A Low–Glycemic Index Meal and Bedtime Snack Prevents Postprandial Hyperglycemia and Associated Rises in Inflammatory Markers, Providing Protection From Early but Not Late Nocturnal Hypoglycemia Following Evening Exercise in Type 1 Diabetes

Matthew D. Campbell,[1] Mark Walker,[2] Michael I. Trenell,[2] Emma J. Stevenson,[1] Daniel Turner,[3] Richard M. Bracken,[3] James A. Shaw,[2] and Daniel J. West[1]

Diabetes Care 2014;37:1845–1853 | DOI: 10.2337/dc14-0186

OBJECTIVE

To examine the influence of the glycemic index (GI) of foods consumed after evening exercise on postprandial glycemia, metabolic and inflammatory markers, and nocturnal glycemic control in type 1 diabetes.

RESEARCH DESIGN AND METHODS

On two evenings (~1700 h), 10 male patients (27 ± 5 years of age, HbA_{1c} 6.7 ± 0.7% [49.9 ± 8.1 mmol/mol]) were administered a 25% rapid-acting insulin dose with a carbohydrate bolus 60 min before 45 min of treadmill running. At 60 min postexercise, patients were administered a 50% rapid-acting insulin dose with one of two isoenergetic meals (1.0 g carbohdyrate/kg body mass [BM]) matched for macronutrient content but of either low GI (LGI) or high GI (HGI). At 180 min postmeal, the LGI group ingested an LGI snack and the HGI group an HGI snack (0.4 g carbohdyrate/kg BM) before returning home (~2300 h). Interval samples were analyzed for blood glucose and lactate; plasma glucagon, epinephrine, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α); and serum insulin, cortisol, nonesterified fatty acid, and β-hydroxybutyrate concentrations. Interstitial glucose was recorded for 20 h postlaboratory attendance through continuous glucose monitoring.

RESULTS

Following the postexercise meal, an HGI snack induced hyperglycemia in all patients (mean ± SD glucose 13.5 ± 3.3 mmol/L) and marked increases in TNF-α and IL-6, whereas relative euglycemia was maintained with an LGI snack (7.7 ± 2.5 mmol/L, $P < 0.001$) without inflammatory cytokine elevation. Both meal types protected all patients from early hypoglycemia. Overnight glycemia was comparable, with a similar incidence of nocturnal hypoglycemia (n = 5 for both HGI and LGI).

CONCLUSIONS

Consuming LGI food with a reduced rapid-acting insulin dose following evening exercise prevents postprandial hyperglycemia and inflammation and provides hypoglycemia protection for ~8 h postexercise; however, the risk of late nocturnal hypoglycemia remains.

[1]Faculty of Health and Life Sciences, Northumbria University, Newcastle-upon-Tyne, U.K.
[2]Institute of Cellular Medicine, Newcastle University, Newcastle-upon-Tyne, U.K.
[3]Applied Sports, Technology, Exercise and Medicine Research Centre, College of Engineering, Swansea University, Swansea, U.K.

Corresponding author: Daniel J. West, d.j.west@northumbria.ac.uk.

Received 21 January 2014 and accepted 18 March 2014.

Clinical trial reg. no. NCT01794650, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-0186/-/DC1.

There is a growing evidence base surrounding the wide range of health benefits from regular exercise for type 1 diabetic patients (1). However, exercise remains the most frequently identified specific cause of severe hypoglycemia (2), the fear of which remains the primary obstacle to patients wishing to engage in regular exercise (3).

Strategies to combat exercise-induced hypoglycemia, such as manipulating exercise intensity (4), insulin dose, diet (5–7), or the order in which various exercise types are undertaken (8), have predominantly been tested for morning exercise (5–7). However, many individuals prefer to exercise in the evening because of study and work commitments or for social reasons. Unfortunately, exercise in the evening is associated with a greater risk of postexercise hypoglycemia (4,9), with low blood glucose levels likely to occur particularly nocturnally (2). Incorporation of evening exercise safely into the lives of people with type 1 diabetes is thus significantly hampered by the lack of appropriate evidence necessary for informed self-management strategies.

We recently demonstrated that mealtime insulin adjustment, specifically, reducing the dose of rapid-acting insulin before and after exercise, is vital to minimizing the risk of postexercise hypoglycemia (5). However, little advice currently exists on optimal carbohydrate types for patients with type 1 diabetes who exercise (1). American Diabetes Association guidance focuses on the quantity rather than on the composition of the carbohydrate to be consumed after exercise (10). Consumption of ~5 g carbohydrate per kilogram body mass (BM) is typically recommended for moderate-intensity exercise (11,12); however, the food composition is also an important consideration because the type of carbohydrate can exert a major influence on postprandial glycemia in diabetic patients (13). Meals containing identical macronutrient compositions are digested and absorbed at varying rates, producing a range of glycemic responses (14). Carbohydrate-rich foods with a low glycemic index (LGI) elicit a more gradual rise and fall in blood glucose levels compared with their high glycemic index (HGI) equivalents. As a result, more favorable postprandial glycemic profiles have been shown after ingestion of LGI foods in patients with type 1 diabetes (15–17).

Thus, optimizing postexercise glycemia may be possible by manipulating the composition of foods and drinks consumed during this time. The protracted absorption rates of LGI foods and drinks may be beneficial for reducing postprandial hyperglycemia. However, slower delivery of carbohydrates to postexercise musculature, and potentially slower rates of muscle glycogen replenishment following exercise (18,19), may increase the risk of postexercise hypoglycemia (11,20). Inversely, consuming HGI foods may promote accelerated muscle glycogen restoration (18,19), reducing the incidence of postexercise hypoglycemia (11,20). However, the need to reduce the insulin-to-carbohydrate ratio may be associated with postprandial hyperglycemia following ingestion of HGI foods (15,16), potentially leading to metabolic, hormonal, and inflammatory disturbances (21–23). The aim of the current study was to examine the influence of the glycemic index (GI) of a meal and subsequent bedtime snack consumed after evening exercise on postprandial glycemia, metabolism, and circulating inflammatory markers in addition to nocturnal glycemic control in type 1 diabetes.

RESEARCH DESIGN AND METHODS

Patients

Eligibility criteria were age 18–35 years; a duration of diabetes >2 years; an HbA_{1c} <8.0% (64 mmol/mol); an absence of diabetes-related complications, including impaired awareness of hypoglycemia; and insulin therapy alone without any other medication. Ten male patients with type 1 diabetes were recruited (mean ± SD age 27 ± 5 years, BMI 25.5 ± 0.9 kg/m^2, duration of diabetes 15 ± 6 years, HbA_{1c} 6.7 ± 0.7% [49.9 ± 8.1 mmol/mol], VO_{2peak} 52 ± 4 mL/kg/min). C-peptide was not measured. All patients had been treated on a stable basal-bolus regimen comprising insulin aspart and once-daily insulin glargine for a minimum of 6 months. Fifty percent of patients were injecting insulin glargine in the morning and 50% in the late evening or before bed. All patients undertook regular and consistent exercise (participating in aerobic-based exercise for at least 30 min at a time at least three times a week). All patients were familiar with carbohydrate counting, administering 1.0 ± 0.7 units of insulin aspart per 10 g of carbohydrate. All patients successfully completed the study.

Following approval from the local National Health Service Research Ethics Committee, fully informed written consent was obtained from all patients. Patients first attended the Newcastle National Institute for Health Research Clinical Research Facility exercise laboratory for a preliminary screening visit, as described by Campbell et al. (5), before returning on three more occasions. On visit 1, peak cardiorespiratory parameters were collected during the completion of an incremental–maximal treadmill run protocol, as previously described (5,6). Computer randomization was then used to determine the sequence of the two subsequent experimental visits.

Prelaboratory Phase

Continuous Glucose Monitoring

Patients were fitted with a continuous glucose monitor (CGM) (Paradigm Veo; Medtronic Diabetes, Northridge, CA) using an Enlite Sensor (Medtronic MiniMed; Northridge, CA) for a minimum of 48 h before attending the laboratory on each occasion. The Paradigm Veo provides real-time glucose profiles as part of an insulin pump. Patients did not use the continuous subcutaneous insulin infusion facility, however, but continued their usual basal-bolus regimen. Glucose alerts were set at ≤3.5 and ≥16 mmol/L during the pretrial period. The high glucose alert was discontinued once patients left the laboratory after the experimental trials. Sensors were placed in the posterolateral abdominal region to minimize the physiological time lag between blood and interstitial glucose (24). Insertion site was replicated across visits. During sensor wear, patients performed a minimum of four daily capillary blood glucose tests (GlucoMen LX; Menarini Diagnostics, Berkshire, U.K.), entering all values into the CGM device for calibration. Capillary glucose values and not CGM data were used to inform self-administered insulin aspart doses. Downloaded data were retrospectively processed and analyzed using CareLink Pro software (Medtronic Diabetes).

CGM data obtained from each patient were complete; there were no missing data streams in CGM recordings. The mean absolute difference between interstitial glucose and capillary blood glucose meter readings over both trials was 1.4 ± 1.1 mmol/L.

Diet and Activity Replication

Over the 24 h preceding main trial visits, patients replicated their diet (assessed using weighed dietary recording sheets) and were instructed to maintain their normal insulin regimen, with basal dose standardized (dose, injection site, and time of injection) across trials. During this time, patients used a pedometer (Omron Healthcare Europe B.V., Hoofddorp, the Netherlands) to record total step count. Avoidance of strenuous exercise was required in the previous 48 h, with maintenance of similar activity patterns between trials, which were separated by at least 7 days. On the day of the trial, patients were provided with two standardized meals, a cereal-based breakfast (sugar-coated corn flakes, semiskimmed milk, and peaches) equating to 1.3 g carbohdyrate/kg BM (549 ± 46 kcal) and a pasta-based lunch (pasta, tomato-based sauce, cheddar cheese, olive oil) equating to 1.3 g carbohdyrate/kg BM (968 ± 62 kcal). Meal composition was based on the habitual dietary patterns of patients with type 1 diabetes and current recommendations for exercise in diabetic patients (11,12). When combined with meals provided in the laboratory during experimental trials, total dietary intake across the day was calculated to constitute ~5.0 g carbohdyrate/kg BM, with a macronutrient content consisting of 77% carbohydrate, 12% fat, and 11% protein (11,12).

Testing Procedure

Patients arrived at the laboratory in the late afternoon (~1700 h), replicating their start time across conditions. A 12-mL resting venous blood sample was taken of which 20 μL was used for the immediate quantification of blood glucose and lactate (Biosen C-Line; EKF Diagnostic GmbH, London, U.K.) and 10 μL was analyzed for hemoglobin and hematocrit (Hemo Control; EKF Diagnostic GmbH) used to correct for changes in plasma volume (25). The remaining sample was measured by equal aliquots into lithium-heparin and serum (Vacuette; Greiner Bio-One GmbH, Kremsmünster, Austria) separation tubes; centrifuged for 15 min at 4,000 rpm at 4°C; and stored at −80°C for retrospective analysis of serum rapid-acting insulin analog (Invitron Insulin Assay; Invitron, Monmouth, U.K.) (see West et al. (6) for details of assay cross-reactivity), cortisol (Cortisol Parameter Assay Kit; R&D Systems, Roche Diagnostics, West Sussex, U.K.), nonesterified fatty acids by colorimetric assay (RANBUT; Randox Laboratories, London, U.K.), and β-hydroxybutyrate by D-3-hydroxybutyrate kinetic enzymatic assay (RANBUT, with a lower limit of detection of 0.004 mmol/L) and of plasma glucagon (Glucagon EIA; Sigma-Aldrich, St. Louis, MO), adrenaline (CAT ELISA; Eagle Biosciences, London, U.K.), interleukin-6 (IL-6) (Human IL-6 Quantikine ELISA; R&D Systems, Roche Diagnostics), and tumor necrosis factor-α (TNF-α) (Human TNF-α Quantikine ELISA; R&D Systems, Roche Diagnostics). The coefficient of variation was <10% for all biochemical analyses.

Immediately after the resting sample, patients were administered a 25% (2.0 ± 0.4 units) dose (i.e., a 75% reduction) of insulin aspart into the abdomen, with the injection site standardized across trials as equidistant between the iliac crest and naval based on current recommendations (5,6,26). Patients then consumed a pre-exercise carbohydrate bolus (sugar-coated corn flakes, semiskimmed milk, and peaches) equating to 1.0 g carbohdyrate/kg BM (423 ± 37 kcal) within a 5-min period (5).

Patients remained at rest for 60 min following consumption of the pre-exercise carbohydrate bolus. On 60 min, a blood sample was drawn immediately before commencing 45 min of treadmill (Woodway, Weil am Rhein, Germany) running at a speed calculated to elicit 70% of their VO_{2peak}, an intensity falling within recommendations of the American College of Sports Medicine (27) for diabetic patients who exercise. Breath-by-breath respiratory parameters (MetaLyzer 3B; CORTEX, Leipzig, Germany) and heart rate (S810; Polar, Kempele, Finland) were continuously recorded during exercise. Immediately following cessation of exercise, a blood sample was taken, with subsequent samples taken at 15, 30, and 60 min postexercise. At 60 min postexercise, patients were administered a 50% (4.0 ± 0.8 units) dose of insulin aspart into the contralateral abdominal site to the pre-exercise insulin aspart injection site (5). With this, in a random and counterbalanced fashion, patients were assigned to consume one of two evening meals calculated to be of either LGI or HGI. Following this meal, patients continued to rest with further blood samples taken every 30 min for 180 min. All patients then consumed a trial-specific bedtime snack of either LGI or HGI. Patients could drink water ad libitum throughout. All patients received transportation home and were instructed to continue their usual basal insulin dose and replicate sleeping patterns as best as possible across trials. Hypoglycemia was defined as a blood or interstitial glucose concentration of ≤3.9 mmol/L, and hyperglycemia was defined at ≥8.0 mmol/L (5).

Meal Composition and Bedtime Snack

All meals were preprepared by the research team and comprised food to elicit either an HGI or LGI response. The beverage component of the meal and bedtime snack contained either HGI maltodextrin or LGI isomaltulose (Palatinose; BENEO, Mannheim, Germany) and was calculated to be a 10% solution. We calculated the GI of each meal using methods described by Brouns et al. (28) in 10 nondiabetic control participants. Patients consuming the LGI evening meal subsequently consumed the LGI bedtime snack, and those consuming the HGI evening meal consumed the HGI snack. Both evening meals and bedtime snacks were matched for macronutrient content and palatability and had negligible fiber content (Supplementary Table 1). Bedtime snacks equated to 0.4 g carbohdyrate/kg BM (29).

Calculation of Substrate Oxidation

During exercise, at 15 min before the postexercise meal, and at 45, 105, and 165 min following the postexercise meal, expired gases were analyzed (MetaLyzer 3B). Substrate oxidation rates and energy expenditure were determined from VO_2 and CO_2 production values using stoichiometric equations (30).

Postlaboratory Period

While wearing a CGM, patients continued to self-record and replicate their

diet throughout both trials using a weighed food diary. Patients were required to report additional carbohydrate ingestion and administration of corrective doses of insulin aspart, and instructed to keep meal times as well as insulin aspart and insulin and glargine doses consistent across trials.

Data Analysis

Statistical analysis was performed using PASW Statistics 18 software (IBM, Armonk, NY). A repeated-measures ANOVA on two levels (condition and time) was conducted, with Bonferroni-corrected pairwise comparisons and paired sample *t* tests used to examine time and condition effects, respectively. Statistical significance was accepted at $P \leq 0.05$. Area under the curve was calculated using the methods described by Wolever and Jenkins (31).

RESULTS

Prelaboratory Phase

Glycemic control was comparable over the 24 h before the patients' arrival at the laboratory for both experimental trials (CGM mean glucose: HGI 7.9 ± 2.2 mmol/L, LGI 7.9 ± 2.2 mmol/L, P = 0.465; total interstitial glucose area under the curve: HGI 11,277 ± 3,208 mmol/L/min, LGI 10,971 ± 3,186 mmol/L/min, P = 0.215). Dietary intake was also similar during the 24 h before both trials. There were no differences in total energy consumed (HGI 2,143 ± 673 kcal, LGI 2,358 ± 668 kcal, P = 0.508), with similar contributions from carbohydrates (HGI 51 ± 11%, LGI 46 ± 10%, P = 0.896), fat (HGI 30 ± 9%, LGI 32 ± 11%, P = 0.301), and protein (HGI 20 ± 5%, LGI 22 ± 10%, P = 0.556). The total amount of insulin administered (HGI 26 ± 13 units, LGI 26 ± 14 units, P = 0.609) and levels of activity (HGI 6,949 ± 105 steps, LGI 7,041 ± 118 steps, P = 0.372) were comparable over the 24 h before each trial.

Laboratory Phase

There was a significant time effect ($P < 0.001$), condition effect (P = 0.05), and condition × time interaction for absolute blood glucose concentrations ($P < 0.001$) (Fig. 1). Blood glucose values were comparable before the standardized pre-exercise carbohydrate bolus and insulin injection and after the 1-h pre-exercise rest period during both experimental trials (Fig. 1). Serum insulin and all other hormone and metabolite levels were similar at rest and immediately before exercise ($P > 0.05$) (Fig. 2*A* and *B*, Table 1).

Patients exercised at a similar intensity (%VO_{2peak}: HGI 77 ± 0.09, LGI 74 ± 0.09, P = 0.352; peak heart rate: HGI 80 ± 6, LGI 79 ± 7, P = 0.631). Patients ran at a velocity of 10.1 ± 1.0 km/h, completing 7.6 ± 0.7 km and expending 718 ± 143 kcal. Similar peak lactate levels were elicited immediately postexercise (HGI 4.1 ± 2.4 mmol/L, LGI 4.2 ± 2.7 mmol/L, P = 0.137) (Table 1). Exercise induced a similar decrease in blood glucose from pre-exercise concentrations (HGI −5.4 ± 1.6 mmol/L, LGI −6.8 ± 1.3 mmol/L, P = 0.733) (Fig. 1), such that immediately following the cessation of exercise, blood glucose values were comparable to baseline under both conditions (P = 0.304) (Fig. 1). There were no incidences of hypoglycemia during exercise, with all patients completing the exercise protocol on both occasions. Immediately before the postexercise meal, serum insulin concentrations were similar to resting concentrations ($P > 0.05$) (Table 1), as were all other hormone, metabolite, and cytokine levels ($P > 0.05$) (Fig. 2*A–C*, Table 1).

Postexercise Intervention

Serum insulin peaked similarly at 60 min following the postexercise meal before declining under both conditions, with concentrations returning to resting values at 180 min ($P > 0.05$) (Table 1). Blood glucose levels increased over the 180 min after both postexercise meals, but this was significantly attenuated

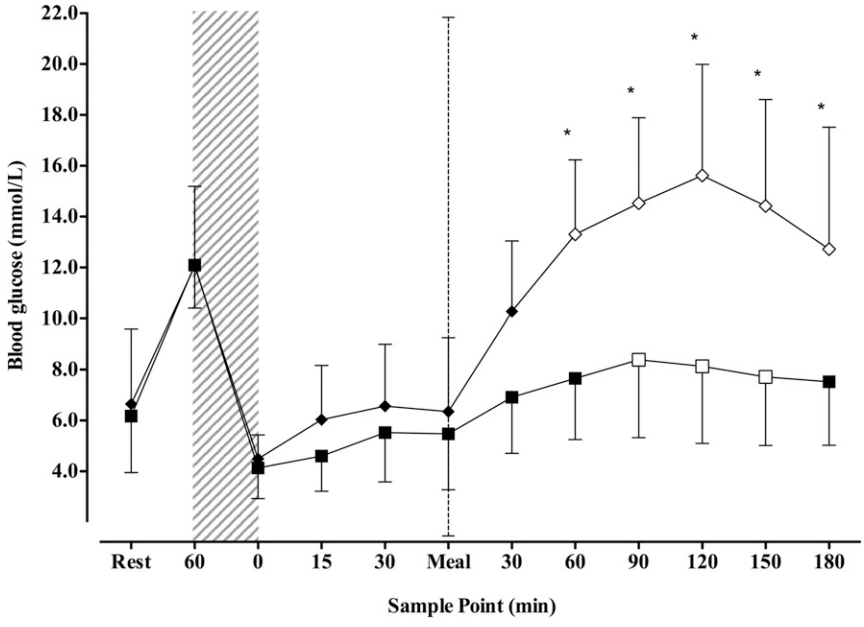

Figure 1—Time-course changes in blood glucose from rest, during exercise, and over 3 h postexercise. Data are presented as mean ± SD (error bars). ■, LGI; ◆, HGI; □ and ◇, significant difference from premeal concentrations ($P \leq 0.05$). *Significant difference between conditions ($P \leq 0.05$). Shaded area indicates exercise; dashed line indicates postexercise meal intervention. Note that the test meal and insulin were administered immediately following rest and 60 min postexercise.

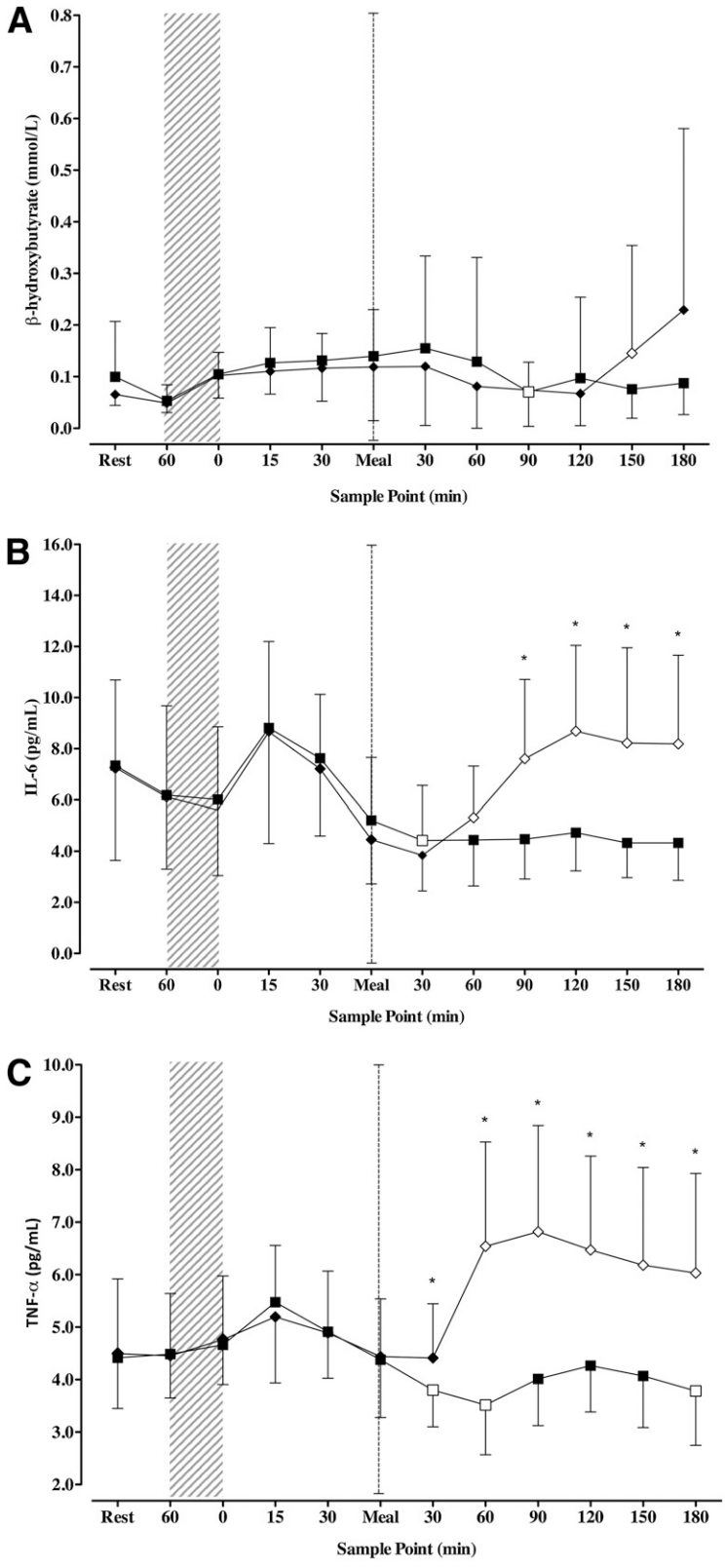

Figure 2—Time-course changes in serum β-hydroxybutyrate concentration (*A*), plasma IL-6 concentration (*B*), and plasma TNF-α concentration (*C*). Data are presented as mean ± SD (error bars). ■, LGI; ◆, HGI; □ and ◇, significant difference from premeal concentrations ($P \leq 0.05$). *Significant difference between conditions ($P \leq 0.05$). Shaded area indicates exercise; dashed line indicates postexercise meal intervention. Note that the test meal and insulin were administered immediately following rest and 60 min postexercise.

under LGI compared with HGI ($P < 0.05$) (Fig. 1). Over this time, all patients were protected from hypoglycemia under both conditions. However, all patients were exposed to hyperglycemia after the HGI meal, whereas this was limited to four patients after LGI. Moreover, hyperglycemia was less pronounced (mean peak blood glucose: LGI 8.8 ± 3.1 mmol/L, HGI 15.9 ± 3.8 mmol/L) and tended to be only transient (time spent while hyperglycemic: LGI 81 ± 43 min, HGI 165 ± 32 min) following the LGI meal. On leaving the laboratory, blood glucose remained significantly greater after the HGI meal (HGI 12.7 ± 4.8 mmol/L, LGI 7.5 ± 2.5 mmol/L, P = 0.004) (Fig. 1), with more patients leaving the laboratory hyperglycemic (n = 9 HGI; n = 4 LGI).

Counterregulatory hormonal and metabolic responses are presented in Table 1 with inflammatory cytokine and β-hydroxybutyrate responses shown in Fig. 2*A–C*. There were no differences in serum β-hydroxybutyrate concentrations between the two experimental trials ($P > 0.05$) (Fig. 2*A*). Following the postexercise meal, IL-6 and TNF-α concentrations significantly increased from rest and premeal concentrations in the HGI trial and were significantly greater than LGI during the postprandial period ($P < 0.05$) (Fig. 2*B* and *C*). During this period, concentrations in the LGI trial were significantly lower than baseline measures ($P < 0.05$) (Fig. 2*B* and *C*). There were no differences in substrate oxidation responses during the postexercise meal period of both trials, with carbohydrate (HGI 14.5 ± 4.1 g/h, LGI 14.7 ± 4.0 g/h, P = 0.927) and lipid (HGI 3.0 ± 01.2 g/h, LGI 3.1 ± 1.2 g/h, P = 0.809) oxidation rates similar.

Postlaboratory Phase

Late Evening

After leaving the laboratory, interstitial glucose concentrations in the HGI trial were significantly greater than LGI in the time before sleep (Fig. 3), with individualized mean peak interstitial glucose levels higher (HGI 18.3 ± 4.1 mmol/L, LGI 13.9 ± 2.5 mmol/L, P = 0.009).

Nocturnal Glycemic Control

During sleep, falling glucose levels were evident under both conditions such that concentrations became comparable 8 h after exercise ($P > 0.05$) (Fig. 3). Five

Table 1—Serum insulin counterregulatory hormonal and blood metabolite responses to postexercise meals of varying GIs

														ANOVA *P* value	
	Rest	60	Exer.	0	15	30	Premeal	30	60	90	120	150	180	T	T*C
Serum insulin (pmol/L)															
HGI	126 ± 47	137 ± 58		201 ± 112†	138 ± 62	128 ± 59	105 ± 49	179 ± 101‡	180 ± 97‡	143 ± 68‡	127 ± 69‡	95 ± 53	94 ± 56	<0.001	0.992
LGI	124 ± 52	150 ± 64		203 ± 108†	137 ± 64	125 ± 57	102 ± 42	172 ± 99‡	174 ± 97‡	144 ± 57‡	126 ± 54‡	105 ± 49	98 ± 47		
Plasma glucagon (pg/mL)															
HGI	730 ± 280	591 ± 286†		682 ± 316	760 ± 360	768 ± 383	833 ± 332	953 ± 437†	922 ± 437†	872 ± 410†	798 ± 399	690 ± 284‡	669 ± 286‡	<0.001	0.306
LGI	733 ± 290	611 ± 296†		658 ± 309	792 ± 369	818 ± 403	816 ± 355	947 ± 481†‡	937 ± 451†‡	907 ± 421†	862 ± 398	806 ± 340	840 ± 394		
Plasma adrenaline (nmol/L)															
HGI	0.09 ± 0.05	0.15 ± 0.10		0.55 ± 0.35†	0.35 ± 0.37†	0.15 ± 0.10	0.15 ± 0.12	0.17 ± 0.07	0.16 ± 0.11	0.11 ± 0.12	0.09 ± 0.06	0.11 ± 0.09	0.08 ± 0.08	0.013	0.497
LGI	0.08 ± 0.06	0.15 ± 0.08		0.54 ± 0.40†	0.28 ± 0.32†	0.14 ± 0.11	0.14 ± 0.12	0.15 ± 0.05	0.13 ± 0.10	0.11 ± 0.07	0.11 ± 0.06	0.10 ± 0.08	0.07 ± 0.05		
Serum cortisol (nmol/L)															
HGI	0.17 ± 0.09	0.18 ± 0.07		0.28 ± 0.06†	0.33 ± 0.13†	0.24 ± 0.09†	0.19 ± 0.08	0.14 ± 0.07	0.14 ± 0.08	0.13 ± 0.06‡	0.11 ± 0.05†‡	0.08 ± 0.03†‡	0.08 ± 0.05†‡	<0.001	0.099
LGI	0.17 ± 0.09	0.15 ± 0.05		0.24 ± 0.11†	0.32 ± 0.16†	0.23 ± 0.12†	0.18 ± 0.10	0.13 ± 0.06‡	0.12 ± 0.05‡	0.10 ± 0.04†‡	0.10 ± 0.05‡	0.10 ± 0.03‡	0.09 ± 0.04‡		
Serum NEFA (mmol/L)															
HGI	0.18 ± 0.15	0.12 ± 0.10		0.25 ± 0.19	0.35 ± 0.20†	0.43 ± 0.37†	0.53 ± 0.49†	0.37 ± 0.25	0.24 ± 0.20‡	0.24 ± 0.25‡	0.27 ± 0.36‡	0.27 ± 0.29‡	0.35 ± 0.43	0.011	0.514
LGI	0.27 ± 0.24	0.18 ± 0.10		0.27 ± 0.23	0.34 ± 0.23†	0.33 ± 0.24	0.39 ± 0.32†	0.39 ± 0.33†	0.27 ± 0.22	0.24 ± 0.16	0.24 ± 0.16	0.27 ± 0.18	0.30 ± 0.16		
Blood lactate (mmol/L)															
HGI	1.0 ± 0.7	1.1 ± 0.9		4.1 ± 2.4†	2.1 ± 1.5†	1.3 ± 1.1	1.0 ± 0.9	0.7 ± 0.6	0.9 ± 0.6	0.8 ± 0.4	0.7 ± 0.5	0.5 ± 0.4	0.4 ± 0.4†	0.001	0.129
LGI	0.9 ± 0.2	1.0 ± 0.6		4.2 ± 2.7†	1.7 ± 0.4	1.2 ± 0.3	1.0 ± 0.2	0.8 ± 0.2†	1.0 ± 0.3	1.1 ± 0.3	1.2 ± 0.2‡	0.6 ± 0.2	0.5 ± 0.2		

Data are mean ± SD. Test meal and insulin were administered immediately following rest and premeal sample points. Exercise commenced 60 min after rest. C, condition; Exer., exercise; NEFA, nonesterified fatty acid; T, time. *Significantly different between conditions ($P \leq 0.05$). †Significantly different from rest. ‡Significantly different from premeal.

patients during the LGI trial and five during the HGI trial experienced nocturnal hypoglycemia. Some patients experienced multiple bouts of hypoglycemia (n = 10 HGI; n = 8 LGI). Mean interstitial glucose nadir was similar between conditions (HGI 3.6 ± 1.9 mmol/L, LGI 3.4 ± 1.7 mmol/L, P = 0.650), as was time spent in hypoglycemic (P = 0.569), euglycemic (P = 0.705), and hyperglycemic (P = 0.765) ranges (Fig. 3).

Next-Day Glycemic Responses

On waking, interstitial glucose levels were comparable (HGI 8.5 ± 2.8 mmol/L, LGI 8.3 ± 2.8 mmol/L, P = 0.614) (Fig. 3), and glycemia remained similar between conditions for the remainder of the 24-h postexercise window ($P > 0.05$). During the postlaboratory period, total energy consumed (HGI 719 ± 256 kcal, LGI 686 ± 289 kcal, P = 0.774) was similar, with contribution from carbohydrate (HGI 72 ± 17%, LGI 64 ± 26%, P = 0.767), fat (HGI 20 ± 15%, LGI 22 ± 22%, P = 0.834), and protein (HGI 8 ± 10%, LGI 14 ± 19%, P = 0.548) also similar between conditions. Activity patterns for 24 h after exercise were comparable (HGI 6,086 ± 94 steps, LGI 6,478 ± 112 steps, P = 0.369).

CONCLUSIONS

The aim of this study was to determine whether manipulating the GI of foods and drinks consumed following evening exercise could modulate postprandial glycemia and metabolism to provide protection from postexercise hyperglycemia and hypoglycemia in patients with type 1 diabetes. To our knowledge, this study is the first to show that consumption of LGI food under conditions of reduced rapid-acting insulin dose after evening exercise improves postprandial glycemia, reducing hyperglycemia and concentrations of circulating inflammatory markers in combination with providing protection from hypoglycemia for ~8 h after exercise. However, beyond this time, risk of late-onset nocturnal hypoglycemia persists, regardless of the GI of the postexercise meal and bedtime snack.

We recently demonstrated the importance of reducing the rapid-acting insulin dose administered with the meal after as well as before exercise to extend the period of protection from postexercise hypoglycemia (5). Now, we demonstrate that under these conditions, the

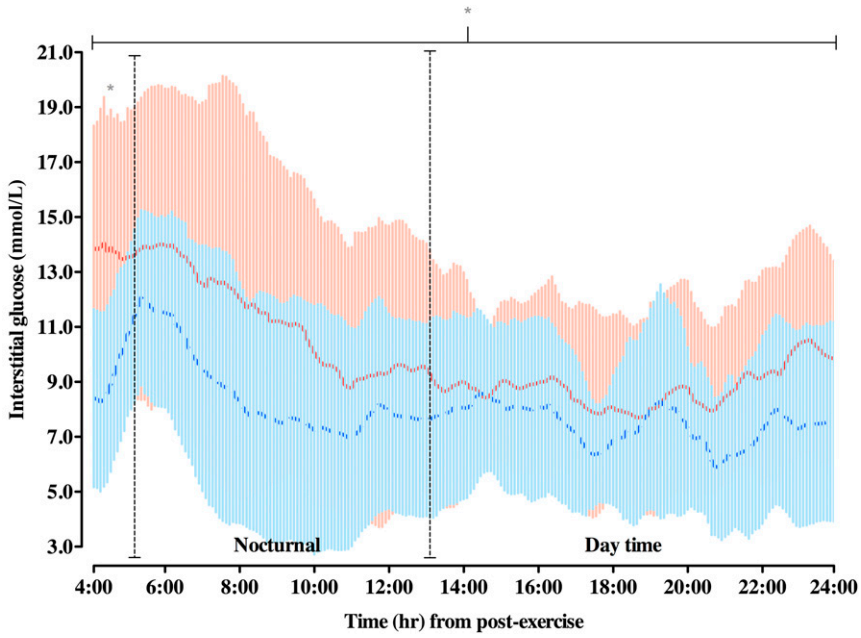

Figure 3—Time-course changes in interstitial glucose throughout the postlaboratory period. Data are presented as mean ± SD. Red trace, HGI; blue trace, LGI. *Interstitial glucose area under the curve is significantly different between conditions ($P \leq 0.05$). Vertical lines indicate nocturnal or daytime periods. End of nocturnal period indicates when patients awoke.

composition of the postexercise meal plays an important role in modulating postprandial glycemia. Blood glucose concentrations were significantly greater with the HGI than with the LGI postexercise meal and snack, consequently exposing all patients in the HGI condition to hyperglycemia during the laboratory observation period. Conversely, the incidence of hyperglycemia was reduced by 60% after the LGI condition (40%) versus the HGI condition (100%). Indeed, in the affected patients, hyperglycemia was less pronounced and tended to be only transient and short lasting after LGI meals. Despite clear postprandial differences in glycemia between the two conditions, all patients were still protected from hypoglycemia during their time in the laboratory. Presently, there are relatively few dietary guidelines to assist individuals with type 1 diabetes in managing postexercise glycemia. However, we have shown that by consuming an LGI postexercise meal and drink, postprandial hyperglycemia can be reduced without exposure to hypoglycemia. This observation is important because the aim of diabetes management is to normalize blood glucose concentrations (32), especially when incorporating exercise into patients' lives (1).

Given the potential for such large differences in postprandial glycemia with this strategy, we examined this impact on metabolic, hormonal, and inflammatory measures. This is important because regular exposure to metabolic, hormonal, or inflammatory disturbances could significantly influence long-term diabetes-related complications in patients who regularly exercise (26). Here, we show that meal GI has significant implications for postprandial circulating inflammatory markers; specifically, we demonstrate for the first time with nonclamp techniques and replication of free-living conditions that TNF-α and IL-6 were dramatically increased following an HGI meal. An otherwise comparable LGI meal completely prevented rises in these inflammatory cytokines. The clinical relevance of these findings should not be underestimated because offsetting hyperglycemia and inflammation is important for preventing early pathogenic diabetes-related complications (23). Additionally, β-hydroxybutyrate concentrations did not rise significantly during either condition (Fig. 2*A*), remaining similar to premeal and resting concentrations. Basal insulin dose remained unchanged, and despite a reduction in rapid-acting insulin dose, circulating insulin concentrations remained sufficient for a suppression in β-hydroxybutyrate production (33) and to drive ketone body disposal (34). Concentrations during both trial conditions were well below those deemed clinically significant (>1.0 mmol/L) (22).

When type 1 diabetic patients exercise in the evening, consumption of a carbohydrate-based snack before bed is recommended (29). Blood glucose was typically within the euglycemic range before the consumption of the bedtime snack following LGI but still hyperglycemic following HGI (LGI ~7.5 mmol/L, HGI ~12.2 mmol/L). Outside formal studies, patients within normal blood glucose range before bed often choose to raise blood glucose concentrations by consuming a carbohydrate-based snack (29) due to fear of nocturnal hypoglycemia (35). However, patients in the hyperglycemic range before bed may be tempted to administer corrective insulin units, which in an exercise-induced insulin-sensitized state (36,37) is likely to cause a rapid fall in glucose during the night. Avoidance of the bedtime snack, and hence missing a valuable source of carbohydrate before sleep, is likely to exacerbate the risk of nocturnal hypoglycemia. Despite large differences in blood glucose concentrations before bed following HGI and LGI in the current study, levels fell in both conditions, becoming comparable at 3 h after consuming the bedtime snack, with similar rates

of nocturnal hypoglycemia thereafter. This finding indicates the patients are at risk for late-onset nocturnal hypoglycemia despite the consumption of a bedtime snack, with a predicted nadir >8 h postexercise (5,9) and regardless of the GI of the snack or blood glucose levels before bed.

So that we could investigate the impact of the GI of evening meals and snacks, patients consumed enough carbohydrates (consuming 2.6 g/kg BM during the evening) to cover the cost of the bout of exercise, with patients using ~1.7 g/kg in total during exercise and with total daily carbohydrate intake matching current recommendations [~5.0 g/kg (11,12)], thus establishing a positive carbohydrate balance. Despite consuming sufficient carbohydrates for the recovery of muscle glycogen postexercise and perhaps even consuming more carbohydrate than is typical, hypoglycemia was still encountered late after exercise in the early hours of the morning. These findings direct attention toward the role of basal insulin administration in avoiding nocturnal hypoglycemia after evening exercise. Considering that once-daily insulin glargine administration is associated with a glucose nadir 4–14 h later (38,39), not only basal insulin dose but also the timing of administration may be of particular importance.

It is important to consider that the patients in this study were treated on a basal-bolus regimen; therefore, outcomes may differ in patients using continuous subcutaneous insulin infusion therapy. However, the strategies we used are likely to carry practical and useful implications, so we suggest that patients tailor these strategies according to their own treatment regimen and exercising habits. Indeed, this should not detract from the importance of the findings because this study shows for the first time that consuming LGI foods and drinks in tandem with reduced rapid-acting insulin dose following evening exercise can play an important role in normalizing glycemia, preventing postprandial hyperglycemia and inflammation, and protecting patients from postexercise hypoglycemia for up to 8 h. The clinical utility of these findings is clear because foods that patients habitually consume can be easily exchanged with foods that offer the same macronutrient content but are of an LGI (e.g., substituting particular types of breads, strains of rice, pastas, and potatoes or sports drinks with various carbohydrate compositions) to facilitate more desirable postprandial glycemic responses. However, it does not seem that carbohydrate type or total carbohydrate intake alone are factors in the development of late-onset hypoglycemia because patients may still be exposed to nocturnal hypoglycemia following evening exercise. Future research on basal insulin adjustment will determine whether late-onset nocturnal hypoglycemia following evening exercise can be avoided while harnessing the benefits of consuming LGI foods with a reduced rapid-acting insulin dose during the postexercise period.

Acknowledgments. The authors thank the study participants for their time, effort, and commitment and the research team at the National Institute for Health Research Clinical Research Facility, Newcastle University, for assistance.

Duality of Interest. This study was partially funded by BENEO. BENEO reserves the exclusive right to use the results and data for regulatory proceedings. Instant drink powders containing maltodextrin or isomaltulose (Palatinose) were specially developed for this study and produced by BENEO and Südzucker AG (Central Department Research, Development, and Technological Services). CGM equipment was provided by Medtronic Europe. Neither party had any role in the design of this study or the preparation of the manuscript. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. M.D.C. and D.J.W. contributed to the study concept and design, researched data, and wrote the manuscript. M.W. and J.A.S. contributed to participant recruitment and reviewed and edited the manuscript. M.I.T. and E.J.S. contributed to the data collection and reviewed and edited the manuscript. D.T. contributed to the CGM data analysis and reviewed and edited the manuscript. R.M.B. contributed to the CGM data analysis and preparation of the manuscript. D.J.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Chu L, Hamilton J, Riddell MC. Clinical management of the physically active patient with type 1 diabetes. Phys Sportsmed 2011;39:64–77
2. Taplin CE, Cobry E, Messer L, McFann K, Chase HP, Fiallo-Scharer R. Preventing postexercise nocturnal hypoglycemia in children with type 1 diabetes. J Pediatr 2010;157:784–788, e1
3. Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. Diabetes Care 2008;31:2108–2109
4. Davey RJ, Bussau VA, Paramalingam N, et al. A 10-s sprint performed after moderate-intensity exercise neither increases nor decreases the glucose requirement to prevent late-onset hypoglycemia in individuals with type 1 diabetes. Diabetes Care 2013;36:4163–4165
5. Campbell MD, Walker M, Trenell MI, et al. Large pre- and postexercise rapid-acting insulin reductions preserve glycemia and prevent early- but not late-onset hypoglycemia in patients with type 1 diabetes. Diabetes Care 2013;36:2217–2224
6. West DJ, Morton RD, Bain SC, Stephens JW, Bracken RM. Blood glucose responses to reductions in pre-exercise rapid-acting insulin for 24 h after running in individuals with type 1 diabetes. J Sports Sci 2010;28:781–788
7. West DJ, Stephens JW, Bain SC, et al. 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. J Sports Sci 2011;29:279–289
8. Yardley JE, Kenny GP, Perkins BA, et al. Resistance versus aerobic exercise: acute effects on glycemia in type 1 diabetes. Diabetes Care 2013;36:537–542
9. McMahon SK, Ferreira LD, Ratnam N, et al. Glucose requirements to maintain euglycemia after moderate-intensity afternoon exercise in adolescents with type 1 diabetes are increased in a biphasic manner. J Clin Endocrinol Metab 2007;92:963–968
10. Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. Diabetes Care 2014;37(Suppl. 1):S120–S143
11. Riddell MC, Perkins BA. Type 1 diabetes and vigorous exercise: applications of exercise physiology to patient management. Can J Diabetes 2006;30:63–71
12. Perry E, Gallen I. Guidelines on the current best practice for the management of type 1 diabetes, sport and exercise. Pract Diabetes Int 2009;26:116–123
13. Parillo M, Riccardi G. Dietary carbohydrates and glucose metabolism in diabetic patients. Diabete Metab 1995;21:391–401
14. Jenkins DJ, Wolever TM, Taylor RH, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr 1981;34:362–366
15. Nansel TR, Gellar L, McGill A. Effect of varying glycemic index meals on blood glucose control assessed with continuous glucose monitoring in youth with type 1 diabetes on basal-bolus insulin regimens. Diabetes Care 2008;31:695–697
16. Parillo M, Annuzzi G, Rivellese AA, et al. Effects of meals with different glycaemic index on postprandial blood glucose response in patients with type 1 diabetes treated with continuous subcutaneous insulin infusion. Diabet Med 2011;28:227–229
17. West DJ, Morton RD, Stephens JW, et al. Isomaltulose improves post-exercise glycemia by reducing CHO oxidation in T1DM. Med Sci Sports Exerc 2011;43:204–210
18. Jensen TE, Richter EA. Regulation of glucose and glycogen metabolism during and after exercise. J Physiol 2012;590:1069–1076
19. Jentjens R, Jeukendrup AE. Determinants of post-exercise glycogen synthesis during short-term recovery. Sports Med 2003;33:117–144

20. MacDonald MJ. Postexercise late-onset hypoglycemia in insulin-dependent diabetic patients. Diabetes Care 1987;10:584–588
21. Wallace TM, Matthews DR. Recent advances in the monitoring and management of diabetic ketoacidosis. QJM 2004;97:773–780
22. Laffel L. Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. Diabetes Metab Res Rev 1999;15:412–426
23. Rosa JS, Oliver SR, Flores RL, et al. Altered inflammatory, oxidative, and metabolic responses to exercise in pediatric obesity and type 1 diabetes. Pediatr Diabetes 2011;12: 464–472
24. Keenan DB, Mastrototaro JJ, Zisser H, et al. Accuracy of the Enlite 6-day glucose sensor with guardian and Veo calibration algorithms. Diabetes Technol Ther 2012;14:225–231
25. Dill DB, Costill DL. Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. J Appl Physiol 1974;37: 247–248
26. Rabasa-Lhoret R, Bourque J, Ducros F, 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;24:625–630
27. Clinical Exercise Testing. In *ACSM's Guidelines for Exercise Testing and Prescription.* Walter R, Gordon NF, Pescatello LS, Eds. Baltimore, American College of Sports Medicine, 2010, p. 114–141
28. Brouns F, Bjorck I, Frayn KN, et al. Glycaemic index methodology. Nutr Res Rev 2005;18: 145–171
29. Hernandez JM, Moccia T, Fluckey JD, Ulbrecht JS, Farrell PA. Fluid snacks to help persons with type 1 diabetes avoid late onset postexercise hypoglycemia. Med Sci Sports Exerc 2000;32:904–910
30. Jeukendrup AE, Wallis GA. Measurement of substrate oxidation during exercise by means of gas exchange measurements. Int J Sports Med 2005;26(Suppl. 1):S28–S37
31. Wolever TM, Jenkins DJ. The use of the glycemic index in predicting the blood glucose response to mixed meals. Am J Clin Nutr 1986;43: 167–172
32. Thomas D, Elliott EJ. Low glycaemic index, or low glycaemic load, diets for diabetes mellitus. Cochrane Database Syst Rev 2009;(1): CD006296
33. McGarry JD, Foster DW. Ketogenesis. In: *Ellenberg and Rifkin's Diabetes Mellitus*, Porte D, Sherwin RS, Editors. 1996, New York, McGraw-Hill, 1996, p. 19–28
34. Balasse EO, Féry F. Ketone body production and disposal: effects of fasting, diabetes, and exercise. Diabetes Metab Rev 1989;5:247–270
35. Cryer PE, Childs BP. Negotiating the barrier of hypoglycemia in diabetes. Diabetes Spectr 2002;15:20–27
36. Mikines KJ, Sonne B, Farrell PA, Tronier B, Galbo H. Effect of physical exercise on sensitivity and responsiveness to insulin in humans. Am J Physiol 1988;254:E248–E259
37. Maarbjerg SJ, Sylow L, Richter EA. Current understanding of increased insulin sensitivity after exercise - emerging candidates. Acta Physiol (Oxf) 2011;202:323–335
38. Ashwell SG, Gebbie J, Home PD. Optimal timing of injection of once-daily insulin glargine in people with Type 1 diabetes using insulin lispro at meal-times. Diabet Med 2006;23:46–52
39. Thomas RM, Aldibbiat A, Griffin W, Cox MA, Leech NJ, Shaw JA. A randomized pilot study in Type 1 diabetes complicated by severe hypoglycaemia, comparing rigorous hypoglycaemia avoidance with insulin analogue therapy, CSII or education alone. Diabet Med 2007;24:778–783