Simulated games activity versus continuous running exercise: a novel comparison of the glycaemic and metabolic responses in T1DM patients

Authors

Matthew D Campbell[3], Daniel J West[3], Stephen C Bain[2], Michael I C Kingsley[5], Paul Foley[4], L. Kilduff[1], Daniel Turner[1], Benjamin Gray[1], Jeffrey W Stephens[2], Richard M Bracken[1,2]

Affiliation

[1]Applied Sports, Technology, Exercise and Medicine Research Centre, College of Engineering, Swansea University, Swansea, UK; [2]Diabetes Research Group, College of Medicine, Swansea University, Singleton Park, Swansea UK. [3]Department of Sport, Exercise and Rehabilitation, Faculty of Health and Life Sciences, Northumbria University, Newcastle-upon-Tyne, UK. [4]Cardiff School of Health Sciences, Cardiff Metropolitan University, Cardiff, UK. [5]Department of Allied Health, Faculty of Health Sciences, La Trobe Rural Health University, Victoria, Australia.

Corresponding author

Matthew D Campbell

Department of Sport, Exercise and Rehabilitation, Faculty of Health and Life Sciences, Northumbria University, Newcastle-upon-Tyne, UK

Tel: 0044+ 0191 243 7018

Email: matthew.campbell@northumbria.ac.uk

Running title: Intermittent vs continuous running exercise in T1DM

Key words: T1DM, post-exercise hypoglycaemia, intermittent running

Abstract

AIM: To compare the glycaemic and metabolic responses to simulated intermittent games activity and continuous running exercise in T1DM. **METHODS:** Nine patients (7 male, 2 female; 35±4 years; HbA1c 8.1±0.2% / 65±2 mmol.mol^{-1}) treated on a basal-bolus regimen completed two main trials, a continuous treadmill run (**CON**) or an intermittent running protocol (**INT**). Patients arrived to the laboratory fasted at ~08:00 h, replicating their usual pre-exercise meal and administering a 50% reduced dose of rapid-acting insulin before exercising. Blood glucose (BG), K$^+$, Na^{++}, pH, triglycerides, serum cortisol and NEFA were measured at baseline and for 60 minutes post-exercise. Interstitial glucose was measured for a further 23 hours under free-living conditions. **RESULTS:** Following exercise, BG declined under both conditions but was less under **INT** (**INT** -1.1±1.4 vs. **CON** -5.3±0.4 mmol.l^{-1}, p=0.037) meaning more patients experienced hypoglycaemia (BG≤3.5mmol.l^{-1}; **CON** n=3 vs. **INT** n=2) but less hyperglycaemia (BG≥10.9 mmol.l^{-1}; **CON** n=0 vs. **INT** n=6) under **CON**. Blood lactate was significantly greater, and pH lower, with a temporal delay in K$^+$ under **INT** (p<0.05). No conditional differences were observed in other measures during this time, or in interstitial glucose concentrations during the remaining 23 hours after exercise. **CONCLUSIONS:** Simulated games activity carries a lower risk of early, but not late-onset hypoglycaemia than continuous running exercise in T1DM.

Introduction

Despite recommendations from the American College of Sports Medicine (2009), performance of continuous or prolonged aerobic based exercise carries with it a heightened risk of hypoglycaemia in patients with type 1 diabetes (T1DM) (Rabasa-Lhoret et al. 2001; West et al. 2010; Campbell et al. 2013). This not only has potentially dangerous implications (Brazeau et al. 2008), but also discourages individuals wishing to exercise (Brazeau et al. 2008) and reduces long-term adherence to exercise programs that might convey health benefits (Perkins and Riddell 2006).

Not all forms of exercise acutely lower blood glucose however, meaning some types of exercise carry a lower risk of hypoglycaemia (Fahey et al. 2012). High-intensity exercise often causes an acute increase in blood glucose concentrations in patients with T1DM (Marliss and Vranic 2002; Fahey et al. 2012), and the inclusion of this type of activity in an intermittent form (i.e. short bursts of high intensity exercise interspersed with moderate intensity aerobic exercise) has been demonstrated to abate the risk of hypoglycaemia early after exercise (Guelfi et al. 2005; Bussau et al. 2006; Bussau et al. 2007; Guelfi et al. 2007).

From a practical perspective, much of the work in this area was designed to simulate the demands of team games such as soccer, rugby and hockey by creating exercise patterns in controlled laboratory environments (Guelfi et al. 2005; Bussau et al. 2006; Bussau et al. 2007; Guelfi et al. 2007; Iscoe and Riddell 2011). A major limitation of much of this research is the predominant use of cycling as an exercise modality (Guelfi et al. 2005; Bussau et al. 2006; Bussau et al. 2007; Guelfi et al. 2007; Iscoe and Riddell 2011). Cycling fails to adequately replicate the physiological demands of games-type activities in which repeated changes in speed *and* direction are a major component. Cycling involves primarily concentric muscle actions (Bijker et al. 2002) meaning the muscle shortens as it contracts, whereas in the majority of intermittent game-type activities, which typically involve running, a significant proportion of eccentric muscle action occurs, where the muscle lengthens during contraction. This is a particularly important consideration for individuals with T1DM, as eccentric muscle actions have the potential to hinder insulin action and glucose uptake following exercise (Asp et al. 1995). In addition, eccentric-based intermittent shuttle-running exercises which incorporate vast changes in speed and direction have been demonstrated to induce severe muscle soreness and muscular

dysfunction (Bailey et al. 2007). Indeed, sprinting exercise has previously been observed as a primary mechanism of injury (Hawkins et al. 2001; Woods et al. 2004); the frequency of speed changes places greater emphasis on the acceleration and deceleration phases of the running cycle, thus applying more eccentric load than conventional cycling based sprinting protocols (Greig and Siegler 2009).

Furthermore, the observation window in many studies investigating intermittent exercise is typically short (< 3 hours) (Guelfi et al. 2007; Harmer et al. 2007). A recent study conducted by Iscoe and Riddell (Iscoe and Riddell 2011) demonstrated that intermittent cycling exercise was associated with a reduction in late onset post-exercise hypoglycaemia. However, in light of the afore limitations, the glycaemic and metabolic demands of intermittent *cycling* exercise may not be directly transferable to games-like activities, thus limiting the application of current research investigating intermittent exercise.

Clearly, the inclusion of intermittent exercise has favorable effects for reducing the occurrence of hypoglycaemia. However, many investigations demonstrating a preservation of glycaemia and a reduced risk of hypoglycaemia are often compromised by poor ecological validity. Therefore, it would be prudent to measure the glycaemic and metabolic effects of intermittent *running* early, and also late after exercise. Therefore the aim of the present study was to examine and compare the acute and 24 hour post-exercise glycaemic and metabolic responses to intermittent running exercise which closely simulates team and games-play activity, and continuous moderate-intensity exercise, in type 1 diabetes patients.

Materials and methods

Following local research ethics committee approval, nine T1DM patients (seven males and two females, [mean±SEM] age 35 ± 4 years, mass 84.1 ± 3.9 kg, height 177 ± 3 cm, BMI 26.8 ± 1.1 $kg.m^{-2}$, HbA_{1c} 8.1 ± 0.2 % / 64.8 ± 2.3 $mmol.l^{-1}$, VO_{2peak} 41.8 ± 1.6 $ml.kg^{-1}.min^{-1}$) were recruited to participate in this study. Patients were eligible if treated on a basal bolus regimen composed of slow-acting insulin glargine (n=8) or detemir (n=1), and fast-acting insulin analogues aspart (n = 7) or lispro (n = 2) for a minimum of 6 months, with a duration of diabetes >2 years on enrollment. Patients were habitually active and regularly exercising (3 times per week for 30 minutes or more), familiar with carbohydrate counting, free of any diabetes related

complications, and not receiving any other medication other than insulin (both females were taking progesterone only oral contraception).

Having provided full written informed consent, patients attended two preliminary laboratory visits before completing 2 main trials, a continuous treadmill run (**CON**), or an intermittent running protocol (**INT**). On visit 1, peak cardiorespiratory parameters were collected during the completion of an incremental-maximal treadmill run protocol. This was used to determine the speed to be undertaken by patients during **CON**. The treadmill exercise test started at a velocity of 8 $km.hr^{-1}$ increasing 1 $km.hr^{-1}$ every three minutes as described previously (West et al. 2010; West et al. 2011; Campbell et al. 2013). During this visit, anthropometric variables were also collected (stature, weight, BMI). Following this, patients returned to the laboratory to complete a multistage fitness test (MSFT), as per Ramsbottom et al (1988). The performance during this test was used to calculate appropriate running speeds for **INT**. During this visit, patients completed 30 minutes of the intermittent exercise protocol for familiarization. Visits 3 and 4 were experimental trials (INT or CON) conducted in a random and counter-balanced fashion.

Prior to their arrival to the laboratory for each main trial, patients were fitted with a continuous glucose monitoring system (CGMS® System Gold™, Medtronic Minimed, Northridge, CA, USA). Interstitial glucose concentrations were obtained for 23 hours following their discharge from the laboratory, and during this time patients were instructed to adhere to similar diets. Both main trials were conducted on a morning ~08:00 h with patients replicating their trial start time. Patients arrived to the laboratory having fasted overnight replicating their dietary intake (assessed using weighed dietary recording sheets) in the previous 24 hours. Additionally, patients were instructed to maintain their normal insulin regimen with basal insulin dose (dose, injection site, and time of injection) standardised across trials. Patients were required to abstain from exercise during the preceding 48 hours and maintain similar activity patterns between trials. Upon arrival, patients replicated their usual pre-exercise meal, and administered a 50% reduction in their typical rapid-acting insulin dose (1.6 ± 1.2 IU). Following this, patients were seated whilst a 21-gauge cannula (Vasofix; B.Braun Melsungen AG, Melsungen, Germany) was inserted into the anti-cubital vein of their non-dominant arm. The trials began when participants displayed BG values in the range of 7-12 $mmol.l^{-1}$ (Perry and Gallen 2009). Following a pre-exercise resting venous blood sample (10 ml), patients performed either the **CON** or **INT**

exercise protocol, with subsequent blood samples at 0, 5, 15, 30 and 60 minutes post-exercise. Blood samples were collected in serum separation tubes, with 300 μl removed for the immediate quantification of blood glucose, lactate, potassium (K^+), sodium (Na^{++}) as well as hematocrit (GEM premier 3000; Instrumentation laboratory, Werfen Group, Spain), and hemoglobin (Hemocue AB, Sweden) which were used to correct for changes in plasma volume changes (Dill and Costill 1974). An aliquot of 1 ml was placed on ice and measured for blood pH. The remaining sample was centrifuged for 15 minutes at 3000 rev.min^{-1} before being stored at -80˚C for the subsequent analysis of cortisol (Cortisol, Cobas-Roche, UK), triglycerides (Triglycerides GPO-PAP, Cobas-Roche, UK), and NEFA (NEFA-HR(2), Wako Chemicals, Germany).

The **CON** exercise protocol consisted of a 45 minute bout of treadmill running (Woodway, Germany) at 77.0 ± 2.5% VO$_{2peak}$, 8.3 ± 0.6 km.hr^{-1}. The **INT** exercise protocol consisted of patients performing 45 minutes of an intermittent running protocol (Loughborough Intermittent Shuttle Test; (Nicholas et al. 2000)) designed to simulate games play activity. During both exercise protocols breath-by-breath respiratory parameters (Metamax 3B; cortex, Germany) and heart rate (S810; Polar, Finland) were recorded continuously throughout. Hypoglycaemia was defined as a blood glucose concentration of ≤ 3.5 mmol.l^{-1} and hyperglycaemia ≥ 10.9 mmol.l^{-1} (Yardley et al. 2012). If patients experienced hypoglycaemia during their laboratory stay, a 20 g carbohydrate bolus was administered (Lucozade; GlaxoSmithKline, UK).

Statistical analysis was performed using SPSS software (version 13; SPSS Inc; USA). Data is presented as mean ± SEM, with statistical significance set at $p < 0.05$. A repeated-measures ANOVA on two levels (condition x time) was conducted, with Bonferroni-corrected pairwise comparisons and paired samples Student t tests used to examine time and condition effects, respectively.

Results

On the day of the trial, dietary patterns were similar, with no differences in total energy intake (**CON** 2249 ± 110 vs. **INT** 2130 ± 128 kcal, $p = 0.750$), with percentage contribution from carbohydrate (**CON** 53 ± 3.3 vs. **INT** 54 ± 3.9 %, $p = 0.619$), fat (**CON** 29 ± 2.8 vs. **INT** 31 ± 3.6 %, $p = 0.401$), and protein (**CON** 17.5 ± 1.8 vs. **INT** 14.5 ± 1.3 %, $p = 0.167$), similar between conditions.

The blood glucose responses are presented in Figure 1. There was a significant time effect (p <0.001, partial-η^2 = 0.559) and a significant condition X time interaction (p = 0.004, partial-η^2 = 0.375) for absolute blood glucose concentrations. Fasting and rested blood glucose was similar between conditions (**CON** 10.6 ± 0.9 vs. **INT** 11.2 ± 0.7 mmol.l^{-1}, p = 0.648). Exercise induced a drop in blood glucose from resting concentrations under both **CON** and **INT** (Figure 1). The decline in blood glucose following exercise was significantly less under **INT**, (**INT** -1.1 ± 1.4 vs. **CON** -5.3 ± 0.4 mmol.l^{-1}, p = 0.037), despite patients exercising at a similar %VO$_{2peak}$ (**CON** 77.0 ± 2.5 vs. **INT** 77.6 ± 4.6 %VO$_{2peak}$, p = 0.829) and HR (**CON** 157 ± 4 vs. **INT** 159 ± 2 bpm). During the post-exercise period, blood glucose AUC was on average greater, but not significant, under **INT** (**INT** 1604 ± 74 vs. **CON** 1093 ± 54 mmol.l^{-1}.min^{-1}, p = 0.112). Resultantly, more patients under **CON** experienced hypoglycaemia (blood glucose ≤ 3.5mmol.l^{-1}; **CON** n = 3 vs. **INT** n = 2). Inversely, fewer patients under **CON** experienced hyperglycaemia (blood glucose ≥ 10.9 mmol.l^{-1}; **CON** n = 0 vs. **INT** n = 6).

Blood lactate was significantly higher under **INT** for 60 minutes post-exercise (Figure 2; Table 1). Blood pH concentrations were significantly lower under **INT** for 30 minutes post-exercise (Table 1). The serum cortisol, triglycerides, NEFA, blood potassium and sodium responses are presented in table 1.

No conditional differences were observed in interstitial glucose concentrations during the remaining 23 hours after exercise, with mean interstitial glucose (**CON** 9.1 ± 0.8 vs. **INT** 8.6 ± 0.6 mmol.l^{-1}, p = 0.715), and total average time spent in hypoglycaemic (**CON** 157 ± 59 vs. **INT** 223 ± 55 mins, p = 0.808) and hyperglycaemic ranges (**CON** 693 ± 140 vs. **INT** 684 ± 93 mins, p = 0.982) similar between conditions. Additionally, no conditional differences were observed between the average maximum (**CON** 15.7 ± 1.3 vs. **INT** 17.1 ± 0.8 mmol.l^{-1}, p = 0.674) or minimum interstitial glucose concentrations (**CON** 3.2 ± 0.4 vs. **INT** 2.6 ± 0.1 mmol.l^{-1}, p = 0.729) or the total number of patients experiencing hypoglycaemia **INT** (n = 6) compared to **CON** (n = 6).

INSERT FIGURE 1

INSERT FIGURE 2

INSERT TABLE 1

Discussion

This study demonstrates for the first time that intermittent running exercise designed to closely simulate team and games-play activity, carries a lower risk of early post-exercise hypoglycaemia than continuous moderate-intensity exercise in individuals with type 1 diabetes. Beyond this time however, patients, under free-living conditions, remain at risk from hypoglycaemia irrelevant of exercise modality.

Both types of exercise were performed at a similar intensity, which was largely aerobic (**CON** 77.0 ± 2.5 vs. **INT** 77.6 ± 4.6 %VO_{2peak}), and with no incidences of hypoglycaemia during either condition. Despite this, the fall in blood glucose immediately following exercise was significantly less under **INT**, measured as a change from rest, with a greater preservation of glycaemia for 60 minutes post-exercise under this condition. As such, all patients were protected from hypoglycaemia for up to 1 hour post-exercise under **INT**. Conversely, blood glucose under **CON** tended to be lower and resulted in 66% of patients experiencing at least one hypoglycaemic episode during this time.

Intermittent exercise consists of repeated bouts of intense activity (> 80% of VO_{2peak}) interspersed with periods of rest or moderate-intensity exercise. During intense activity there is a marked increase in catecholamine release (Purdon et al. 1993; Sigal et al. 1994; Guelfi et al. 2005; Bussau et al. 2006; Guelfi et al. 2007), which mediates a pronounced increase in glucose production (Marliss and Vranic 2002) largely through stimulation of muscle glycogenolysis (Purdon et al. 1993; Sigal et al. 1994). Importantly, the metabolic responses during each intense bout are additive when recovery intervals are short (Bogardus et al. 1981), meaning that in the present study there would likely be insufficient time for full clearance of catecholamines from

the circulation which have a half-life of ~2-3 minutes in plasma (Goldstein et al. 2003). In contrast, moderate-intensity exercise achieves only modest increases in catecholamine concentrations in healthy and T1DM individuals (West et al. 2011). Resultantly, the deficit between glucose uptake and glucose production is much narrower during intense exercise, meaning there is generally a lower rate of net glucose loss from the circulation during intermittent exercise compared to continuous moderate-intensity exercise. Indeed it is this which makes intermittent exercise an attractive strategy for preventing hypoglycaemia in T1DM patients. Although we did not measure catecholamines during this study, responses to high-intensity exercise are known to be comparable (Purdon et al. 1993; Sigal et al. 1999) or slightly attenuated (Purdon et al. 1993; Sigal et al. 1994) in individuals with T1DM. Moreover, cortisol another counter-regulatory hormone was significantly elevated from rest for 60 minutes post exercise under **INT**. If patients experienced similar increases in catecholamines, this would offer a likely explanation towards the attenuation in the decline in blood glucose over the 1 hour post-exercise period under **INT** and the avoidance of hypoglycaemia under this condition (Yuen et al. 2013). In addition, a recent study by Adolfsson and colleagues (2012) demonstrated that growth hormone was 2.5-fold higher during, and 10-fold higher 30 minutes after intermittent exercise than responses to endurance exercise in T1DM patients. It is possible that growth hormone (GH) secretion differed between both conditions, and may have potentiated the preservation of glycaemia under **INT** (Yuen et al. 2013).

In our study blood lactate concentrations were 10-fold greater under **INT** following the cessation of exercise, and remained significantly elevated from baseline for 60 minutes post-exercise. It has previously been demonstrated that intermittent cycling increases blood lactate levels during and up to 40 minutes after exercise in individuals with type 1 diabetes (Purdon et al. 1993; Sigal et al. 1994; Bussau et al. 2006; Bussau et al. 2007; Guelfi et al. 2007). Although we are unaware of published data describing blood lactate responses to intermittent running exercise in this patient cohort, similar intermittent shuttle running protocols performed in healthy non-diabetic individuals demonstrate an 8-fold increase in blood lactate concentrations post-exercise (Nicholas et al. 2000). Because elevated lactate levels could serve to increase gluconeogenesis (Consoli et al. 1990; Bussau et al. 2007), we postulate that elevations in lactate concentrations could be a contributing factor to the attenuated decline in glucose during the 60 minutes post-

exercise as it is likely catecholamine concentrations would have returned to baseline after ~20 minutes (Marliss and Vranic 2002).

Whatever the exact mechanism(s) behind our findings, our results indicate intermittent *running* exercise carries a lower risk of early-onset hypoglycaemia than continuous moderate-intensity exercise. In comparison to *cycling* exercise models (Guelfi et al. 2005; Iscoe et al. 2006; Guelfi et al. 2007), the decline in blood glucose following intermittent *running* exercise was less pronounced in our study than previously reported following *cycling* based protocols (Guelfi et al. 2005; Iscoe et al. 2006; Guelfi et al. 2007). This is an important finding that has not been demonstrated previously and suggests that patients engaging in games-type activity may be at a lower risk of early-onset hypoglycaemia than following laboratory-based intermittent cycling.

Increases in lactate concentrations indicate that the exercised muscle is unable to oxidize all of the pyruvate generated by glycolysis via the tricarboxylic acid cycle (Marliss and Vranic 2002). As pH is negatively related to lactate concentrations (Richardson et al. 1998), it is unsurprising that patients under **INT** experienced an increase in acidity (pH significantly lower under **INT**, *p* <0.05); this was accompanied by increased blood K^+ concentrations immediately following exercise, resulting from skeletal Na^{++}- K^+ pump mechanisms. Importantly, shortly following exercise we witnessed a significant conditional drop in K^+ under **INT**. In addition, the temporal restoration of K^+ was not complete until 60 minutes post-exercise under **INT**. This is likely due to an increase in sensitivity of the Na^{++}- K^+ pump to intracellular Na^{++}, as in our study Na^{++} was unchanged between conditions.

The finding that there is a temporal delay in the restoration of K^+ concentrations following intermittent running exercise is particularly important. In the short period following intense exercise (generally termed the vulnerable period) individuals may be at a greater risk of cardiac arrhythmias and grand-mal seizures, in which hypokalemia (2.5 – 3.0 $mmol.l^{-1}$) causes hyperpolarization in the myocytes' resting membrane potential and delayed ventricular repolarization which can provoke cardiac arrhythmias (Young et al. 1992). Although we witnessed only modest changes in blood acidity and K^+, concentrations remained greater than that deemed hypokalemic (< 3.6 $mmol.l^{-1}$; (Gennari 1998)), one must be circumspect when extrapolating these findings across different studies, and to a larger number of individuals, who may be less fit, at a greater risk of diabetes complications and predisposed to cardiac

arrhythmias; HbA_{1c}, hypertension, distal symmetrical polyneuropathy, retinopathy, and exposure to hyperglycaemia have all been shown to be risk factors for developing abnormalities in cardiac function (Vinik and Ziegler 2007). In addition, elevations in K^+ may be further exacerbated by medications such as ACE inhibitors and some diuretics which are known to increase serum K^+ and are commonly prescribed to T1DM patients. Thus, some patients may experience a greater exchange of potassium and may be more susceptible to cardiac arrhythmias following intermittent running-based exercise.

Once patients left the laboratory at 1 hour post-exercise, glycaemia was measured for a further 23 hours under free-living conditions. Our results revealed that patients under both conditions experienced hypoglycaemia during this period. With 67% of patients in hypoglycaemic ranges across trials one form of exercise was no less of a risk than another. Previous work from our group has demonstrated that there is a need to reduce post-exercise rapid-acting insulin dose following continuous moderate-intensity exercise so that glycaemia is preserved and hypoglycaemia prevented for up to 8 hours post-exercise (Campbell et al. 2013). We postulated that the increased uptake of blood glucose during that study was due to patients administering a second full or unchanged dose of insulin during the evening. With this in mind, it may be necessary for patients performing intermittent running exercise to reduce their post-exercise rapid-acting insulin dose. However, dose adjustments are yet to be determined for this exercise modality.

Perspective

This is the first study to investigate the glycaemic and metabolic responses of intermittent running exercise, which closely simulates games-type activity, for comparison with continuous running exercise in type 1 diabetes patients. In conclusion, our data demonstrate that there is a lower risk of early-onset hypoglycaemia following intermittent running exercise that closely simulates team and games-play activity, than continuous running exercise. We postulate that the attenuation in blood glucose early (≤ 1 hour) after intermittent exercise is achieved by increases in counter-regulatory hormones and gluconeogenic substrates induced by this specific exercise modality. However, patients remain at risk from hypoglycaemia late after exercise irrelevant of the type of exercise performed. The declines in glycaemia during this time are suggested to be due to patients administering full or unchanged doses of rapid-acting insulin with their meal after

exercise. We recommend future studies investigate manipulating the dose of rapid-acting insulin to be administered with the meal after intermittent running exercise.

Acknowledgements

References

Adolfsson P, Nilsson S, Albertsson-Wikland K and Lindblad B. Hormonal response during physical exercise of different intensities in adolescents with type 1 diabetes and healthy controls. *Pediatric diabetes*. (2012) 13: 8: 587-596.

Asp S, Kristiansen S and Richter EA. Eccentric muscle damage transiently decreases rat skeletal muscle GLUT-4 protein. *Journal of Applied Physiology*. (1995) 79: 4: 1338-1345.

Bailey D, Erith S, Griffin P, Dowson A, Brewer D, Gant N and Williams C. Influence of cold-water immersion on indices of muscle damage following prolonged intermittent shuttle running. *Journal of Sports Sciences*. (2007) 25: 11: 1163-1170.

Bijker K, De Groot G and Hollander A. Differences in leg muscle activity during running and cycling in humans. *European Journal of Applied Physiology*. (2002) 87: 6: 556-561.

Bogardus C, LaGrange BM, Horton ES and Sims E. Comparison of carbohydrate-containing and carbohydrate-restricted hypocaloric diets in the treatment of obesity. Endurance and metabolic fuel homeostasis during strenuous exercise. *Journal of Clinical Investigation*. (1981) 68: 2: 399.

Brazeau AS, Rabasa-Lhoret R, Strychar I and Mircescu H. Barriers to physical activity among patients with type 1 diabetes. *Diabetes Care*. (2008) 31: 11: 2108-2109.

Bussau V, Ferreira L, Jones T and Fournier P. A 10-s sprint performed prior to moderate-intensity exercise prevents early post-exercise fall in glycaemia in individuals with type 1 diabetes. *Diabetologia*. (2007) 50: 9: 1815-1818.

Bussau VA, Ferreira LD, Jones TW and Fournier PA. The 10-s Maximal Sprint A novel approach to counter an exercise-mediated fall in glycemia in individuals with type 1 diabetes. *Diabetes Care*. (2006) 29: 3: 601-606.

Campbell MD, Walker M, Trenell MI, Jakovljevic DG, Stevenson EJ, Bracken RM, Bain SC and West DJ. Large Pre-and Postexercise Rapid-Acting Insulin Reductions Preserves Glycemia and Prevents Early-but Not Late-Onset Hypoglycemia in Patients With Type 1 Diabetes. *Diabetes Care*. (2013) 36: 8: 2217-2224.

Consoli A, Nurjhan N, Reilly Jr J, Bier D and Gerich J. Mechanism of increased gluconeogenesis in noninsulin-dependent diabetes mellitus. Role of alterations in systemic, hepatic, and muscle lactate and alanine metabolism. *Journal of Clinical Investigation*. (1990) 86: 6: 2038.

Dill D and Costill DL. Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. *Journal of Applied Physiology*. (1974) 37: 247-248.

Fahey A, Paramalingam N, Davey R, Davis E, Jones T and Fournier P. The Effect of a Short Sprint on Postexercise Whole-Body Glucose Production and Utilization Rates in Individuals with Type 1 Diabetes Mellitus. *Journal of Clinical Endocrinology and Metabolism*. (2012) 97: 11: 4193-4200.

Gennari FJ. Hypokalemia. *New England Journal of Medicine*. (1998) 339: 7: 451-458.

Goldstein DS, Eisenhofer G and Kopin IJ. Sources and significance of plasma levels of catechols and their metabolites in humans. *Journal of Pharmacology and Experimental Therapeutics*. (2003) 305: 3: 800-811.

Greig M and Siegler JC. Soccer-specific fatigue and eccentric hamstrings muscle strength. *Journal of Athletic Training*. (2009) 44: 2: 180-184.

Guelfi K, Ratnam N, Smythe G, Jones T and Fournier P. Effect of intermittent high-intensity compared with continuous moderate exercise on glucose production and utilization in individuals with type 1 diabetes. *American Journal of Physiology-Endocrinology and Metabolism*. (2007) 292: 3: 865-870.

Guelfi KJ, Jones TW and Fournier PA. The decline in blood glucose levels is less with intermittent high-intensity compared with moderate exercise in individuals with type 1 diabetes. *Diabetes Care*. (2005) 28: 6: 1289-1294.

Harmer AR, Chisholm DJ, McKenna MJ, Morris NR, Thom JM, Bennett G and Flack JR. High-intensity training improves plasma glucose and acid-base regulation during intermittent maximal exercise in type 1 diabetes. *Diabetes Care*. (2007) 30: 5: 1269-1271.

Hawkins R, Hulse M, Wilkinson C, Hodson A and Gibson M. The association football medical research programme: an audit of injuries in professional football. *British Journal of Sports Medicine*. (2001) 35: 1: 43-47.

Iscoe KE, Campbell JE, Jamnik V, Perkins BA and Riddell MC. Efficacy of continuous real-time blood glucose monitoring during and after prolonged high-intensity cycling exercise: spinning with a continuous glucose monitoring system. *Diabetes Technology and Therapeutics*. (2006) 8: 6: 627-635.

Iscoe KE and Riddell MC. Continuous moderate-intensity exercise with or without intermittent high-intensity work: effects on acute and late glycaemia in athletes with Type 1 diabetes mellitus. *Diabetic Medicine*. (2011) 28: 7: 824-832.

Marliss EB and Vranic M. Intense Exercise Has Unique Effects on Both Insulin Release and Its Roles in Glucoregulation Implications for Diabetes. *Diabetes*. (2002) 51: 1: 271-283.

Nicholas CW, Nuttall FE and Williams C. The Loughborough Intermittent Shuttle Test: a field test that simulates the activity pattern of soccer. *Journal of Sports Sciences*. (2000) 18: 2: 97-104.

Perkins BA and Riddell MC. Type 1 diabetes and exercise: using the insulin pump to maximum advantage. *Canadian Journal of Diabetes*. (2006) 30: 1: 72-79.

Perry E and Gallen I. Guidelines on the current best practice for the management of type 1 diabetes, sport and exercise. *Practical Diabetes International*. (2009) 26: 3: 116-123.

Purdon C, Brousson M, Nyveen S, Miles P, Halter J, Vranic M and Marliss E. The roles of insulin and catecholamines in the glucoregulatory response during intense exercise and early recovery in insulin-dependent diabetic and control subjects. *Journal of Clinical Endocrinology and Metabolism*. (1993) 76: 3: 566-573.

Rabasa-Lhoret R, Bourque J, Ducros F and Chiasson JL. Guidelines for premeal insulin dose reduction for postprandial exercise of different intensities and durations in type 1 diabetic subjects treated intensively with a basal-bolus insulin regimen (ultralente-lispro). *Diabetes Care*. (2001) 24: 4: 625-630.

Ramsbottom R, Brewer J and Williams C. A progressive shuttle run test to estimate maximal oxygen uptake. *British Journal of Sports Medicine*. (1988) 22: 4: 141-144.

Richardson RS, Noyszewski EA, Leigh JS and Wagner PD. Lactate efflux from exercising human skeletal muscle: role of intracellular. *Journal of Applied Physiology*. (1998) 85: 2: 627-634.

Sigal R, Purdon C, Fisher S, Halter J, Vranic M and Marliss E. Hyperinsulinemia prevents prolonged hyperglycemia after intense exercise in insulin-dependent diabetic subjects. *Journal of Clinical Endocrinology and Metabolism*. (1994) 79: 4: 1049-1057.

Sigal RJ, Fisher SJ, Halter JB, Vranic M and Marliss EB. Glucoregulation during and after Intense Exercise: Effects ofβ-Adrenergic Blockade in Subjects with Type 1 Diabetes Mellitus. *Journal of Clinical Endocrinology and Metabolism*. (1999) 84: 11: 3961-3971.

Thompson WR, Gordon NF and Pescatello LS (2009). ACSM's guidelines for exercise testing and prescription, Hubsta Ltd.

Vinik AI and Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation*. (2007) 115: 3: 387-397.

West D, Morton R, Stephens J, Bain S, Kilduff L, Luzio S, Still R and Bracken R. Isomaltulose improves post-exercise glycemia by reducing CHO oxidation in T1DM. *Journal of Medicine and Science in Sports and Exercise*. (2011) 43: 2: 204-210.

West DJ, Morton RD, Bain SC, Stephens JW and Bracken RM. Blood glucose responses to reductions in pre-exercise rapid-acting insulin for 24 h after running in individuals with type 1 diabetes. *Journal of Sports Science*. (2010) 28: 7: 781-788.

West DJ, Stephens JW, Bain SC, Kilduff LP, Luzio S, Still R and Bracken RM. A combined insulin reduction and carbohydrate feeding strategy 30 min before running best preserves blood glucose concentration after exercise through improved fuel oxidation in type 1 diabetes mellitus. *Journal of Sports Science*. (2011) 29: 3: 279-289.

Woods C, Hawkins R, Maltby S, Hulse M, Thomas A and Hodson A. The Football Association Medical Research Programme: an audit of injuries in professional football—analysis of hamstring injuries. *British Journal of Sports Medicine*. (2004) 38: 1: 36-41.

Yardley JE, Kenny GP, Perkins BA, Riddell MC, Malcolm J, Boulay P, Khandwala F and Sigal RJ. Effects of Performing Resistance Exercise Before Versus After Aerobic Exercise on Glycemia in Type 1 Diabetes. *Diabetes Care*. (2012) 35: 4: 669-675.

Young DB, Srivastava TN, Fitzovich DE, Kivlighn SD and Hamaguchi M. Potassium and catecholamine concentrations in the immediate post exercise period. *The American Journal of the Medical Sciences*. (1992) 304: 3: 150-153.

Yuen K, Chong L and Riddle M. Influence of glucocorticoids and growth hormone on insulin sensitivity in humans. *Diabetic Medicine*. (2013) 30: 6: 651-663.

Tables

Table 1. The metabolic and hormonal responses to continuous versus simulated games type running exercise

		Rest	Exercise	0	5	15	30	60	Time	Time*Condition
Blood pH	CON.	7.38±0.01		7.42±0.01†	7.43±0.01†	7.42±0.01†	7.42±0.01†	7.40±0.01	$p < 0.001$	$p < 0.001$
	INT.	7.38±0.01		7.34±0.01*†	7.36±0.01*	7.39±0.01*†	7.40±0.01†	7.39±0.01		
Serum triglycerides **(nmol.l^{-1})**	CON.	1.16±0.18		1.34±0.22†	1.26±0.20	1.15±0.17	1.09±0.18	1.06±0.23	$p = 0.001$	$p = 0.156$
	INT.	1.23±0.24		1.35±0.27†	1.31±0.26	1.23±0.24	1.13±0.22	1.25±0.26		
Serum NEFA **(mmol.l^{-1})**	CON.	0.31±0.06		0.21±0.05†	0.53±0.11	0.53±0.13	0.44±0.11	0.43±0.07	$p = 0.001$	$p = 0.092$
	INT.	0.26±0.07		0.16±0.04†	0.40±0.10†	0.43±0.11	0.50±0.13	0.65±0.14		
Blood K$^+$ **(mmol.l^{-1})**	CON.	3.96±0.10		4.91±0.08†	4.24±0.08†	4.18±0.07†	4.10±0.09†	4.20±0.14	$p < 0.001$	$p < 0.001$
	INT.	4.21±0.12		4.65±0.21†	3.83±0.15*†	4.10±0.13*	4.19±0.13	4.51±0.19		
Blood Na^{++} **(mmol.l^{-1})**	CON.	135±0.45		140±0.60†	140±0.57†	139±0.65†	138±0.73†	137±0.67†	$p < 0.001$	$p = 0.369$
	INT.	134±0.98		139±1.16†	139±1.00†	138±0.91†	137±1.05†	135±1.31		
Serum cortisol **(nmol.l^{-1})**	CON.	1.03±0.10		1.35±0.13	1.48±0.15	1.59±0.18†	1.28±0.13	1.18±0.17	$p < 0.002$	$p = 0.264$
	INT.	1.34±0.26		1.99±0.26†	2.10±0.11†	2.10±0.11†	1.85±0.12†	1.60±0.14†		

NOTE: Data presented as mean ± SEM (n = 9). K$^+$ = blood potassium, Na^{++} = blood sodium. * indicates a statistically significant difference between **CON** and **INT**. † indicates a statistically significant difference from Rest. Statistical significance accepted at $p < 0.05$.

Figure legends

(1) Data presented as mean ± SEM. Circles = **CON**, squares = **INT**. Transparent sample point within a condition indicates significance difference from resting concentrations ($p < 0.05$). * indicates significantly different from **CON** ($p < 0.05$). Thatched area indicates exercise.

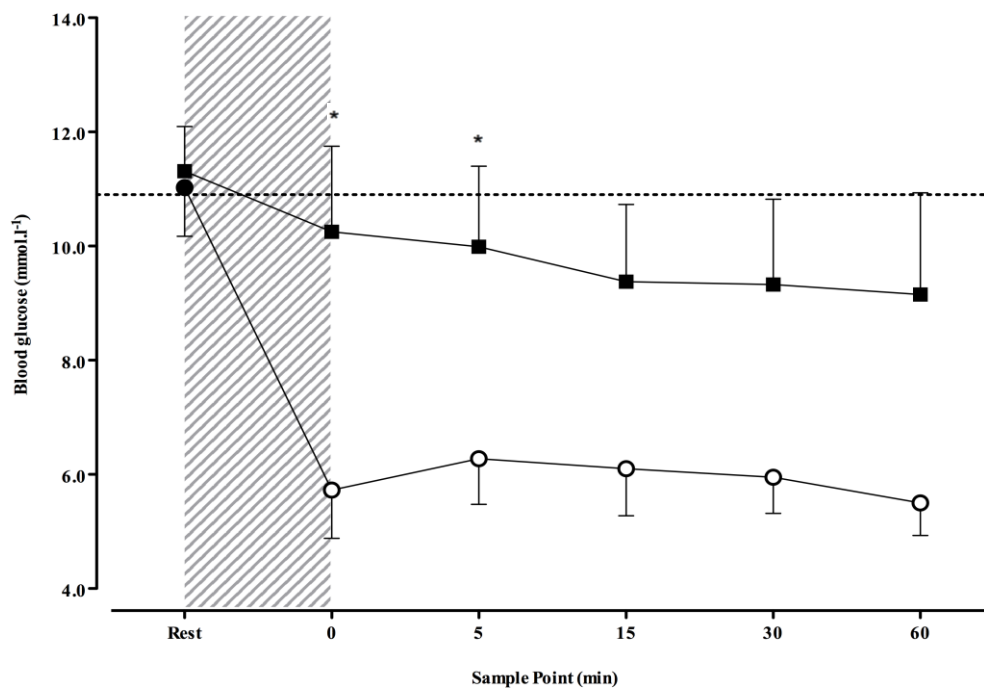**(2)** Data presented as mean ± SEM. Circles = **CON**, squares = **INT**. Transparent sample point within a condition indicates significance difference from resting concentrations ($p < 0.05$). * indicates significantly different from **CON** ($p < 0.05$). Thatched area indicates exercise.

Figures

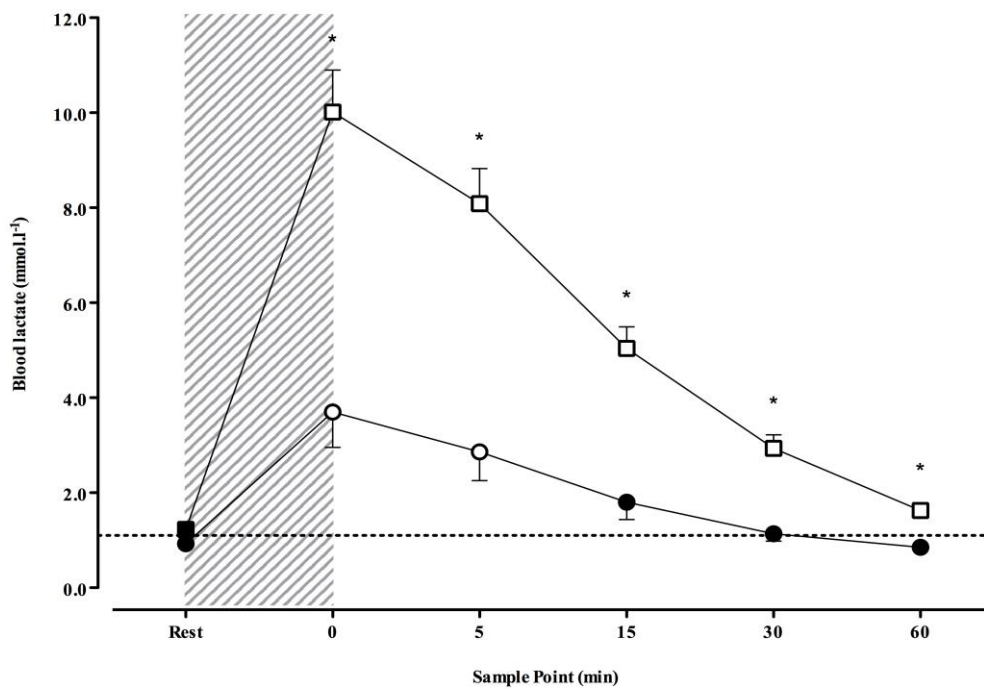**Figure 1.** Time course changes in glycaemia from rest.

Figure 2. Time course changes in blood lactate from rest.