Original articles

Comparison of venous, capillary and interstitial blood glucose data measured during hyperbaric oxygen treatment from patients with diabetes mellitus

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Blood sugar level; Endocrinology; Hyperbaric medicine; Hyperbaric research; Patient monitoring

Abstract
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Introduction: Patients undergoing hyperbaric oxygen treatments (HBOT) have been shown to experience a reduction in blood glucose (BG) levels during a treatment. This necessitates frequent assessment of BG levels. Continuous glucose monitoring (CGM) may represent an alternative to the current finger prick monitoring method in-chamber, however, continuous sensor glucose (SG) data has not been validated *in situ*. The aim was to determine the validity of continuous SG and intermittent BG monitoring with serum BG levels in diabetic patients during HBOT.
Methods: Measurements were obtained (finger prick [capillary sample], CGM [interstitial fluid], and serum [venous sample]) at baseline, and at 30, 60, 90 and 120 minutes during the hyperbaric treatment. Data were analysed by calculating intraclass correlation coefficients (ICC) and using mixed effects linear regression.
Results: The ICC results (n = 10 patients) between the three methods indicated very high and statistically significant absolute agreement at baseline (pre-dive) (ICC = 0.90, 95% CI 0.74–0.97), at 30 minutes (ICC = 0.85, 95% CI 0.61–0.96), 60 minutes (ICC = 0.86, 95% CI 0.58–0.96), 90 minutes (ICC = 0.87, 96% CI 0.63–0.96) and 120 minutes (ICC = 0.90, 95% CI 0.70–0.97). Capillary glucose and CGM SG readings were each within 1 mmol·L^{-1} on average of the serum glucose reading, with multi-level linear regression finding the average difference between the CGM SG and capillary glucose methods of BG sampling was not statistically significant (P = 0.81).
Conclusions: The CGM SG data were comparable with glucose readings from capillary monitoring. Both CGM and capillary data were consistent with serum values.

Introduction

In Australia, there are 1.2 million people who are known to have diabetes, with an estimated 500,000 living with undiagnosed diabetes.[1] People living with diabetes are at risk of long-term secondary complications especially micro- and macrovascular complications that predispose them to an increased risk of skin ulceration and subsequent limb amputations.[2] For the group of patients that have diabetes and a wound, one therapeutic modality prescribed regularly is hyperbaric oxygen treatment (HBOT). HBOT is the administration of 100% oxygen in a pressurised environment,[3] and has been demonstrated to increase tissue oxygenation, cause vasoconstriction, fibroblast activation, down-regulation of inflammatory cytokines, up-regulation of growth factors, have antibacterial effects, potentiate antibiotics and produce a reduction in leukocyte chemotaxis.[4–6] Evidence from clinical trials further support this data.[7,8]

There is, however, a documented inconsistent and unpredictable impact on glucose levels in patients with diabetes during HBOT. One study reported that there was an average drop of '2.8 mmol·L^{-1} in 25 insulin dependent patients' under hyperbaric conditions.[9] The unpredictability of hypoglycaemic events during hyperbaric treatment impacts on the patient in several areas, including feelings of additional apprehension and stressfulness. There is evidence

cited elsewhere[10] of patients artificially raising their blood glucose and broadly adjusting their own diabetes medication to avoid a hyperbaric treatment related hypoglycaemic event.

Monitoring blood glucose (BG) levels in patients with diabetes during HBOT is essential as it provides reassurance to the patient and is a clinical reference for ongoing medical management. Usual BG monitoring includes intermittent testing with a lancet, a test-strip and a glucometer (point-of-care/finger prick monitoring) prior, during and often after the patient's routine two-hour daily HBOT. Given that most HBOT programmes require daily treatments for several weeks, repeated finger prick testing, in addition to usual BG level monitoring, can be onerous for both the patient and medical team.

An alternative to finger prick testing is a continuous glucose monitor (CGM). The CGM measures glucose from the patient's interstitial fluid and provides sensitive glucose trend data which is then applied to a patient-specific predictive algorithm.[11] Improvements in CGM technology over the last 10 years, the growing evidence for its clinical efficacy and recent supportive funding initiatives have resulted in increased usage of this monitoring modality in the clinical arena. Some authors suggest CGM allows for a much-improved chance of metabolic glucose control thus lessening the chances of hypoglycaemic events.[12–14]

Recent studies have reached a consensus on the use of the CGM for recreational divers.[15–19] There is agreement that CGM reduces risk but cannot currently be used while diving.[20] However, the use of the CGM to predict glucose trends during HBOT has not been thoroughly examined. There is a need to bolster the existing body of knowledge regarding CGM accuracy, reliability and safety when used in HBOT conditions in the diabetic population, prior to considering a change in clinical practice. The aim of this study was to examine the degree of agreement between continuous sensor glucose (SG) and intermittent capillary BG monitoring with serum BG levels under hyperbaric conditions in patients with diabetes.

Methods

This study was approved by the University of Tasmania, Human Research Ethics Committee (HREC) (H0015975).

An observational study was conducted to compare blood glucose levels ($mmol \cdot L^{-1}$) obtained from three simultaneous sampling points throughout a hyperbaric oxygen treatment among patients with diabetes. The three sampling methods included:

i Intermittent (finger prick) blood glucose (point-of-care monitoring);
ii Continuous glucose monitoring (CGM) measures of interstitial fluid glucose;
iii Serum blood glucose levels.

The study was undertaken in the Department of Diving and Hyperbaric Medicine (DDHM) at the Royal Hobart Hospital, Tasmania, Australia. The DDHM provided approximately 17,191 treatments delivered to 915 patients between 2010–2020.

The study group was drawn from patients receiving HBOT at the DDHM. The study eligibility criteria included adults (≥ 18 years), who were living with diabetes (type 1 or type 2), and who were deemed medically suitable to undergo HBOT in a multi-place hyperbaric chamber. All non-consenting adults, children or young people (< 18 years), and pregnant women were excluded from the study. A sample size of 29 participants was required assuming a correlation coefficient of 0.5, $\alpha = 0.05$, and $\beta = 0.2$. To accommodate the potential for 20% attrition or missing data, a sample target of $n = 35$ was pursued. Patients attending the service for medical assessment to ascertain their suitability for hyperbaric treatment, were screened for eligibility.

Venous serum samples were processed on site at the hospital laboratory using the hexokinase enzymatic reference method with the GLUC3 kit of the Cobas 6000 laboratory analyzer's c501 module (Roche Diagnostics, Rotkreuz, Switzerland), accredited by National Association of Testing Authorities (NATA), Australia.

The venous serum samples were drawn from each participant by a registered nurse (RN) into a blood collection tube containing sodium fluoride, a glycolysis inhibitor, used to limit the ex vivo consumption of glucose.[21] To minimise the effect on glycolysis of known variables, such as temperature and white blood cell count,[22] lapsed time from collection-to-separation of the blood sample did not exceed the test site's laboratory recommendation.

Capillary samples were obtained via the finger prick method and analysed on-site in the hyperbaric chamber using the FreeStyle Optium™ Neo glucometer (Abbott Healthcare, Massachusetts, USA). This glucometer measures glucose capillary whole-blood samples ($mmol \cdot L^{-1}$). Calibration is completed manually and all glucose measurements are performed using a glucose dehydrogenase (GDH) test strip as per the manufacturer's instructions. GDH test strips are the preferred electrochemical glucose measurement method as this counteracts the interference of oxygen in the blood sample, which in turn makes them more suited to the hyperbaric oxygen environment. The FreeStyle Optium™ Neo has been tested in the hyperbaric environment and found to be consistently accurate.[23]

A Minimed™ Medtronic Guardian™ Connect CGM device (Medtronic, Minneapolis, USA) was used in this study. The CGM provided a constant digital display of interstitial SG ($mmol \cdot L^{-1}$) that was refreshed every six minutes, a process grounded in a 'learned' predictive algorithm.[11,24] It involves an internal electronic calculation delivered via a predicted time lag.[25,26] The CGM sensor (TGA number 172028)

attached to the CGM transmitter (TGA number 138452) was worn by the participant during HBOT. The digital display of the CGM was via an app on a smart device (iPod). The iPod remained on the outside of the hyperbaric chamber during treatment. The Minimed™ Medtronic Guardian™ Connect CGM requires calibration against a capillary glucose every 12 hours. Calibration was performed as per the manufacturer's guidelines, using the same glucometer at all times.

Additional information collected at the time of sampling included date of birth, type of diabetes, diet (that day), current diabetes medication management, and any adverse event occurring in the hyperbaric chamber that resulted in additional medical treatment to the participant.

PROCEDURE

Insertion of the CGM into the participant occurred on day one of HBOT. Data collection for the study commenced on day two of their HBOT to allow for the sensor to be sufficiently 'warmed' but not 'bio fouled'.[27] The participant presented to the DDHM for routine hyperbaric treatment with the CGM in situ. The CGM site was inspected for any signs of infection and was calibrated using a finger prick glucose value obtained using the participant-specific allocated glucometer. A venous access cannula was placed in the participant's antecubital fossa vein by a medical practitioner using the research site's approved method. The in-situ venous cannula was accessed to draw serum samples.

Prior to the commencement of HBOT, baseline (time point 0 [T0]) blood glucose measures were obtained, including serum values, a finger prick value and the CGM-displayed sensor glucose value. During the two-hour HBOT, serum and finger prick sampling along with CGM sensor glucose reading interrogation was repeated at 30-minute intervals throughout the treatment – a total of four repeated sampling points (30, 60, 90 and 120 minutes being T1, T2, T3, T4 respectively). At completion of HBOT, the venous access cannula was removed, and the patient monitored for 30 minutes as a clinical precaution prior to discharge home.

DATA ANALYSIS

Absolute agreement between the three methods was assessed for each of the five monitoring time points. This was done by calculating an intraclass correlation coefficient (ICC) and its 95% confidence interval (CI) for each time point, using a multilevel linear regression with a random intercept for patients. The first ICC, termed 'intraclass correlation coefficient – absolute agreement' (ICC_{AA}), was defined as:

$$\frac{\text{variability (individual differences) between patients}}{\text{variability (individual differences) between patients + variability of the methods within a patient + random error}}$$

The test/retest or reliability of the three methods was assessed by calculating a second ICC and its 95% CI using a second multilevel linear regression with a random intercept for patients and for methods. This was based on pooling the data over the five time points. The second ICC, termed "*intraclass correlation coefficient – reliability/re-test*" (ICC_{RR}), was defined as:

$$\frac{\text{variability (individual differences) between patients + variability of the methods within a patient}}{\text{variability (individual differences) between patients + variability of the methods within a patient + random error}}$$

The ICC_{RR} assessed the correlation between measurements on the same subject with the same method. This model also allowed for patients' individual glucose responses while they were in the hyperbaric chamber by allowing each patient a random coefficient for time. Further, there was no assumption that each method had the same mean for its glucose measurements and hence a fixed term for method was entered into the regression. In other words, this model was a mixed effects model.[28]

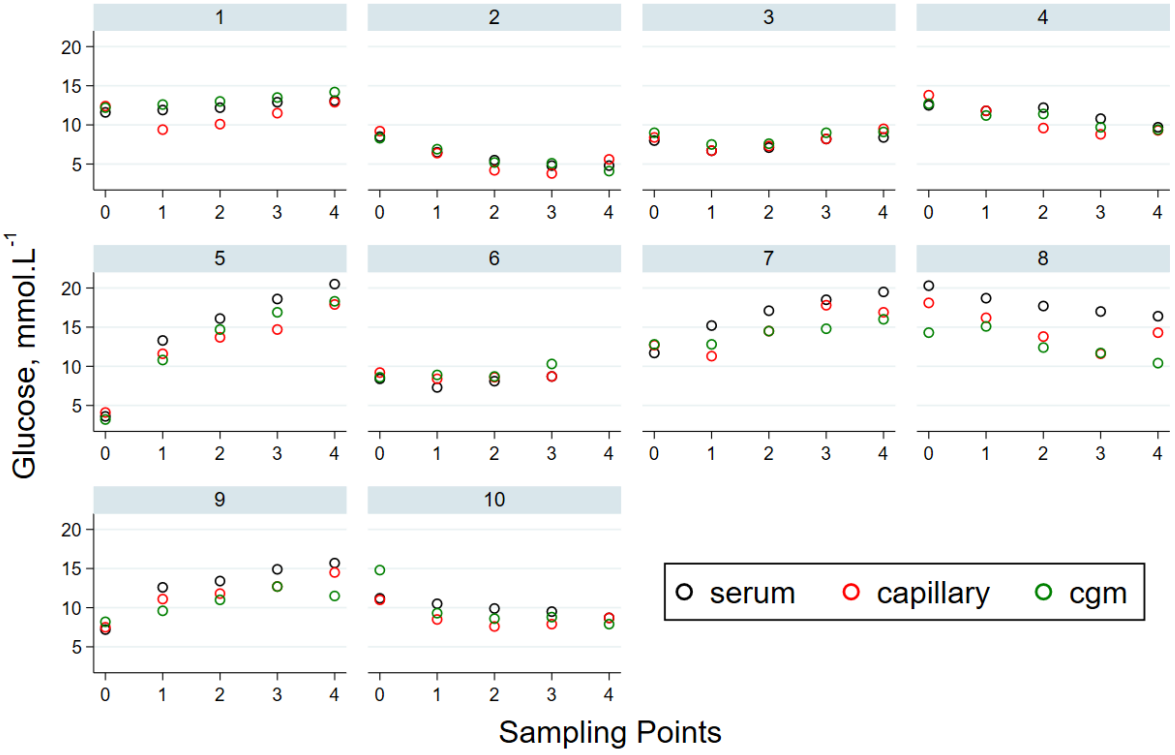
A third model, also mixed effects, was developed to use CGM SG readings to predict serum glucose readings. This is referred to as the recalibration model and was also based on a random intercept for each individual along with random coefficients for time. Glucose was modelled as a fixed effect in order to predict corresponding serum levels. Agreement between serum readings and the recalibrated CGM readings was assessed with a Bland-Altman plot.[29] Calculation of the ICCs, the mixed effects modelling, and generation of the Bland-Altman plot were done with Stata statistical software.[30]

Accuracy of the CGM is often validated using an accuracy metric termed the mean average relative difference (MARD). MARD is the mean of the sum of the differences between reference and sensor glucose values divided by the number of data points. A small MARD indicates that the CGM SG readings are close to the reference glucose value, whereas a larger MARD indicates greater discrepancies between the CGM SG and reference glucose values.[27,31] The MARD for blood samples were assessed. Statistical significance was set at $P < 0.05$.

Results

The study recruited 10 participants: nine males and one female. A sample size of $n = 35$ was intended but due to the lengthy recruitment phase, acceptance of a smaller number was necessary to progress the project. Participants were aged between 52–81 years of age. Two participants were classified as type 1 diabetes mellitus, one participant type 1 diabetes mellitus - latent autoimmune diabetes in adults (LADA), and seven were classified as type 2 diabetes mellitus who were either on insulin or oral hypoglycaemic medicines.

Figure 1
Participant glucose readings (mmol·L^{-1}) from serum, capillary and continuous glucose monitor (CGM) sampling at baseline (point 0) and the four subsequent sampling points at 30-minute intervals (points 1–4 on the Y axis) during HBOT



Glucose levels were obtained from the 10 participants from three separate measurements (capillary, interstitial CGM [SG], and serum) over the five time points during HBOT and are presented in Figure 1. Measurements for patient six at the 120-minute point were not taken due to the venous access cannula blocking. Measurements at each time point with the three methods indicate high similarity within each individual at any given time point. Over time, the three measurements for each participant track each other closely and there are no sudden reversals or changes in direction in glucose trend. Patients' glucose levels tracked differently for each patient. Some patients' glucose levels tended to rise, e.g., patients five and seven, others tended to decrease, e.g., patients four and ten, while some patients' trajectories were flat, e.g., patients one and three. The heterogeneity of patient trajectories was the reason for allowing each patient a random coefficient for time within the second and third multilevel model.

The results of the second model (mixed effects) are displayed in Table 2. Capillary glucose and CGM SG readings were each within about 1 mmol·L^{-1} on average of the serum glucose reading. The average difference of approximately 0.11 between capillary glucose and CGM SG readings were not statistically significant, $P = 0.81$. This model indicated that, across all time points, the three methods were in very close agreement with each other, ICC_{AA} 0.88, 95% CI

Table 1
Intraclass correlation coefficient – absolute agreement (ICC_{AA}) with 95% CIs for each glucose sample time; CI – confidence interval

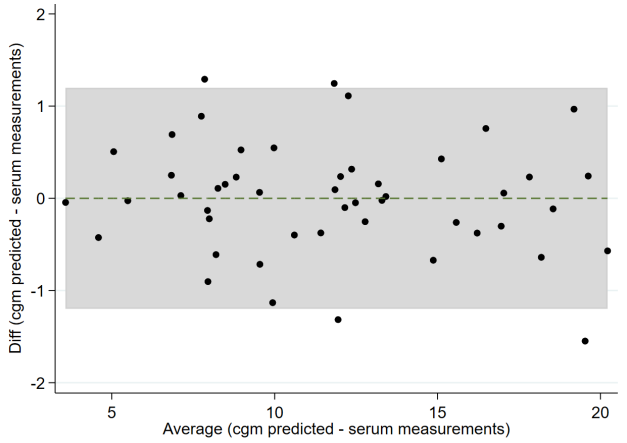
Sample	ICC_{AA} (95% CI)	*P*-value
Pre	0.90 (0.74–0.97)	< 0.0005
30 min	0.85 (0.61–0.96)	< 0.0005
60 min	0.86 (0.58–0.96)	< 0.0005
90 min	0.87 (0.63–0.96)	< 0.0005
120 min	0.90 (0.70–0.97)	< 0.0005

Table 2
Comparison of sampling methods across all time points.; * – denotes comparison with serum levels; CI – confidence interval; ICC_{AA} – Intraclass correlation coefficient – absolute agreement; ICC_{RR} – Intraclass correlation coefficient – reliability/retest

Variable	Estimate	95% CI	*P*-value
Fixed effects			
Constant	11.15	(8.84–13.47)	< 0.0005
Capillary*	-1.06	(-1.94–0.17)	0.019
CGM*	-0.95	(-1.84–0.07)	0.035
ICC			
ICC_{AA}	0.88	(0.72–0.96)	< 0.0005
ICC_{RR}	0.94	(0.86–0.98)	

Figure 2

Bland-Altman plot for the agreement between serum and recalibrated continuous glucose monitoring (CGM) (mmol·L^{-1})



0.72–0.96. The three methods' reliability (test/retest) was high, ICC_{RR} 0.94, 95%CI 0.86–0.98.

The results of the third model (mixed effects) which recalibrated CGM measurements to serum measurements are displayed in the Bland-Altman plot in Figure 2. The average difference between the calibrated and actual serum measurements was 0 with 95% limits of agreement of (1.2). This indicates that, based on this study's data, the recalibrated measurements were not biased and that 95% of recalibrated CGM measurements will be within (1.2) of serum measurements.

Mean average relative differences (MARDs) were generated, and the similarity of the CGM and capillary relative to serum were confirmed first using a repeated measures one-way analysis of variance (ANOVA) for each time point. A statistically significant effect was found for time for the mean capillary values [Wilks Lambda = 0.065, F (4,5) = 17.889, P < 0.01]. The multivariate partial eta squared result was 0.935, suggesting a moderate to large effect as per Cohen's classification.[32] *Post hoc* tests were examined to determine between which time points the differences were statistically significant. Mean capillary results pre-HBOT (T0) differ from subsequent readings at 30, 60, and 90 minutes (P < 0.05 in all cases), but do not differ from the 120-minute measurement (P = 1.000). Differences in CGM values across the time points were not statistically significant [Wilks Lambda = 0.487, F (4,5) = 0.1.315, P = 0.378]. The influence of time point was further examined by conducting repeated measures ANOVA using the mean capillary results as well as the serum values. MARD values are presented in Table 3.

Table 3

Mean average relative difference (MARD) values between finger prick and continuous glucose monitor (CGM) readings at different time points; Note: n = 10 except for Time 4 where n = 9. CI – confidence interval; IQR – interquartile range; Min–Max – minimum–maximum; SD – standard deviation

MARD	Finger prick	CGM
Time 0: pre-HBOT		
Mean (SD)	-5.40 (7.08)	-3.40 (16.30)
Median (IQR)	-7.56 (7.06)	-3.77 (17.39)
Min–Max	-13.89–10.84	-32.14–29.56
95% CI	-10.46–0.33	-15.06–8.25
Time 1: 30 min		
Mean (SD)	9.02 (12.29)	4.82 (15.48)
Median (IQR)	12.34 (19.54)	8.25 (26.51)
Min–Max	-15.07–25.66	-21.92–23.81
95% CI	0.22–17.82	-6.25–15.90
Time 2: 60 min		
Mean (SD)	14.04 (10.55)	7.58(12.20)
Median (IQR)	16.20 (14.08)	7.62 (22.56)
Min–Max	-6.17–23.64	-7.41–29.94
95% CI	6.49–21.59	-1.14–16.32
Time 3: 90 min		
Mean (SD)	13.83 (10.25)	5.3 (15.04)
Median (IQR)	15.80 (18.03)	8.25 (23.20)
Min–Max	0.00–31.76	-18.39–31.18
95% CI	6.49–21.16	-5.40–16.12
Time 4: 120 min		
Mean (SD)	2.48 (11.03)	11.35 (14.91)
Median (IQR)	4.12 (19.29)	10.73 (24.97)
Min–Max	-16.67–13.33	-8.40–36.59
95% CI	-5.99–10.96	-0.11–22.81

Discussion

The aim of this study was to investigate the use of the CGM under hyperbaric pressure. To achieve this, repeated glucose sampling measures using different techniques at pre-set time points were undertaken throughout a standard hyperbaric chamber treatment. At each time point (baseline, 30 minutes, 60 minutes, 90 minutes, and post-treatment), serum blood (via venous canula), capillary blood (via a finger prick) and CGM (via trend interstitial fluid) data were sampled. The results suggest that the three methods of measuring blood glucose yielded values that were statistically and clinically comparable before as well as during HBOT.

These results build on several studies published over the last decade that have examined the accuracy, reliability and functional properties of a CGM device when exposed to conditions associated with recreational diving or HBOT.[15–18,33] Early work identified the CGM as beneficial to the recreational diver as an accurate means of detecting hypoglycaemic episodes.[15] Others investigated the use of CGM in young, fit, recreational divers[17] and reported issues with the CGM housing and consequently device flooding. However, the CGM was accurate in detecting hypoglycaemic events. Although obtaining paired values (for example matching serum to CGM value) were impossible to obtain in a diving situation, it has been observed that the CGM detected significant numbers of hypoglycaemic events and can be used with confidence in diving situations.[16]

In an investigation of the "*Enlite*" sensor using *in vitro* methodology,[33] 16 sensors (n = 8 connected to iPro and n = 8 connected to Guardian REAL-Time) were exposed to hypobaric and hyperbaric conditions and different glucose concentrations. The sensors provided a constant stream of data during testing and no significant difference was seen in the hyperbaric conditions. In contrast, hypobaric conditions affected results in the low and high concentrations of glucose. The authors concluded that the general stability and level of accuracy that the CGM offers would support its use in both the hypobaric and hyperbaric environment. Finally, a small pilot study was undertaken using the Dexcom CGM and two diabetic participants involved in recreational diving.[18] Despite variations in how data were obtained and acknowledgement of excursions of acceptability according to the IOS standard, the authors recommended that diabetics continue to use CGM in recreational diving. The continuous glucose monitor offers an important alternative to intermittent BG monitoring via glucometer.

In addition to contrasting the three methods of glucose sampling, this study provided data about individual BG levels during HBOT. Glucose levels changed over the course of a single hyperbaric treatment. The change in glucose levels recorded by the three methods (venepuncture, finger prick, CGM) varied over time between participants, demonstrating that although some participants had a similar diagnosed physiology to their chronic diabetes, their glucose response varied. It was postulated that this was linked to their diet on the treatment day and consequently the metabolism of the carbohydrate load. All participants had a close alignment of their glucose readings by the three methods with a clear directional trend in their individual glucose data.

While the modelling was based on a small data set with repeated measurements, the recalibration results show the CGM may be a useful method compared to sampling serum and hence potentially interchangeable. It would be possible, after further validation, to incorporate recalibration with serum levels as part of the patient specific predictive algorithm. This is noteworthy, given that venous sampling is not usual practice during HBOT due to the invasive and time-consuming nature of the method.

It has been demonstrated that capillary (finger prick) sampling is considered painful, intrusive and burdensome by patients.[34] Evidence indicates that patients are supported by the CGM system and its ability to provide predictive trend data.[35] These findings facilitated management decisions that consequently reduced the rate of hypoglycaemia.[17] Given the heightened glucose testing that applies in a HBOT environment, the opportunity to integrate CGM SG readings to aid BG level monitoring and management, whilst minimising the impost to patients should be further explored. A larger study would be required of non-repeated measurements to verify the utility of this monitoring system. The ability to monitor BGL continuously whilst diving underwater or in a hyperbaric chamber has progressed and the development of the CGM has created greater and safer opportunities for divers and patients. Healthcare clinicians must recognise there are physiological differences between the glucose concentration in blood sources from veins, capillaries, arteries and interstitial fluid.[36] There is a need to bolster the existing body of knowledge regarding CGM accuracy, reliability and safety when used in HBOT conditions. Studies have reached consensus in the use of the CGM for recreational divers but the use of the CGM to predict glucose trends during HBOT is not yet fully established.

Although the introduction of a CGM for patients with diabetes undergoing HBOT is conceivably best practice, this would not make the glucometer/strip combination redundant. There will be instances where a short course of HBOT is prescribed and one-off blood glucose monitoring will be necessary. A glucometer would suffice in this situation. To date, a glucometer is necessary to assist in the calibration process of the CGM, however, future modelling of the CGM will explore the removal of this requirement. The use of the CGM will be patient- and treatment-course specific and as such there will be an ongoing role for both types of glucose monitoring equipment.

A limitation of the study is the small number of participants that were recruited. To assess the general utility of CGM SG readings as a good predictor of serum levels of glucose, further testing on a larger number of patients is required. It would not, however, be necessary to perform serial glucose measurements which have added unnecessary statistical burden.

Conclusion

CGM provides a real-time glucose trend that allows interventional treatment to be instigated at appropriate times, thus proactively managing hypoglycaemic situations as they eventuate in hyperbaric conditions. The CGM SG measurements were as accurate as those provided by a venous serum or finger prick glucose test. With routine use in the hyperbaric environment, the CGM device will likely prove to be a method of glucose monitoring that can be trusted by both clinicians and patients.

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