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ORIGINAL RESEARCH

THE UTILITY OF CONTINUOUS GLUCOSE MONITORING IN EXERCISE AND HEALTH SCIENCE

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Abstract

Continuous glucose monitoring (CGM) is an evolving technology which provides information about the direction, magnitude, duration, frequency, and causes of fluctuations in blood glucose levels. This review summarises the rationale for ambulatory continuous glucose monitoring in the exercise sciences, the current literature to date, and potential future directions of research. It is concluded that CGM data collected during exercise/physical activity related trials would facilitate the improvement of glucoregulatory exercise programmes and development of more appropriate evidence based physical activity guidelines for glycaemic control.

Keywords: blood glucose, glycaemic regulation, physical activity, exercise.

Introduction

A sedentary lifestyle is considered an important modifiable risk factor for type 2 diabetes. It is well established that physical activity reduces the risk of developing insulin resistance and glucose intolerance [1], although the 'dose' a function of intensity, frequency, and duration, of activity required for optimal protection continues to be debated [2]. Current guidelines [3] suggest that to improve glycaemic control at least 150 min per week of moderate-intensity aerobic physical activity (40–60% of VO_{2max} or 50–70% of HR_{max}) and/or at least 90 min per week of vigorous aerobic exercise (60% of VO_{2max} or 70% of HR_{max}) is required.

A comprehensive review of prospective studies published between the years 1990 and 2000 concluded that the reduction in the risk of type 2 diabetes associated with a physically active, compared with a sedentary, lifestyle is 30–50% [4]. Further, the participation in regular physical activity may slow the initiation and progression of type 2 diabetes; via the amelioration of the effects of increased body mass, insulin sensitivity, glycaemic control, blood pressure, lipid profile, fibrinolysis, endothelial function, and inflammatory defence systems [2].

The effect of exercise upon glucose metabolism is well documented; exercise is known to increase the rate of glycogen uptake into the surrounding skeletal muscle [3]. Likewise blood glucose response to exercise has been well documented in diabetics; numerous experimental studies having observed tighter glycaemic control [5]. The greater proportion of research conducted upon blood glucose response to exercise is of a long-term experimental design, detailing chronic adaptations to exercise in diabetics. However recent developments have enabled clinicians and exercise scientists to reliably monitor plasma and/or interstitial glucose concentrations in an ambulatory and continuous fashion [6].

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Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) has emerged as a tool for patients with type 1 diabetes mellitus to help maintain euglycaemia (normal glycaemic control). The monitors provide information on ambulatory, postprandial and/or nocturnal glucose excursions [7]. In contrast to intermittent self-monitoring of blood glucose, usually via finger stick devices (SMBG), CGM systems (e.g., Guardian® RT by Minimed) allow glucose levels to be measured continuously from a small electrode inserted into the interstitial fluid under the skin. A transmitter sends information wirelessly to a monitor that displays current glucose readings and stores the data for viewing and downloading to a personal computer [8]. Alternatively newer models such as the MiniMed iPro® CGMS (CGMS iPro, Medtronic, Northridge, USA) have a digital recorder attached to the electrode sensor, which stores data onboard negating the need for an LCD monitor display, see Figure 1 below.

Figure 1. The iPro® CGMS, pictured with sensor (in grey) and digital recorder (in white). The sensor is inserted below the skin, into the abdomen [10].

CGM provides information about the direction, magnitude, duration, frequency, and causes of fluctuations in blood glucose levels. Compared with traditional glucose monitoring (defined as three to four blood glucose measurements per day) CGM provides much greater insight (measurements at a 5 minute resolution) into blood glucose levels throughout the day [9]. Figure 2 shows the high resolution of data which CGM can provide.

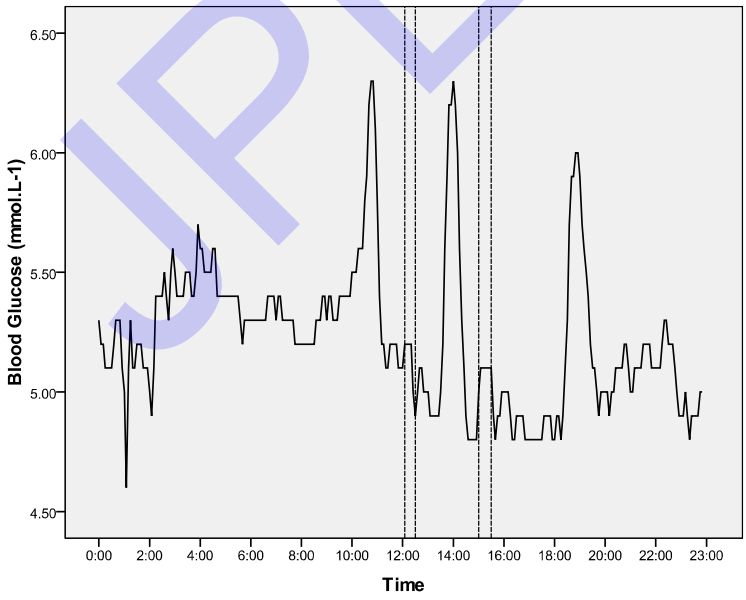

Figure 2. Twenty-four hour CGM blood glucose profile for a 22 year old non-diabetic male. The dashed lines represent times of exercise bouts, and the prominent spikes are meal times. [10].

The advent of CGM technology has facilitated the management of diabetes by providing acute blood glucose trends and the ability to detect extreme fluctuations in glucose concentrations that would previously go undetected using conventional measures [11]. The availability of such high resolution data provides clear rationale for investigating the pattern of blood glucose response to physical activity and or exercise.

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For exercise scientists and health practioners alike, this is an exciting field, but as yet one in which many questions remain unanswered. There is a growing body of research beginning to use CGM systems, the majority of which has charted normative glycaemic characteristics in diabetics, with little data available in apparently healthy non-diabetic populations. Several large controlled clinical trials have demonstrated that CGM has successfully aided in glucose control and insulin therapy adjustment [5]. Out of five randomised control trials that have used HbA1c (glycated haemoglobin) as an outcome measure of mortality and morbidity related to diabetes, four utilised CGM to monitor glucose levels, in particular to detect unrecognised hypoglycaemic events. In the four studies which employed CGM compared with standard monitoring, this was associated with significant improvements in mean HbA1c levels [12-16].

There are a small number of studies to date that have used CGM for therapeutic adjustment. For example, Schaepelynck-Belicar et al. [17] reported the findings of a nonrandomized, uncontrolled trial of a 72 hour course of CGM. CGM was used to determine rational adjustments in insulin therapy in 12 type 1 diabetic participants. Changes involved alterations of the dosage in three participants, insulin type in seven participants, the number of daily injections in five participants, and the delivery technology (from insulin injection to pump therapy) in one subject. A two month follow-up demonstrated a significant reduction of glycaemic excursions in eight participants and a decrease in the mean HbA1c from 10.3 to 8.75% ($p < 0.05$). The findings of this study add weight to the efficacy of CGM as a key tool in diabetic management, and its future promise in clinical interventions [9]

The availability of such high resolution data, allows an understanding of extremely acute periods of glucose excursion such as postprandial hyperglycaemia. This was highlighted by Praet et al. [6] who assessed the level of 24 hour glycaemic control in eleven male patients with Type II diabetes and 11 normoglycaemic controls who participated in a 24 hour CGM trial under standardized dietary and physical activity conditions. Alongside, finger stick glucose measures were recorded. The results showed that CGM is far more sensitive to acute glucose changes in daily life than traditional finger stick methods. This is highly important when taking into account the vascular damage caused by postprandial hyperglycaemia, given that the traditional methods may miss some periods of hyperglycaemia.

Why do we need Continuous Glucose Monitoring?

Optimal glycaemic control is defined by the American Diabetes Association (ADA) as a glycated haemoglobin (HbA1C) value of < 7.0% for a population, or as close to 6.0% as possible without unacceptable risk of hypoglycaemia for an individual [18]. The regulation of blood glucose for a diabetic individual can be an elusive task, despite the efforts of the patient to monitor and manage therapeutic intervention i.e. insulin dose. This may be difficult as blood glucose levels are influenced by a wide variety of variables which are often in flux, such as diet, insulin dosage, stress, physical activity, and the rate of nutrient absorption. Traditional blood glucose meters provide a small snapshot of blood glucose at a given moment, with no indication of whether the value is moving up or down, thus modulation of behaviour in response to a finger stick blood glucose value is often an educated guess [19].

For example increasing insulin dosage in response to an elevated finger stick blood glucose value following vigorous intensity exercise (a feed forward mechanism stimulates increased hepatic glucose production during vigorous exercise) could trigger a period of hypoglycaemia if in fact blood glucose was actually declining despite at that time point being relatively high. The real-time data provided by CGM allows for optimal therapeutic intervention to be administered, as the direction of blood glucose trends following food intake or exercise can be observed by the patient or clinician [19].

Continuous Glucose Monitoring during Exercise

Of the extant literature, three studies have charted acute blood glucose response to exercise using CGM. As established prior, exercise improves glycaemic control. Information attained from CGM could be used to identify exercise- or diet induced changes in glucose tolerance and provides a useful source of additional information for healthcare professionals to formulate evidence based exercise programmes to alter the glycaemic profiles of individuals with type 2 diabetes [20].

Macdonald et al. [21] aimed to determine the efficacy of CGM during moderate intensity exercise. CGM was used to monitor the changes in whole day glucose profiles in individuals with and without type 2 diabetes. Six obese individuals (type 2 diabetics) and four age matched non-diabetic controls were monitored for 3 days. Participants cycled for 1 hour on day 2 at ~ 90% of lactate threshold, venous blood was drawn for sampling every 10 minutes. As a result of the cycling intervention there were significant improvements in glycaemic control in the diabetic group compared to control ($p < 0.001$). Indeed it was concluded that CGM was able to demonstrate that a period of moderate exercise improved whole-day glycaemic control in obese individuals with type 2 diabetics, compared to controls.

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It was however recommended that CGM should only be used as an adjunct and not as an alternative when examining the changes in glucose values during exercise in individuals with and without type 2 diabetes [21]. However with the current development of more accurate devices, CGM should be embraced by exercise scientists; real time data will allow an understanding of the acute blood glucose response to a range of exercise modes, across differing exercise intensities, and between differing populations and ages.

Similarly a pilot study [11] aimed to determine the efficacy of using a CGM system (Guardian® RT, Minimed, Northridge, CA) to detect blood glucose excursions associated with exercise and Late onset hyperglycaemia (LOH) after exercise in individuals with type 1 diabetes. Five participants with type 1 diabetes were monitored before, during, and after a 60 minute vigorous spin class using the Guardian RT® CGM (48 hour in total). The Guardian RT® monitor was found to be effective in identifying all participants' glycaemic excursions over the 48 hour surveillance period. A strong correlation ($rr = 0.89$, $p < 0.001$) was found between conventional self-monitoring of blood glucose and Guardian RT® data.

Preliminary data has shown that different patterns of physical activity, may impact upon acute blood glucose regulation [10]. In a single participant case study one physically active non-diabetic male (age: 22 y; mass: 71.5 kg; height: 181 cm) underwent 7 days CGM, performing 3 trial conditions: a sedentary control (< 2500 steps, pedometer controlled), a continuous vigorous exercise condition (2 x 30 min treadmill running at 70% HR_{max}), and a lifestyle-embedded physical activity condition (100 min fractionalized moderate activity). Diet was standardised and physical activity levels were monitored via accelerometry throughout.

Results showed a significant difference of -0.24 $mmol.L^{-1}$ in twenty-four hour mean glucose levels between the sedentary and continuous condition ($p = 0.00$), and a significant difference of -0.038 $mmol.L^{-1}$ in twenty-four hour mean glucose levels between the sedentary and lifestyle embedded physical activity condition ($p = 0.004$). Descriptive results displayed a post exercise decrease in glucose levels (2 hours pre- 6 hours post (5.3 – 5.1 $mmol.L^{-1}$)) with a carryover effect for the following day (reduced mean glucose 24 hours pre-post (5.5 ± 0.5 - 5.2 ± 0.3 $mmol.L^{-1}$)) in the continuous exercise condition. Whilst from a case study, these findings illustrate that both continuous vigorous exercise and lifestyle activity bouts have a beneficial effect upon whole day glucose regulation compared to a sedentary control, with tighter glycaemic variation observed in the continuous vigorous exercise condition. Importantly continuous vigorous exercise reduces and maintains mean glucose levels for the acute period of 6 hours post exercise and promotes a carry over effect for the ensuing 24 hours [10]. Clearly these findings are not generalisable to the wider population, however the predominant message here is that CGM can be employed to investigate intermittent lifestyle related physical activity, which previous traditional methods of blood glucose sampling could not measure.

Saliently there are few studies that have employed CGM within exercise protocols. Moderate exercise may aid in the control of blood glucose, and reduce the number of hyperglycaemic excursions in both diabetic and non-diabetic individuals. However, very little is known regarding the dose-response relationship between physical activity and acute blood glucose response determined via CGM, and the influence this may have on long term measures of glycaemic control such as HbA1c.

Accuracy of Continuous Glucose Monitoring

The findings of studies employing CGM must be quantified in relation to measurement error. To date the accuracy of CGM devices has shown to be acceptable, the mean absolute difference between sensor and blood glucose meter values is normally reported as between 1.3 and 2.6 $mmol.L^{-1}$, likely reflecting the biological time delay (approximately 5 minutes) between interstitial and blood glucose concentrations [22, 23].

The International Organization for Standardization (ISO) state that standards for accuracy of point blood glucose tests require that a CGM blood glucose value be within ± 20% of a reference criterion value. The DirectNEt study [24] used the ISO standards to determine the accuracy of the CGMS over a range of glucose excursions in 78 children with type 1 diabetes. It was observed that the performance of the CGMS was acceptable. The CGMS glucose values were ~ 3% lower than the reference glucose values (median relative difference = −3%, $p < 0.001$). The median relative absolute difference (RAD) was 12% and the ISO criteria were met by 72% of all paired values. Accuracy varied with the glucose level, being greater at higher glucose levels than lower glucose levels ($p < 0.001$). For 556 paired glucose values where the reference value was >240 $mg.dL^{-1}$, the median RAD was 10% and 77% of pairs met the ISO criteria whereas for the 176 pairs where the reference value was ≤70 $mg.dL^{-1,}$ the median RAD was 20% and 66% of pairs met the ISO criteria. This study suggests that the performance of CGM is greatest in the euglycaemia and/or hyperglycaemic range [24].

More recent research has shown that the monitors show strong agreement compared with venous blood concentrations, with approximately 80% accuracy system over a five day period being reported in some CGM models [25]. The accuracy of CGM devices in exercise protocols is limited; Macdonald et al. [21] showed that the number of data points outside of the 95% confidence intervals was < 5% in both groups, suggesting that there is a good level of agreement between venous blood glucose and CGM values during exercise. Future studies

employing CGM in exercise related studies should assess and report the agreement between CGM and reference blood glucose samples.

Future Directions

Clearly there is great potential for the employment of CGM in exercise related trials. In particular a number of questions remain unanswered that, could be elucidated upon using CGM devices. For example: 1) what is the minimum intensity required to achieve improved glycaemic regulation? 2) What pattern of activity should be prescribed? 3) Should the activity be continuous or fractionalized into shorter bouts? These are just a few of the answered questions. Thus there is salient justification for the need to further understand the prophylactic benefit of physical activity upon glycaemic regulation as to identify the most effective exercise therapy.

Conclusions

CGM devices show acceptable accuracy but to date are not fully evaluated during exercise parameters. The use of CGM during exercise may support the development of guidelines for individuals engaging in various types and intensities of exercise. Data collected during such studies would facilitate the improvement of glucoregulatory exercise programmes and development of more appropriate evidence based physical activity guidelines.

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