Original article

Accuracy assessment of online glucose monitoring by a subcutaneous enzymatic glucose sensor during exercise in patients with type 1 diabetes treated by continuous subcutaneous insulin infusion

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Abstract

Aim. – Online continuous glucose monitoring (CGM) during physical exercise would be highly useful in patients with insulin-treated diabetes. For this reason, this study assessed whether such a goal could be reached with a subcutaneous 'needle-type' enzymatic sensor.

Methods. – Ten patients (five women/five men), aged 51 ± 12 years, with type 1 diabetes for 24 ± 11 years treated by continuous subcutaneous insulin infusion (CSII) for more than 1 year (HbA$_{1c}$: $7.5 \pm 0.8\%$) performed a 30-min bout of exercise at a constant high-intensity load (15% above their individual ventilatory threshold) on a cycle ergometer. All patients wore a subcutaneous 'needle-type' enzymatic glucose sensor linked to a portable monitor (Guardian® RT, Medtronic-MiniMed, Northridge, CA, USA) that had been inserted the previous evening. Sensor calibration was performed against capillary blood glucose immediately before the exercise. CGM values were recorded every 5 min from T$_{-10}$ to T$_{+30}$, then every 10 min during the recovery period from T$_{+30}$ to T$_{+90}$. These recorded values were compared with blood glucose assays performed on simultaneously collected venous samples.

Results. – Sensor functioning and tolerability raised no problems except for one sensor that could not be adequately calibrated. Data from this patient were excluded from the data analysis. An average blood glucose decrease of 63 ± 63 mg/dL (3.5 ± 3.5 mmol/L) (median decrease: 58 mg/dL [3.22 mmol/L]; range: –3 mg/dL [0.16 mmol/L] to 178 mg/dL [9.8 mmol/L]) occurred during exercise bouts, while CGM values decreased by 38 ± 49 mg/dL (2.11 ± 2.72 mmol/L) (median: 32 mg/dL [1.7 mmmol/L]; range: –15 mg/dL [0.83 mmol/L] to 58 mg/dL [3.22 mmol/L]). Cumulative paired glucose values ($n = 135$) could be analyzed. The correlation factor between CGM and blood glucose values was 0.957 with an intercept of 0.275. The mean difference between paired values according to Bland–Altman analysis was 10 ± 31 mg/dL (0.56 ± 1.72 mmol/L). Clarke error grid analysis showed 91% of paired points in A and B zones, while 0%, 9% and 0% of paired points were in the C, D and E zones, respectively.

Conclusion. – Blood glucose changes during intensive physical-exercise bouts performed by CSII-treated type 1 diabetes patients can be estimated with acceptable clinical accuracy by online CGM.

Résumé

Évaluation de l'exactitude d'une mesure continue du glucose en temps réel par un capteur de glucose enzymatique sous-cutané lors d'un exercice musculaire chez des patients diabétiques de type 1 traités par perfusion continue sous-cutanée d'insuline.

Objectif. – Une mesure continue du glucose (MCG) en temps réel lors de l'exercice musculaire serait très utile pour les malades diabétiques traités par l'insuline. Nous avons évalué l'atteinte de cet objectif au moyen d'un capteur enzymatique sous-cutané de type « aiguille ».

Méthodes. – Dix patients (5F/5H), âgés de 51 ± 12 ans, diabétiques de type 1 depuis 24 ± 11 ans, traités par pompe à insuline depuis plus d'un an (HbA1c : $7,5 \pm 0,8$ %), ont réalisé un exercice musculaire à charge constante et à haute intensité (+15 % du seuil ventilatoire) de 30 minutes sur cyclo-ergomètre lors d'une évaluation de routine de leur capacité à la pratique du sport de compétition. Tous étaient porteurs d'un capteur de glucose enzymatique sous-cutané relié à un moniteur portable (Guardian® RT, Medtronic-MiniMed, Northridge, CA, État-Unis) mis en place la veille de l'épreuve, étalonné sur une glycémie capillaire juste avant l'épreuve. La glycémie estimée par la MCG a été mesurée toutes les cinq minutes

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de T-10 à T+30 puis toutes les dix minutes pendant la phase de récupération de T+30 à T+90, et comparée à la glycémie contemporaine, dosée à partir de prélèvements veineux.

Résultats. – Les capteurs ont été fonctionnels et bien tolérés durant toutes les épreuves, sauf pour un capteur qui n'a pas pu être correctement étalonné. Les données obtenues chez ce patient ont été exclues de l'analyse. Une baisse glycémique veineuse moyenne de 63 ± 63 mg/dl $(3,5 \pm 3,5$ mmol/l), dont la médiane est 58 mg/dl (3,22 mmmol/l) avec des extrêmes de –3 mg/dl (0,16 mmol/l) à 178 mg/dl (9,8 mmol/l), a été observée, contre 38 ± 49 mg/dl $(2,11 \pm 2,72$ mmol/l), avec une médiane de 32 mg/dl (1,7 mmol/l) dont les extrêmes sont de –15 mg/dl (0,83 mmol/l) à 58 mg/dl (3,22 mmol/l) d'après la MCG. Un cumul de 135 valeurs glycémiques ponctuelles appariées a pu être analysé. La corrélation entre la glycémie mesurée et celle estimée par la MCG montre un coefficient r de 0,957 et un intercept de 0,275. La moyenne des différences calculées par la méthode de Bland–Altman est de 10 ± 31 mg/dl $(0,56 \pm 1,72$ mmol/l). La grille d'erreur de Clarke montre 91 % des points dans les zones A et B, 0, 9 et 0 % des points en zones C, D et E, respectivement.

Conclusions. – L'évolution glycémique lors d'un exercice intensif mené sous pompe à insuline peut être estimée en temps réel avec une exactitude cliniquement acceptable par la MCG au moyen d'un capteur de glucose enzymatique sous-cutané.
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Mots clés : Diabète de type 1 ; Mesure continue du glucose ; Pompe à insuline ; Exercice physique

1. Introduction

Physical exercise in patients with type 1 diabetes mellitus (T1DM) is associated with important benefits such as improved quality of life and decreased cardiovascular risk [1]. Nevertheless, fear of hypoglycaemia is one of the strongest barriers to physical activity in adults with T1DM [2]. Indeed, exercise-induced hypoglycaemia is common in people with insulin-treated diabetes [3]. Intensified self-monitoring of blood glucose (SMBG) is recommended during sports practice, but is cumbersome and unable to provide detailed information allowing early detection of hypoglycaemic trends.

Continuous glucose monitoring (CGM) using enzymatic glucose sensors has been developed for clinical use during the last decade and shown benefit by detecting glucose excursions that remained unrecognized by SMBG [4], including asymptomatic hypoglycaemia [5]. As CGM accuracy has been investigated mostly in sedentary situations, it has been poorly assessed during physical exercise [6]. However, our group has shown good accuracy with CGM using microdialysis with the GlucoDay® sensing system in T1DM patients treated by continuous subcutaneous insulin infusion (CSII) during physical exercise at both low and high intensities, although the high incidence of subcutaneous probe breakage has reduced the applicability of its use in everyday life [7]. Moreover, in the protocol used in the present study, plasma glucose concentrations remained almost stable during exercise because the insulin bolus covering the previous meal had been reduced by 50%, and the insulin basal delivery rate was stopped 1 h before the beginning of exercise and throughout its duration. Therefore, it is difficult to draw any conclusions as to the accuracy of CGM when large glucose changes are observed, especially when exercise-induced hypoglycaemia arises.

The present study aimed to assess the accuracy and tolerability of another glucose-sensing device (Guardian® RT) during sports activities in CSII-treated T1DM patients. According to the experimental protocol tested in this study, the usual insulin delivery remained unchanged to induce a gradual decrease in plasma glucose concentrations during physical activity, thereby allowing assessment of the performance of the sensing system across a wider range of glucose levels.

2. Methods

Ten adult T1DM patients gave their written informed consent to participate in this observational study, which had been approved by our institutional ethics board. All patients (five women and five men), who were aged 51 ± 12 years and with T1DM for 24 ± 11 years, had been treated by CSII for more than 1 year and had HbA$_{1c}$ levels of $7.5 \pm 0.8\%$ at inclusion. These patients also usually participated in physical activity and had attended at least four outpatients visits at our department for their treatment follow-up during the previous year. All were subjected to two standardized exercise tests more than 7 days apart as a routine evaluation of their ability to participate in competition sports. First, they performed an incremental exercise test (8–12 min) for determination of their maximum oxygen consumption (VO$_{2max}$) and first ventilatory threshold. Second, they performed a 30-min exercise bout at a constant high-intensity load (15% above their individual ventilatory threshold) on a cycle ergometer. The complete protocol for the evaluation of this aerobic capacity and ventilatory threshold is the same as described previously except for the lack of adjustment of insulin delivery [7].

All patients wore a subcutaneous 'needle-type' enzymatic glucose sensor linked to a portable monitor with a visual display of estimated blood glucose (Guardian RT, Medtronic-MiniMed, Northridge, CA, USA). This device displays the average sensor glucose concentration every 5 min and stores all of these values. The study was performed in 2009, thus using the first-generation of MiniMed sensors available for CGMS®. The Guardian RT was set up the previous evening in our outpatients unit. Initial sensor calibration was performed against the participants' capillary blood glucose values 2 h after insertion of the sensor. Calibration of the Guardian RT was carried out again immediately before exercise against one blood venous glucose value. The exercise session was performed 2 h after a standardized breakfast (40-g carbohydrate intake) preceded by the usual insulin bolus. The usual basal insulin delivery rate was purposely maintained during and after the exercise to allow large glucose changes to occur. The device was removed 1 h after the end of the exercise and recovery period, and the patients left the hospital 2 h later. Blood glucose values

according to the sensor were recorded every 5 min from T_{-10} to T_{+30}, then every 10 min during the recovery period from T_{+30} to T_{+90}. These recorded values were compared with blood glucose assays performed on simultaneously collected venous samples.

2.1. Statistical analyses

Venous samples were stored in fluoride tubes for plasma glucose determination using the reference standard method (Beckman Coulter, Fullerton, CA, USA). At the time of each venous sampling, glucose values as given by the CGM device and the corresponding time shown on the monitor were recorded. The performance of the Guardian RT was evaluated by comparing its readings (sensor values) to the glucose values obtained at the same time with the assay reference method using the Bland–Altman method [8–10], which plots the mean from all paired data of the absolute value of the difference between the sensor and reference glucose, divided by the reference glucose. The mean $\pm$ 1.96 SD represented the 95% confidence interval (CI).

Also used was Clarke error grid analysis, which separates a Cartesian diagram [in which the values generated by the CGM device (Guardian RT) are displayed on the y axis, while values received from the reference method are displayed on the x axis] into five zones of clinical significance [11].

Data were expressed as means $\pm$ SEM. The decrease in blood glucose was also expressed by the median.

3. Results

Sensor functioning and tolerability raised no problems involving the skin, and no loss of insertion or breakage of the sensor was observed. Only one patient faced a problem because adequate calibration could not be obtained. Thus, the 10 paired points coming from this patient were excluded from the study analysis. The average blood glucose concentration was 154 ± 92 mg/dL (8.56 ± 5.11 mmol/L) at T_{-0} min and 180 ± 70 mg/dL (10 ± 3.89 mmol/L) at T_0 min (Fig. 1). An average blood glucose decrease of 63 ± 63 mg/dL (3.5 ± 3.5 mmol/L) and a median decrease of 58 mg/dL (3.22 mmol/L), with a range of –3 mg/dL (–0.16 mmol/L) to 178 mg/dL (9.8 mmol/L), were seen during exercise bouts, while sensor glucose levels decreased by an average of 38 ± 49 mg/dL (2.11 ± 2.72 mmol/L) (median: 32 mg/dL [1.7 mmmol/L]; range: –15 mg/dL [–0.83 mmol/L] to 58 mg/dL [3.22 mmol/L]). Overall, 135 paired glucose values were included in the analysis. The correlation factor between sensor and blood glucose values was 0.957, with an intercept of 0.275. The mean absolute difference between paired values according to Bland–Altman analysis was 10 ± 31 mg/dL (0.56 ± 1.72 mmol/L; Fig. 2). Clarke error grid analysis showed 91% of paired points in the A and B zones, while 0%, 9% and 0% of paired points were in the C, D and E zones, respectively (Fig. 3).
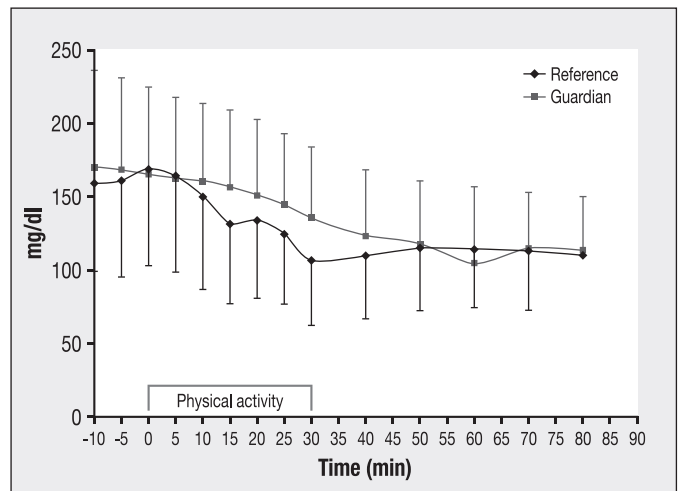

Fig. 1. Blood glucose levels in nine patients with type 1 diabetes treated by continuous subcutaneous insulin infusion over 30 min at a high-intensity load (15% above the patients' individual ventilatory threshold). Glucose values were estimated using a Guardian® RT sensing system (pink line), and plasma glucose values were measured using a reference assay (blue line). Values are presented as means $\pm$ SEM.

4. Discussion

Our present study shows that the Guardian RT can provide clinically acceptable estimations of glycaemia during physical exercise at high intensity. Contrary to a previous experience with a microdialysis system, no loss of insertion or sensor breakage was observed in this study.

Thus far, few studies have tested the accuracy of the Guardian RT device during and after exercise. A small pilot study of five adults with T1DM demonstrated that the device was able to reasonably track the drop in glycaemia over 60 min of rather vigorous cycling with no missing data [12]. However, other than two baseline measurements, only two additional capillary glucose measurements were performed during the exercise.
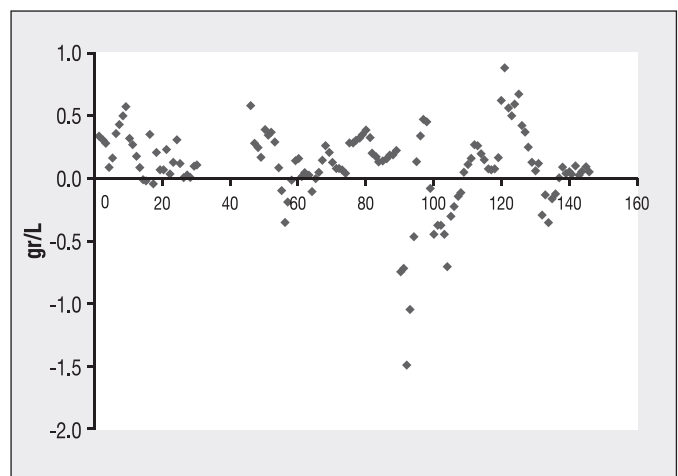

Fig. 2. Bland–Altman plots showing the differences between blood glucose estimations with the Guardian® RT sensing system and reference venous blood glucose measurements in nine patients with type 1 diabetes treated by continuous subcutaneous insulin infusion during high-intensity exercise ($n = 135$).
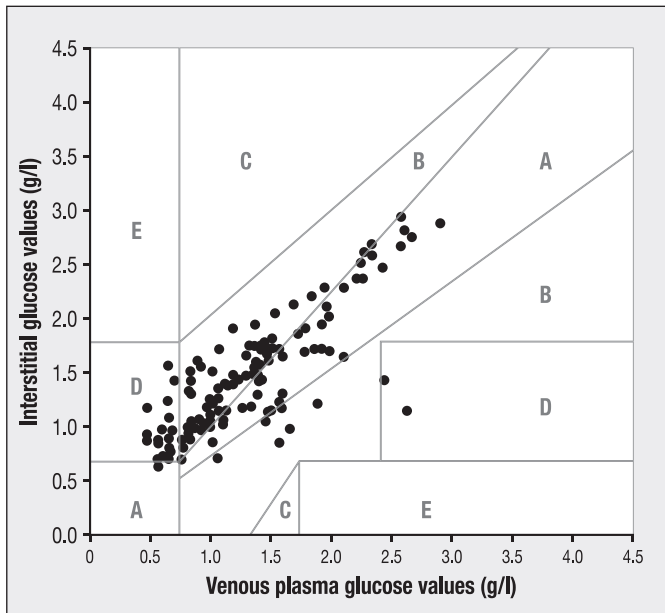
Fig. 3. Clarke error grid analysis of paired glucose values estimated by the Guardian® RT sensing system and glucose measurements by a reference method (*n* = 135) from nine patients with type 1 diabetes treated by continuous subcutaneous insulin infusion during high-intensity exercise: 91% of the paired glucose values are within the A and B zones, while only 0%, 9% and 0% of values are within the C, D and E zones, respectively.

Available data suggested that CGM tended to overestimate glucose levels during exercise compared with blood glucose concentrations, especially when glucose fell to low levels. The proposed hypothetical explanation was a 10- to 20-min time delay in equilibrium between interstitial fluid and capillary glucose [13]. In 19 children and adolescents with T1DM subjected to four 15-min bouts of moderate-intensity exercise on a treadmill, the DirectNet study group reported that CGM with a FreeStyle Navigator® could accurately track the magnitude of blood glucose decreases with around a 10-min delay [14]. As in our present study, the device underestimated the true fall in blood glucose in most subjects, with a mean difference of about 15 mg/dL (0.83 mmol/L). Again, this difference was explained by the sensor glucose lagging behind blood glucose in its response. In one study evaluating the effect of a 75-min treadmill exercise, it was shown that the CGMS® (Medtronic) correctly detected only 65 to 69% of cases of exercise-induced hypoglycaemia (defined as < 70 mg/dL, or < 3.89 mmol/L) [15]. Another trial using a microdialysis technique showed, in 16 patients trained for exercise (before and after a 14-day moderate-to-intense exercise programme), the expected wide variability in glucose profiles before, during and after physical exercise [16]. For longer activities such as marathon or long-distance running, five subjects with T1DM and one patient with type 2 diabetes were monitored with the Medtronic-MiniMed CGMS [17]. The data confirmed that the CGMS can help to identify asymptomatic hypoglycaemia or hyperglycaemia during and after a long-distance run [18]. The CGMS may also be a useful tool for monitoring improvements in glycaemic control after various exercise programmes [19].

Our present data further confirm that glucose decreases during intensive effort can be tracked by a subcutaneous sensor, albeit with a trend towards higher sensor glucose values than reference values, similar to the report mentioned above [20]. This observation can probably be explained by the physiological lag between blood and interstitial glucose levels when blood glucose decreases. Such a lag associated with rapid decrements in blood glucose appears to be unavoidable due to the subcutaneous placement of the sensor. From a practical point of view, this means that the patient can consider the information on glucose trends provided by the sensing system as useful, but should view the absolute value of the displayed glucose level with some caution. If a set point is established as a threshold for setting off a 'hypo' alarm, it should take into account the presence of the lag and therefore be considered to be higher than the intended warning signal for 'true' low blood glucose levels [21]. Interestingly, the effect of this lag vanishes after 10 to 20 min during the recovery period, an observation important in cases of automated cessation of insulin infusion triggered by having reached the 'low glucose' threshold. Indeed, prolonged interruption of insulin infusion could result in undesirable hyperglycaemia during recovery [22].

As one limitation of our study, it should be noted that our observations were obtained in hospital during a standardized experimental protocol supervised by experienced staff. This means that the accuracy of CGM and feasibility of its use under real-life conditions require further careful analysis. Specifically, further investigations would be useful for assessing the accuracy of CGM during exercise of longer durations and, in cases of hypos, for acquiring a greater knowledge of the 'movable' gap between sensor glucose values and actual blood glucose levels in these more complex settings, including physical activity, as well as how insulin infusion would then need to be modulated.

Disclosure of interest

The author declares that they have no conflicts of interest concerning this article.

Acknowledgments

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