoring; SMBG = self-monitoring blood glucose

As briefly anticipated, the most interesting feature as for any extreme working sets, like Aviation as well as ICUs, CGM systems are endowed with is the represented by trend arrows, i.e. sort of artificial horizon providing accurate information on pending glucose changes.
In fact, an ever-enlarging body of literature reports on improved results after harnessing sensors in the ICUs [29-33]. A horizontal arrow stays for a steady state, while up or down arrows side of current glucose reading predict a significant forthcoming increase or decrease, respectively. This way the system alerts the user at glucose readings still within the normal range and, thanks to specific algorithms may even suggest what to do to stabilize glucose levels, i.e. ingest food or sweet beverages or inject extra insulin boluses.

HOW CAN WE PROCEED FURTHER IN PRACTICE?
Whatever CGM system is chosen, then, such technology advances definitely improve working efficiency of insulin treated flight personnel and might well represent a natural extension of the protocol already adopted by UK, Austria e Ireland [2] although it should be stressed that, in order to be clinically effective, CGM management requires a specific training. The latter should include full understanding of best possible system utilization and result interpretation, knowledge about suitable treatment adaptation strategies in response to alarming trend arrows [34,35]. However, we expect that (i) individual pilot aeromedical certification for use of a CGM might be taken in due consideration by aviation regulators in order to suitably adapt the applicable medical requirements to be adopted by the medical assessors. The validation, and might be even certification, from aviation regulators in cooperation with diabetes specialists will be necessary before allowing the new method to enter routinely cockpit activities, as well as, (ii) tested reliable assurance is provided that adopted CGM systems function properly under even extreme flight conditions and fail to interfere with flight instruments.

However, the above and other issues, including privacy in terms of consent to the right of access to personal data for data registration, transmission, upload and download to specific platforms outside the aircraft and accessible to third parties, have to be carefully examined before referring the matter to devoted aviation institutions. Actually there are intricacies, involving different professional competences so that we look forward to the possibility for Italy to raise a circle of experts from most representative national diabetes societies, regulatory institutions, and patient associations to trace the outlines of a new legally, clinically and operationally supportable, as well as, fully safety compliant way of proceeding in the flight sector as for insulin treated pilots and the entire galaxy of aviation professionals/operators.

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No financial disclosures have to be declared by any Authors.
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