J Appl Physiol 121: 1208–1216, 2016.
First published September 29, 2016; doi:10.1152/japplphysiol.00432.2016.

Interstitial glucose concentrations and hypoglycemia during 2 days of caloric deficit and sustained exercise: a double-blind, placebo-controlled trial

Tracey J. Smith, Marques A. Wilson, J. Philip Karl, Krista Austin, Asma Bukhari, Stefan M. Pasiakos, Kristie L. O'Connor, and Harris R. Lieberman

Military Nutrition Division, US Army Research Institute of Environmental Medicine, Natick, Massachusetts

Submitted 9 May 2016; accepted in final form 26 September 2016

Smith TJ, Wilson MA, Karl JP, Austin K, Bukhari A, Pasiakos SM, O'Connor KL, Lieberman HR. Interstitial glucose concentrations and hypoglycemia during 2 d of caloric deficit and sustained exercise: a double-blind, placebo-controlled trial. *J Appl Physiol* 121: 1208–1216, 2016. First published September 29, 2016; doi:10.1152/japplphysiol.00432.2016.—Military personnel and some athlete populations endure short-term energy deficits from reduced energy intake and/or increased energy expenditure (EE) that may degrade physical and cognitive performance due to severe hypoglycemia (<3.1 mmol/l). The extent to which energy deficits alter normoglycemia (3.9–7.8 mmol/l) in healthy individuals is not known, since prior studies measured glucose infrequently, not continuously. The purpose of this study was to characterize the glycemic response to acute, severe energy deficit compared with fully fed control condition, using continuous glucose monitoring (CGM). For 2 days during a double-blind, placebo-controlled, crossover study, 23 volunteers (17 men/6 women; age: 21.3 ± 3.0 yr; body mass index: 25 ± 3 kg/m) increased habitual daily EE [2,300 ± 450 kcal/day [means ± SD)] by 1,647 ± 345 kcal/day through prescribed exercise (~3 h/day; 40–65% peak O_2 consumption), and consumed diets designed to maintain energy balance (FED) or induce 93% energy deficit (DEF). Interstitial glucose concentrations were measured continuously by CGM (Medtronic Minimed). Interstitial glucose concentrations were 1.0 ± 0.9 mmol/l lower during DEF vs. FED ($P < 0.0001$). The percentage of time spent in mild (3.1–3.8 mmol/l) hypoglycemia was higher during DEF compared with FED [mean difference = 20.5%; 95% confidence interval (CI): 13.1%, 27.9%; $P = 0.04$], while time spent in severe (<3.1 mmol/l) hypoglycemia was not different between interventions (mean difference = 4.6%; 95% CI: −0.6%, 9.8%; $P = 0.10$). Three of 23 participants spontaneously reported symptoms (e.g., nausea) potentially related to hypoglycemia during DEF, and an additional participant reported symptoms during both interventions. These findings suggest that severe hypoglycemia rarely occurs in healthy individuals enduring severe, short-term energy deficit secondary to heavy exercise and inadequate energy intake.

caloric restriction; glycemia; interstitial glucose; energy deficit; continuous glucose measurement

NEW & NOTEWORTHY

This paper provides novel data characterizing glucose homeostasis during acute, severe energy deficit, in conjunction with extensive aerobic exercise in normal, healthy volunteers using continuous interstitial glucose monitoring. This study demonstrated that glucose regulation is, generally, tightly-controlled in normal-weight, healthy young adults in response to severe, short-term energy restriction, accompanied by an ~1,500 kcal/day increase in exercise-induced energy expenditure. Findings have practical implications for military personnel, ultra-endurance athletes, and select groups of first responders.

MILITARY PERSONNEL ENCOUNTER short-term scenarios that require high-energy expenditure, coupled with inadequate energy intake secondary to physiological factors and/or logistical constraints, thus inducing an energy deficit (21, 22, 24, 31, 34, 37, 56). The magnitude of short-term energy deficit in military personnel during training and combat operations can be substantial (i.e., 2,500–4,500 kcal/day) (24, 32, 40, 42). Combat sport athletes (e.g., wrestling and judo) also experience acute energy deficits, via energy restriction and exercise, to induce rapid body mass losses of 3–10% to prepare for precompetition weigh-ins (3, 8, 45). Although the largest energy deficits may not commonly occur among most athletes and military personnel, they do have the greatest potential for causing physiological deterioration and can guide design of controlled experiments that characterize human physiological adaptation at physiological extremes.

Severe energy deficit depletes hepatic and muscle glycogen stores, resulting in declines in blood glucose. Whereas counterregulatory responses, such as suppressed insulin release and increased glucagon and growth hormone secretion, act to maintain normoglycemia by stimulating gluconeogenesis, hypoglycemia and subsequent unfavorable physiological consequences can ensue (12, 18, 22, 24, 30, 34, 39, 54). For example, Loy et al. (30) reported mean blood glucose concentrations declined to hypoglycemic (<3.9 mmol/l) levels after an exhaustive cycling test more frequently after 24 h of fasting compared with fed conditions (postexercise: ~1.9 vs. ~2.8 mmol/l), and time to fatigue during high- and moderate-intensity trials was ~1 h shorter in the fasting vs. fed conditions. Additionally, soldiers who underwent a 5-day training course, characterized by high-energy expenditure (~5,000 kcal/day) and inadequate energy intake (~1,800 kcal/day), experienced significant declines from *day 1* (D1) to *day 5* in fasting mean blood glucose concentrations (5.2 to 4.1 mmol/l, respectively), along with reduced power output and maximum O_2 uptake (24).

As glucose is the brain's primary fuel source, hypoglycemia can also disturb brain function, leading to cognitive and behavioral deficiencies (50, 58). Glucose concentrations below ~3.1 mmol/l result in neurogenic/autonomic symptoms (e.g., anxiety, palpitations, and irritability) mediated by autonomic nervous system activation and subsequent release of catecholamines and acetylcholine, as well as neuroglycopenic symptoms (e.g., confusion, weakness, dizziness, blurred vision) directly attributable to central nervous system glucose deprivation) (20, 36, 51, 57). As such, severe energy deficit may disrupt glucose homeostasis, leading to detrimental physical and cognitive consequences.

Address for reprint requests and other correspondence: T. J. Smith, US Army Research Institute of Environmental Medicine, Military Nutrition Division, 10 General Greene Ave., Bldg. 42, Natick, MA 01760 (e-mail: Tracey.smith10.civ@mail.mil).

 8750-7587/16 Copyright © 2016 the American Physiological Society

Downloaded from journals.physiology.org/journal/jappl (151.186.191.116) on July 29, 2026.

While studies indicate hypoglycemia is associated with decrements in cognitive and physical performance, the actual duration that suboptimal glucose is present in scenarios involving inadequate energy intake is unknown because blood sampling has been infrequent, occurring at a few discrete time points (e.g., mostly morning while fasted). Continuous glucose monitoring systems (CGM) can assess the frequency, duration, and magnitude of excursions from normoglycemia by continuously monitoring interstitial glucose concentrations (6, 33, 35). Studies employing CGM (3–7 consecutive days) in healthy, nondiabetic, free-living adults indicate that hypoglycemic excursions, 3.3–3.8 and <3.3 mmol/l, occur at a rate of ~3 and 0.2%, respectively (19, 27, 59). In these populations, hypoglycemic excursions are mild, spontaneous, and asymptomatic and are a normal consequence of metabolism, occurring when peripheral glucose utilization exceeds splanchnic glucose output due to meal timing, nighttime fasting, or during times of stress (1, 13, 19, 26). Whether more frequent bouts of hypoglycemia and with accompanying symptoms occur during periods of energy deficit has not been examined by CGM.

This study characterized interstitial glucose responses using CGM during 2 days of severe energy deficit, coupled with increased energy expenditure induced by sustained, moderate-intensity aerobic exercise. We sought to determine the frequency of hypoglycemic excursions and characterize when these excursions occurred. The severity of the imposed energy deficit was chosen to represent what has been observed in soldiers in the field, and to provide a maximal effect. We hypothesized that, if the frequency and extent of hypoglycemic excursions in young, healthy participants exposed to this severe, acute energy deficit are not substantially different than that of the fed state, then hypoglycemia is unlikely to occur in response to the more commonly experienced, less extreme energy deficits experienced by military personnel and other populations, where energy balance is either difficult to attain due to high-energy demands (e.g., endurance athletes) or where acute weight loss is desirable (e.g., combat sport athletes).

MATERIALS AND METHODS

Participants. Participants ($n = 31$) were military personnel assigned to the Natick Soldier Research, Development and Engineering Center (Natick, MA) between 2012 and 2013. Study participation was voluntary, and each volunteer gave his or her written, informed consent after an oral explanation of the study. Individuals were included if they were at least 18 yr old and generally healthy without any acute or chronic physical limitations that would prevent exercise. All subjects completed an initial screening and were medically cleared for participation. The study was approved by the Institutional Review Board, United States Army Research Institute of Environmental Medicine, Natick, MA. The investigators adhered to the policies for protection of human subjects, as prescribed by Department of Defense Instruction 3216.02 and the research was conducted in adherence with the provisions of 32 CFR Part 219. The National Institutes of Health clinical trials registration number is NCT01603550 (https://clinicaltrials.gov/ct2/show/NCT01603550?term=NCT01603550&rank=11).

Experimental design. This was a double-blind, placebo-controlled, crossover trial, wherein volunteers participated in two, 66-h trials of which 51 h were the diet/exercise intervention. Each trial was separated by 19 ± 7 days (28, 41). This substudy characterized the interstitial glucose response using CGM during near total energy deprivation coupled with sustained aerobic exercise. The effects of the caloric intervention on cognitive function will be reported elsewhere.

Volunteers resided in a research dormitory during the experimental trials, allowing for control and monitoring of energy intake, energy expenditure, and sleep. In a randomized, counterbalanced order, all volunteers participated in one of two experimental treatments over 48-h: *1*) energy balance condition (FED), where volunteers were provided with a predominantly carbohydrate-containing diet to meet their total daily energy expenditure (TDEE); or *2*) energy deficit condition (DEF), where volunteers were provided with predominantly nonnutritive foods matched in volume and sensory characteristics to the energy-containing foods. Daily energy expenditure during the study trials consisted of each volunteer's habitual TDEE, coupled with additional exercise equivalent to their measured resting metabolic rate (RMR). This level of energy deficit was chosen based on data indicating the mid-level of short-term energy deficit in highly active military personnel is ~3500 kcal/day (24, 32, 40, 42). Each participant completed a baseline questionnaire to determine demographic information (age, sex, race, and ethnicity).

Energy Expenditure. During each test session, volunteers' TDEE comprised their individualized RMR, physical activity factor, and exercise energy expenditure:

$$\text{TDEE} = \text{RMR} \times 1.3 + \text{Exercise Energy Expenditure}$$

wherein exercise energy expenditure consisted of volunteers' habitual daily energy expenditure (i.e., estimated from 3-day activity records), coupled with repeat, moderate-to-vigorous intensity [40–65% of peak oxygen consumption ($\dot{V}O_{2peak}$)] exercise bouts to increase individual daily energy expenditure by an amount equivalent to individually measured RMR.

During the preliminary testing phase of the study, RMR was measured at ~0500 following an overnight fast and also on the morning of the first experimental test day, via an open-circuit respiratory system (True Max 2400, Parvomedics, Sandy, UT). Before each measurement, volunteers rested in the supine position in a quiet, dim temperature-regulated room while they remained awake. The test was discontinued when 30-min of steady-state oxygen consumption and carbon dioxide production were recorded; and, the final 20 min of data were averaged.

$\dot{V}O_{2peak}$ was determined during preliminary testing with open-circuit indirect calorimetry (True Max 2400, Parvomedics, Sandy, UT), wherein participants began by running for 4 min at a predetermined, comfortable pace at a 0% grade. At 4 min, the grade was increased to 4%, while pace remained constant, followed by an additional 2% every 2 min thereafter until volitional exhaustion. Volunteers' $\dot{V}O_{2peak}$ was used as a reference point to determine the appropriate exercise workloads necessary to ensure the desired level of energy was expended over multiple, daily endurance exercise bouts. To verify exercise intensity, exercise energy expenditure was measured during the preliminary testing phase and periodically during the test session using open-circuit indirect calorimetry. Timing of exercise relative to other study activities, intensity of exercise, and total exercise energy expenditure were consistent within and between experimental test sessions.

Diet composition. Meals and snacks of the appropriate energy content were prepared based on TDEE. The principal "foods" for the study were custom-made gels differing in energy content but matched for taste, texture, and appearance using hydrocolloids and artificial colors and sweeteners. The gels for FED also contained water (total wet weight: 49%), maltodextrin (18%), canola oil (15%), and isomaltulose (12%), whereas the gels for DEF were mainly composed of water (96%). We have previously demonstrated such gel formulations are acceptable to volunteers and allow conduct of double-blind studies inducing severe caloric deficits (29, 44). The DEF diet was supplemented with artificially sweetened drinks and commercially available, very-low-kilocalorie noodles made from an indigestible fiber (Tofu Shirataki; House of Foods America, Garden Grove, CA), served with very low kilocalorie sauce. The FED diet was supplemented with artificially or naturally sweetened drinks and commercially available

Downloaded from journals.physiology.org/journal/jappl (151.186.191.116) on July 29, 2026.

rice noodles (Maruchan Ramen; Maruchan, Irvine, CA) served with the same sauce used during DEF. All diet components were chemically analyzed for fat, protein, ash, and moisture, and carbohydrate and energy were calculated from the chemical analyses (Covance Laboratories, Madison, WI). Registered dietitians prepared all diet plans and oversaw meal preparation. Meals and snacks were served at specific times each day during each trial, whereas water and noncaloric beverages were consumed ad libitum. No additional food or beverages were allowed during the data collection period.

Anthropometry. Vertical height was measured in duplicate to the nearest 0.1 cm. Body weight was measured during preliminary testing and twice daily (before the morning meal and before bedtime) during the experimental testing using a calibrated electronic battery-powered scale accurate to 0.1 kg (Tanita WB-110A Class III, Tokyo, Japan).

Blood glucose. Blood was sampled by venipuncture three times/day during the intervention period (i.e., morning before breakfast, midday before lunch, and evening before dinner), and, aliquots were analyzed for glucose at the time of sampling (HemoCue201, Brea, CA) to provide a calibration standard for the interstitial glucose results (consistent with manufacturer's guidelines). Serum was prepared and frozen at −80°C for subsequent determination of glucose using the Beckman Coulter DXC 600 Pro analyzer (Fullerton, CA).

Interstitial glucose concentrations. Interstitial glucose concentrations were measured by a Continuous Glucose Monitoring System (CGM; Medtronic MiniMed iPro2 Professional Continuous Glucose Monitoring System, Northridge, CA) for ~34 h during each trial. The CGM was placed on each volunteer at 0630 on D1 and removed at 1630 on *day 2* (D2), before undergoing a functional MRI (data not presented), which required removal of the device. Study participants and staff members were blinded to real-time CGM data. This device has been widely employed in research studies to provide continuous information on changes in glucose levels, thereby avoiding the use of more invasive and painful technologies, such as frequent blood draws or intravenous sampling (7, 9, 29, 46). Briefly, the device uses a glucose oxidase-based sensor to measure extracellular fluid glucose in subcutaneous tissue and was calibrated against corresponding blood glucose levels measured three times each day during the test sessions (i.e., morning before breakfast, midday before lunch, and evening before dinner). The sensor, inserted into the subcutaneous tissue of the lower back on the morning of D1, analyzed data every 10 s and reported average values every 5 min. Glucose values provided by the CGM used in this study are highly correlated with capillary and venous blood glucose levels in healthy persons with and without diabetes (relative reliability 0.70–0.9) (2, 4, 5, 16, 17, 55).

Side effects potentially related to dietary intervention. Volunteers were routinely asked how they were feeling throughout the data collection period to identify unfavorable medical occurrences temporally associated with the individual's participation in the study. These self-reported side effects were recorded in the participant's study record, and we report symptoms potentially related to the energy deficit (e.g., dizziness, nausea, weakness, etc.) herein.

Statistical analyses. The dependent variable of interest was interstitial glucose concentrations during FED and DEF. Sample size calculations indicated that 13 volunteers were necessary to detect a 0.6 ± 0.7 mmol/l difference in average interstitial glucose between FED and DEF at $\alpha = 0.05$ and power = 0.80.

Interstitial glucose concentrations during each test session were analyzed and are presented as 5-min averages and also as mean values recorded during specific activities, e.g., average glucose concentration during evening sleep, during daytime rest, or after a meal. Additionally, interstitial glucose concentrations were also examined to determine excursions from hypoglycemia (<3.9 mmol/l) and hyperglycemia (>7.8 mmol/l). Hypoglycemia was further categorized as "mild" (3.1–3.8 mmol/l) or "severe" (<3.1 mmol/l), based on the fact that glucose counterregulatory hormones are secreted when glucose levels drop below ~3.9 mmol/l (20, 36, 49), whereas neurogenic/autonomic and neuroglycopenic symptoms and cognitive declines generally occur below ~3.1 mmol/l (20, 36). Glucose concentrations during, and percentage of time in, hypoglycemia and hyperglycemia were computed. The timing of hypoglycemic excursions was further categorized as follows: *1*) evening sleep; *2*) daytime sleep/rest; *3*) postprandial meal (i.e., within 120 min of energy consumption) independent of exercise; *4*) postprandial snack (i.e., within 120 min of energy consumption) independent of exercise; *5*) postprandial meal or snack (i.e., within 120 min of energy consumption) coinciding with exercise; and *6*) exercise that did not occur during the postprandial period. Furthermore, the rate of severe hypoglycemic excursions relative to the time spent in each study activity was calculated for each volunteer (i.e., number of minutes spent in severe hypoglycemia divided by the total time spent in each activity).

Body weight change was calculated using body weights recorded pre- and postintervention (i.e., FED and DEF), and paired *t*-tests were used to determine whether there was a significant difference in the weight change between FED and DEF. Pearson's correlation was used to assess associations between interstitial and serum glucose concentrations. For these correlations, the serum glucose value was compared with the interstitial glucose value (i.e., 5-min average) that occurred ~10 min after the serum was sampled, since interstitial glucose changes are somewhat delayed in relation to serum glucose (11).

Coefficients of variation were calculated for the entire CGM collection period, as well as for certain, specific activities (e.g., evening sleep, daytime rest, etc.) to determine variability in glucose concentrations. Specific study activities, and the associated glucose concentrations, were assessed independently, since glucose response is differentially mediated by activity (e.g., energy consumption compared with rest). Linear mixed models with unstructured covariance type were used to determine differences in main effects of time and condition and their interactive effects with regard to interstitial glucose concentrations during study activities involving more than two time points of interest. *t*-Tests were used when there were only two time points of interest. When significant main or interaction effects were observed with the mixed-models ANOVA, all possible *t*-tests were conducted, and the Bonferroni correction was used to control the familywise error rate. χ^2 was used to determine differences in the number of participants who experienced hypoglycemic excursions. Paired samples *t*-tests were used to determine differences in the duration of hypoglycemic excursions between interventions. Linear regression was used to determine if volunteer characteristics predicted time spent in hypoglycemia during FED and DEF.

Statistical analysis was conducted using the SPSS statistical package version 21 (IBM SPSS, Chicago, IL). Data were examined for outliers, both quantitatively and graphically, while normal distribution of data was confirmed via the Shapiro-Wilk test. Complete CGM data (i.e., defined as continuous recordings from 1300 on D1 until 1600 on D2) were collected from 12 of the 23 participants who completed the study, and incomplete CGM data were collected for the remaining 11 participants. Incomplete data resulted from sensors failing to initiate until the evening of D1, sensors becoming dislodged for extended time periods, or sensor disengaging on the afternoon of D2. Fewer than 25% of the CGM data were missing (i.e., 24%) or considered implausible (<0.8 mmol/l; <1%). All available data were included in the analyses, and results of the statistical analyses were not different when analyses were limited to volunteers with "complete" CGM data ($n = 12$). Results are presented as means (± SD), unless otherwise noted. $P \leq 0.05$ was considered statistically significant.

RESULTS

Participant characteristics and dietary intake. Thirty-one participants consented to participate in the study, and, of the 28 participants who began the study, 82% ($n = 23$) finished both experimental conditions: 17 men/6 women; age: 21.3 ± 3.0 yr; body weight: 75.1 ± 13.3 kg; body mass index (BMI): 25 ± 3

Downloaded from journals.physiology.org/journal/jappl (151.186.191.116) on July 29, 2026.

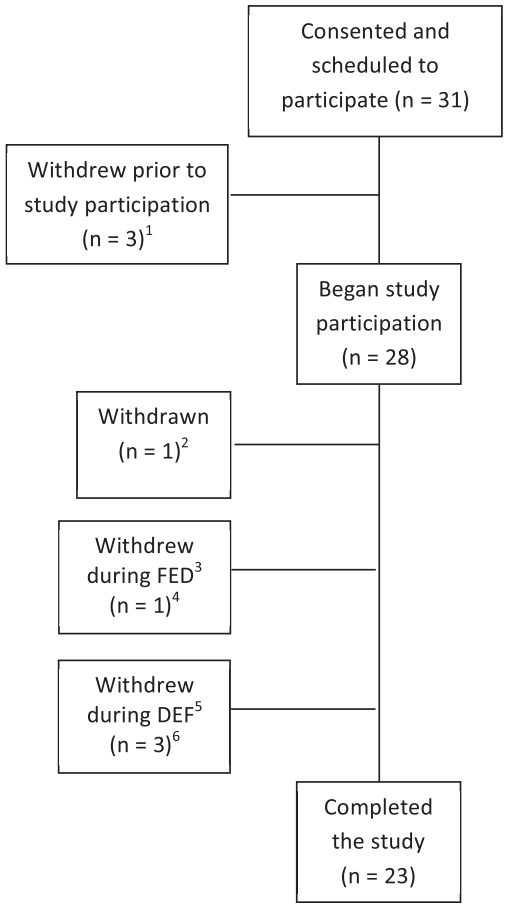


Fig. 1. Participant disposition. [1] Withdrew owing to unexpected departure from the geographical area ($n = 2$) or upper respiratory infection ($n = 1$). [2] Withdrawn by medical oversight due to an unrelated medical condition (i.e., viral costochondritis). [3] FED, study iteration wherein total daily energy intake matched total daily energy expenditure. [4] Withdrew owing to esophageal reflux ($n = 1$). [5] DEF, study iteration wherein volunteers were in severe energy deprivation. [6] Withdrew afternoon of *day 1* due to weakness and hunger ($n = 1$), withdrew morning of *day 2* due to nausea and vomiting ($n = 1$), or withdrew afternoon of *day 2* due to nausea and vomiting ($n = 1$).

kg/m^2; $\dot{V}o_{2peak}$: 46.8 ± 5.2 ml/kg (Fig. 1). Reasons for study attrition are provided in Fig. 1.

During FED and DEF, average TDEE was 3,970 ± 790 and 3,950 ± 750 kcal/day, respectively, as previously reported (28, 41). Per the study design, total energy intake and carbohydrate, protein, and fat intake significantly differed between FED and DEF (Table 1). Although dietary macronutrient proportions differed between conditions, it should be noted that absolute macronutrient intake was extremely low during DEF. There were no differences in recorded body weight at the start of DEF and FED (74.6 ± 13.3 and 74.4 ± 13.4 kg, respectively; $P = 0.40$). Body weight significantly declined for both FED and DEF from the morning of D1 to the end of the study (−0.6 ± 0.7 and −2.5 ± 0.8 kg, respectively, $P < 0.001$), and weight change was greater for DEF compared with FED ($P < 0.001$).

Interstitial glucose concentrations, comparisons with serum glucose concentrations. Interstitial glucose concentrations were significantly correlated with serum glucose concentrations (assessed via Beckman Coulter DXC 600 Pro analyzer) during FED ($r = 0.8–1.0$, $P < 0.0001$) and DEF ($r = 0.7–0.9$, $P < 0.01$).

Interstitial glucose concentrations, differences between FED and DEF. Mean duration of CGM data collected during FED and DEF were 25.3 ± 6.1 h (range: 3.3–32.6 h) and 24.4 ± 7.1 h (range: 3.4–30.5 h), respectively ($P = 0.60$). There was no difference between interventions in terms of duration of available glucose data from CGM during specific study activities. Interstitial glucose concentrations (Fig. 2) over the total collection period were significantly lower during DEF (4.1 ± 0.8 mmol/l; coefficient of variation = 19.9%) compared with FED (5.0 ± 1.2 mmol/l; coefficient of variation = 23.8%), independent of time ($P < 0.0001$), and the intervention-by-time interaction was significant ($P < 0.0001$). The slopes of the lines for FED and DEF were 0.00 and −0.01, respectively.

During all activities, interstitial glucose was lower in response to DEF compared with FED, with the mean difference ranging from 0.6 ± 0.3 (95% confidence interval: 1.7 and 20.9, $P = 0.05$) during evening rest on D1 to 1.2 ± 1.0 mmol/l (95% confidence interval: 0.8 and 1.7, $P < 0.001$) following breakfast on D2 (Fig. 3). Much of the exercise sessions overlapped with the postprandial period; therefore, exercise was not included in this aspect of the analyses.

Interstitial glucose concentrations, hypoglycemic and hyperglycemic excursions. Of the 23 participants, 19 and 9 experienced mild (3.1–3.8 mmol/l) and severe (<3.1 mmol/l) hypoglycemic excursions, respectively, during FED [χ^2 (1) = 3.1; $P = 0.13$], and 22 and 15 experienced mild and severe hypoglycemic excursions, respectively, during DEF [χ^2 (1) = 2.0; $P = 0.35$]. The mean glucose concentrations during all hypoglycemic excursions (<3.9 mmol/l) were 3.2 ± 0.5 mmol/l [range: 2.2–3.8 mmol/l (FED)] and 3.3 ± 0.4 mmol/l [range: 2.2–3.8 mmol/l (DEF)]. The mean duration and percentage of time in all hypoglycemic excursions (<3.9 mmol/l) during the data collection period were significantly greater for DEF (587 ± 425 min and 38.7 ± 25.0%) compared with FED

Table 1. *Energy expenditure and intake of energy and macronutrients*

	FED	DEF
Habitual TDEE, kcal/day	2,300 ± 500	
Resting metabolic rate, kcal/day	1,700 ± 300	1,700 ± 300
Experimental TDEE, kcal/day	4,000 ± 800	4,000 ± 800
Total energy intake, kcal/day	3,940 ± 770	270 ± 60
Energy balance, kcal/day	−40 ± 90	−3,680 ± 720
Protein		
g/day	19 ± 3	8 ± 2
%kcal from protein	1.9 ± 0.4	12.6 ± 1.0
Carbohydrate		
g/day	840 ± 181	44 ± 9
%kcal from carbohydrate	85 ± 2	67 ± 6
Fat		
g/day	56 ± 8	6 ± 2
%kcal from fat	13 ± 2	21 ± 5
Day 1, AM beverage, kcal	490 ± 140	10 ± 0
Day 2, breakfast, kcal	800 ± 150	30 ± 0
Day 2, lunch, kcal	820 ± 140	100 ± 30
Day 2, PM beverage, kcal	430 ± 120	10 ± 0
Day 2, dinner, kcal	780 ± 120	90 ± 50
Day 2, snack, kcal	610 ± 240	20 ± 10

Values are means ± SD; $n = 23$ subjects. FED energy intake was matched to energy expenditure. DEF energy intake was <300 kcal/day. TDEE, total daily energy expenditure.

Downloaded from journals.physiology.org/journal/jappl (151.186.191.116) on July 29, 2026.

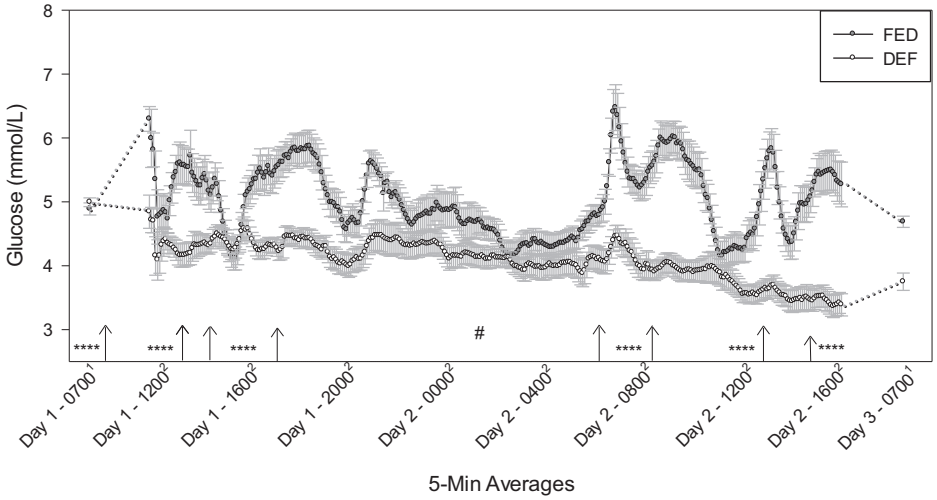


Fig. 2. Glucose concentrations during energy deficit (DEF) and energy balance (FED). [1] Serum glucose sampled via venipuncture. [2] Interstitial glucose sampled via Continuous Glucose Monitor System. ↑, Meal or beverage/snack consumed; #, sleep; **** , exercise.

(205 ± 210 min and 13.6 ± 13.7%, respectively) ($P = 0.04$ for both comparisons). However, the mean duration and percentage of time in severe hypoglycemic excursions (<3.1 mmol/l) during the data collection period were not significantly different between DEF (147 ± 181 min and 8.9 ± 10.9%) and FED (59 ± 134 min and 4.3 ± 9.0%, respectively) ($P = 0.10$). None of the volunteer characteristics (i.e., age, sex, BMI, $\dot{V}O_{2peak}$, baseline blood glucose, and weight change during FED and DEF) were significant predictors of time spent in mild or severe hypoglycemia during FED and DEF (R^2: 0.06–0.23; standardized β-coefficients: −0.3–0.3, $P > 0.4$).

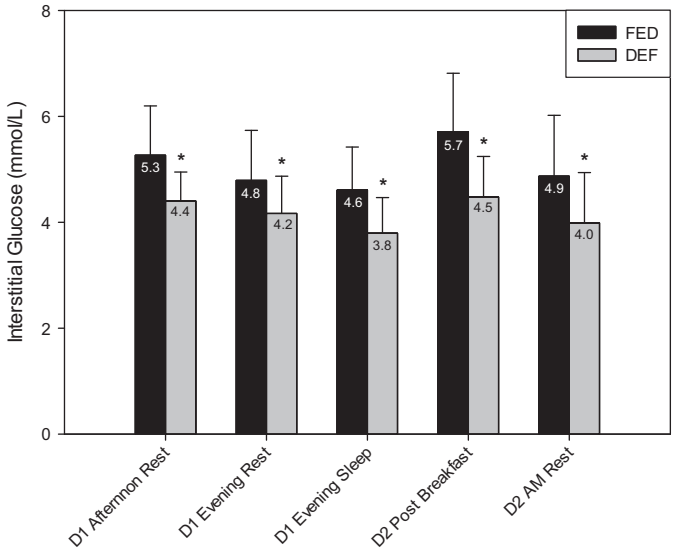


Fig. 3. Interstitial glucose concentrations related to select activities. FED, volunteers maintained energy balance for 2 days; DEF, volunteers were in severe energy deprivation for 2 days; D1, *day 1*; D2, *day 2*. All available CGMS data were included in analyses. Paired samples *t*-tests were used to identify differences between groups with regard to D1 Evening Sleep and D2 Post Breakfast (18 and 21 pairs, respectively). Mixed-models ANOVA were used to identify differences between groups with regard to D1 Afternoon Rest (FED and DEF, $n = 21$), D1 Evening Rest (FED, $n = 21$ and DEF, $n = 19$), and D2 AM Rest (FED, $n = 22$ and DEF, $n = 20$). *Significant differences between groups, after applying Bonferroni correction for multiple comparisons: D1 Afternoon Rest, $P = 0.002$; D1 Evening Rest, $P = 0.05$; D1 Evening Sleep, $P < 0.001$; D2 Post Breakfast, $P < 0.001$; D2 AM Rest, $P = 0.002$.

Volunteers spent a significantly greater percentage of time in severe hypoglycemia during daytime rest periods and the postprandial beverage/snack periods, in response to DEF compared with FED (Fig. 4). However, there were no significant differences between interventions, with respect to the percentage of time spent in severe hypoglycemia during evening sleep, exercise, postprandial meal periods, and postprandial periods with exercise relative to the time spent within each activity during the data collection period (Fig. 4).

None of the participants experienced hyperglycemic excursions during DEF, while 11 of 23 participants experienced hyperglycemic excursions during FED. The mean glucose concentrations during, and percentage of time in, hyperglycemic excursions was 8.4 ± 0.7 mmol/l (range: 7.8–11.2) and

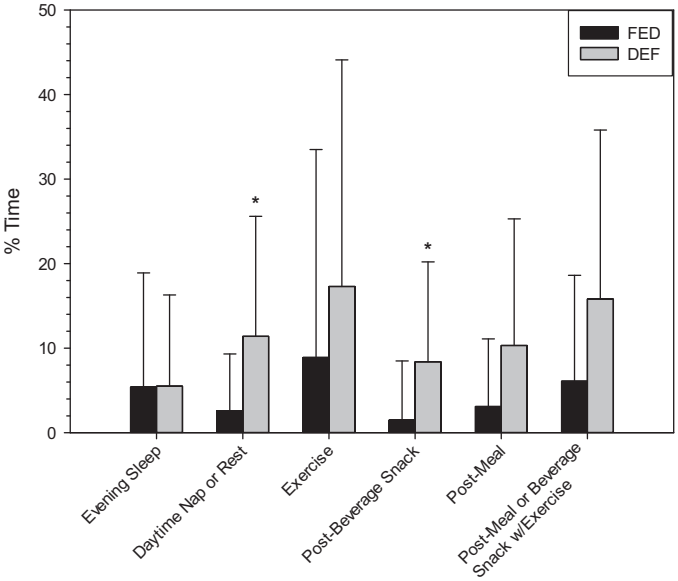


Fig. 4. Rate of hypoglycemic excursions (<3.1 mmol/l) relative to time spent in each study activity. FED, volunteers maintained energy balance for 2 days; DEF, volunteers were in severe energy deficit for 2 days. *Significant differences between groups, after applying Bonferroni correction for multiple comparisons: Daytime Nap or Rest ($n = 23$), $P = 0.04$; Post-Beverage Snack ($n = 23$), $P = 0.05$.

Downloaded from journals.physiology.org/journal/jappl (151.186.191.116) on July 29, 2026.

0.9–2.1% (FED), respectively. Of the hyperglycemic excursions, 83% occurred during the postprandial phase.

Side effects potentially related to the dietary intervention. Seven of the twenty-eight volunteers who began the study self-reported symptoms typically associated with low blood glucose (e.g., weakness, nausea, vomiting) during DEF, and one of the seven volunteers also reported similar symptoms during FED. None of the volunteer characteristics (i.e., age, sex, BMI, $\dot{V}o_{2peak}$, baseline blood glucose) was a significant predictor of self-reported symptoms. Of those seven participants, three withdrew voluntarily from the study during DEF, the other four participants completed the study, and their CGM data are included in the analyses presented. Of the three participants who withdrew during DEF, two reported nausea and vomiting owing to extreme dislike of the study diet, and the other participant withdrew due to weakness/hunger. Available blood glucose concentrations for the three volunteers who withdrew during DEF are as follows: *1*) morning D1: 5.7 mmol/l, evening D1: 2.9 mmol/l, morning of D2: 2.7 mmol/l; *2*) morning D1: 4.6 mmol/l, midday D2: 4.4 mmol/l; and *3*) morning D1: 4.3 mmol/l; midday D1: 3.1 mmol/l, evening D1: 4.3 mmol/l, morning D2: 2.8 mmol/l, midday D2: 1.9 mmol/l. There were no apparent differences between study noncompleters and completers in terms of glucose values, sex, BMI, age, and $\dot{V}o_{2peak}$.

DISCUSSION

This study is the first to characterize glucose homeostasis during acute, severe energy deficit in conjunction with extensive aerobic exercise in normal, healthy volunteers using a continuous measure of glucose concentrations. Interstitial glucose concentrations were lower across the overall measurement period, and the rate of mild hypoglycemia (3.1–3.8 mmol/l) was significantly higher during the energy deficit compared with the fully fed condition. Most notable, this rigorously controlled study demonstrated that the time spent in severe hypoglycemia (<3.1 mmol/l) was not significantly different between treatment conditions, indicating that glucose homeostasis is fairly well maintained in normal, healthy participants in response to severe energy deficit and substantial aerobic exercise.

Interstitial glucose concentrations across the overall measurement period of the FED condition are similar to those reported by other studies using CGM to monitor glucose homeostasis during energy balance in young, healthy, normal-weight participants (9, 19, 25, 46, 59). The magnitude and duration of the fluctuations in glucose during postprandial periods reflect the macronutrient profile (i.e., carbohydrate content) of the meals and snacks, which are rapidly digested and associated with a sharp, initial rise in blood glucose (14, 15, 52, 53). Furthermore, rates of normoglycemia, hypoglycemia, and hyperglycemia observed during the FED condition were generally in agreement with other studies that assessed continuous glucose concentrations in similar populations (19, 27, 59). For example, DeLarosa and colleagues (19), and the Juvenile Diabetes Research Foundation's Continuous Glucose Monitoring Study Group (27), observed similar rates of normoglycemia in free-living, healthy, normal-weight, young adults compared with the present study. As such, the unique high-carbohydrate diet and high volume of physical activity used as a model in this study did not appear to generate abnormal glycemic responses that might bias comparisons between conditions.

As expected, mean interstitial glucose concentrations, over the total measurement period (2 days), were significantly lower in response to energy deficit vs. energy balance. The negative slope of the graphical display of the mean interstitial glucose concentrations indicates a decline over the course of the energy deficit occurred (Fig. 2) and suggests it was more difficult to preserve normoglycemia during the later stages of the trial (i.e., afternoon of D2). Altogether, these observations were unsurprising, given that energy intake averaged only ~250 kcal/day. Buscemi and colleagues (10) studied glycemic homeostasis in nondiabetic, overweight/obese, middle-aged adults and also observed significant declines in response to long-term, moderate energy deficit (20 kcal/kg body wt for 3 mo). Our observations are also consistent with earlier studies investigating the effects of prolonged exercise accompanied by low-energy intake (22, 24, 34). For example, Guezennec et al. (24) studied military conscripts in energy deficit during a 5-day, high-energy expenditure training course and reported a significant decline in fasting blood glucose from pre- to posttraining, as did Friedl et al. (22) who studied Army Rangers during a series of training periods (7–10 days each) in which volunteers were in energy deficit, although neither study reported mean glucose concentrations below the lower limits of the normal fasting range (i.e., 3.9 mmol/l). Unfortunately, these studies did not continuously monitor glucose, limiting comparisons to the current investigation. Our data, therefore, add to the evidence base by using CGM to study glycemic excursions during severe energy deficit.

The absence of between-condition differences in time spent in severe hypoglycemia demonstrates that nadir glucose concentrations were tightly defended over the 2-day study period. This finding provides further evidence that, when a nadir in glucose occurs in healthy adults during routine activities, regulatory mechanisms are actively trying to prevent any further drop in glucose, even during periods of severe exogenous glucose deprivation. That participants spent significantly more time in mild hypoglycemia (3.1–3.8 mmol/l) during the DEF condition vs. the fully fed condition was not surprising, given the severity of the energy deficit, and likely reflects normal physiological responses to fasting. Specifically, during the first ~24 h of fasting, glucagon stimulates the breakdown of liver glycogen via glycogenolysis, and, once glycogen stores are depleted, gluconeogenesis generates glucose predominantly from stored fat (i.e., glycerol moiety of triacylglycerols) and protein (23, 43, 47). Mild hypoglycemia causes the release of homeostatic counterregulatory hormones, which stimulate gluconeogenesis, thereby increasing glucose concentrations, and is typically not accompanied by substantial symptomology (20, 36, 49). Indeed, only 7 of the 23 participants (~30%) experienced symptoms typically associated with hypoglycemia, and, despite minimal caloric intake and mild hypoglycemia during the energy deficit, volunteers were able to complete substantial daily physical activity. Our observations suggest that severe hypoglycemia is not a common metabolic response to the exercise volumes and energy deficits imposed during this study, but rather occurred only in a few individuals who experienced an extreme response to the intervention. We were not able to identify any characteristics that explained why some

Downloaded from journals.physiology.org/journal/jappl (151.186.191.116) on July 29, 2026.

volunteers responded differently than others. However, it is possible that a subset of volunteers were prone to symptomatic hypoglycemia in everyday life or simply were less tolerant of the intervention and subsequent lower blood glucose levels, compared with the other participants. In conclusion, extremely low glucose concentrations are generally prevented by the normal homeostatic processes that occur in healthy participants in response to acute, severe energy restriction.

The present study is not without limitations. There are physiological and technical limitations inherent to CGM systems. Continuous measures of interstitial glucose concentrations are not perfectly correlated with blood glucose measurements (35). In general, however, glucose values derived from the CGM sensors used in this study are well correlated with capillary and venous blood glucose values in healthy persons with and without diabetes ($r = 0.70–0.9$) (2, 4, 5, 16, 17, 55), and we confirmed that serum glucose and interstitial glucose concentrations were significantly correlated across both experimental interventions with r values between 0.7 and 1.0. Furthermore, interstitial glucose from subcutaneous fat correlates well with glucose concentrations from brain tissue, as demonstrated in pigs and humans (38, 48), suggesting that CGM reflects peripheral and central blood glucose concentrations. Although mood changes were noted, cognitive performance decrements were not documented in response to the energy deficit herein (28a), consistent with prior work from our laboratory (29), indicating that larger decrements in glucose are needed to elicit cognitive impairment. Technical issues (e.g., dislodging of the sensor) affecting the stability of the signal lead to delayed recordings or premature termination of recordings (35). Despite these shortcomings, the use of CGM vs. blood sampling at discrete time points is a major strength of the study and provided a means to unobtrusively assess continuous glucose concentrations during ~2 days, notably during sleep and heavy exercise, which is not otherwise feasible. Lastly, findings cannot be generalized to persons with a BMI $>$ 25 kg/m^2 and/or persons with impaired glucose tolerance, since the present study included only normal-weight participants, and variability in glucose homeostasis may be different in those populations.

Conclusion. This study demonstrated that glucose regulation is, generally, tightly controlled in normal-weight, healthy, young adults in response to severe, short-term energy restriction, accompanied by an ~1,500 kcal/day increase in exercise-induced energy expenditure. The fact that severe hypoglycemia did not differ between energy deficit and energy balance conditions, coupled with the low frequency of symptoms typically associated with hypoglycemia, indicates that normal homeostatic mechanisms effectively offer some protection to individuals exposed to 2 days of near-total energy deficit in combination with high-energy expenditure. These findings are applicable to combat sport athletes and select groups of military personnel who may encounter similar or less austere scenarios.

ACKNOWLEDGMENTS

The authors thank the participants, as well as the data collection team, who devoted time and energy to making this study a success. We also thank Ryanne Haskell for assistance with the technical aspects of manuscript preparation.

GRANTS

This research was supported in part by an appointment to the Postgraduate Research Participation Program at the US Army Research Institute of Environmental Medicine (USARIEM), administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and USARIEM.

DISCLAIMERS

The opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or reflecting the views of the Army or the Department of Defense. Any citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement of approval of the products or services of these organizations. Study funded by the US Army Medical Research and Materiel Command.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

T.J.S., M.A.W., A.B., and K.L.O. performed experiments; T.J.S. analyzed data; T.J.S., J.P.K., and H.R.L. interpreted results of experiments; T.J.S. drafted manuscript; T.J.S., M.A.W., J.P.K., K.A., A.B., S.M.P., K.L.O., and H.R.L. approved final version of manuscript; M.A.W. prepared figures; M.A.W., J.P.K., K.A., S.M.P., and H.R.L. edited and revised manuscript; S.M.P. and H.R.L. conception and design of research.

REFERENCES

1. **Ahlborg G, Felig P.** Lactate and glucose exchange across the forearm, legs, and splanchnic bed during and after prolonged leg exercise. *J Clin Invest* 69: 45–54, 1982. doi:10.1172/JCI110440.
2. **Akintola AA, Noordam R, Jansen SW, de Craen AJ, Ballieux BE, Cobbaert CM, Mooijaart SP, Pijl H, Westendorp RG, van Heemst D.** Accuracy of Continuous Glucose Monitoring Measurements in Normo-Glycemic Individuals. *PLoS One* 10: e0139973, 2015. doi:10.1371/journal.pone.0139973.
3. **Artioli GG, Gualano B, Franchini E, Scagliusi FB, Takesian M, Fuchs M, Lancha AH Jr.** Prevalence, magnitude, and methods of rapid weight loss among judo competitors. *Med Sci Sports Exerc* 42: 436–442, 2010. doi:10.1249/MSS.0b013e3181ba8055.
4. **Bailey TS, Ahmann A, Brazg R, Christiansen M, Garg S, Watkins E, Welsh JB, Lee SW.** Accuracy and acceptability of the 6-day Enlite continuous subcutaneous glucose sensor. *Diabetes Technol Ther* 16: 277–283, 2014. doi:10.1089/dia.2013.0222.
5. **Bay C, Kristensen PL, Pedersen-Bjergaard U, Tarnow L, Thorsteinsson B.** Nocturnal continuous glucose monitoring: accuracy and reliability of hypoglycemia detection in patients with type 1 diabetes at high risk of severe hypoglycemia. *Diabetes Technol Ther* 15: 371–377, 2013. doi:10.1089/dia.2013.0004.
6. **Bode B, Gross K, Rikalo N, Schwartz S, Wahl T, Page C, Gross T, Mastrototaro J.** Alarms based on real-time sensor glucose values alert patients to hypo- and hyperglycemia: the guardian continuous monitoring system. *Diabetes Technol Ther* 6: 105–113, 2004. doi:10.1089/152091504773731285.
7. **Boyne MS, Silver DM, Kaplan J, Saudek CD.** Timing of changes in interstitial and venous blood glucose measured with a continuous subcutaneous glucose sensor. *Diabetes* 52: 2790–2794, 2003. doi:10.2337/diabetes.52.11.2790.
8. **Brito CJ, Roas AF, Brito IS, Marins JC, Córdova C, Franchini E.** Methods of body mass reduction by combat sport athletes. *Int J Sport Nutr Exerc Metab* 22: 89–97, 2012. doi:10.1123/ijsnem.22.2.89.
9. **Brynes AE, Adamson J, Dornhorst A, Frost GS.** The beneficial effect of a diet with low glycaemic index on 24 h glucose profiles in healthy young people as assessed by continuous glucose monitoring. *Br J Nutr* 93: 179–182, 2005. doi:10.1079/BJN20041318.
10. **Buscemi S, Cosentino L, Rosafio G, Morgana M, Mattina A, Sprini D, Verga S, Rini GB.** Effects of hypocaloric diets with different glycemic indexes on endothelial function and glycemic variability in overweight and in obese adult patients at increased cardiovascular risk. *Clin Nutr* 32: 346–352, 2013. doi:10.1016/j.clnu.2012.10.006.

Downloaded from journals.physiology.org/journal/jappl (151.186.191.116) on July 29, 2026.

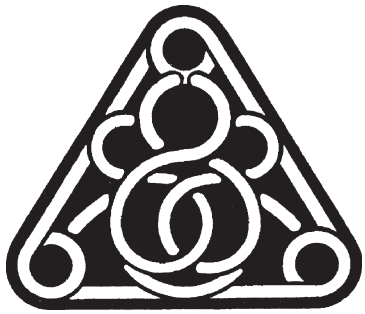
11. **Cengiz E, Tamborlane WV.** A tale of two compartments: interstitial versus blood glucose monitoring. *Diabetes Technol Ther* 11, *Suppl* 1: S11–S16, 2009. doi:10.1089/dia.2009.0002.
12. **Choma CW, Sforzo GA, Keller BA.** Impact of rapid weight loss on cognitive function in collegiate wrestlers. *Med Sci Sports Exerc* 30: 746–749, 1998. doi:10.1097/00005768-199805000-00016.
13. **Conn JW, Seltzer HS.** Spontaneous hypoglycemia. *Am J Med* 19: 460–478, 1955. doi:10.1016/0002-9343(55)90130-3.
14. **Crapo PA, Reaven G, Olefsky J.** Plasma glucose and insulin responses to orally administered simple and complex carbohydrates. *Diabetes* 25: 741–747, 1976. doi:10.2337/diab.25.9.741.
15. **Crapo PA, Reaven G, Olefsky J.** Postprandial plasma-glucose and -insulin responses to different complex carbohydrates. *Diabetes* 26: 1178–1183, 1977. doi:10.2337/diab.26.12.1178.
16. **Damiano ER, El-Khatib FH, Zheng H, Nathan DM, Russell SJ.** A comparative effectiveness analysis of three continuous glucose monitors. *Diabetes Care* 36: 251–259, 2013. doi:10.2337/dc12-0070.
17. **Damiano ER, McKeon K, El-Khatib FH, Zheng H, Nathan DM, Russell SJ.** A comparative effectiveness analysis of three continuous glucose monitors: the Navigator, G4 Platinum, and Enlite. *J Diabetes Sci Technol* 8: 699–708, 2014. doi:10.1177/1932296814532203.
18. **Degoutte F, Jouanel P, Bègue RJ, Colombier M, Lac G, Pequignot JM, Filaire E.** Food restriction, performance, biochemical, psychological, and endocrine changes in judo athletes. *Int J Sports Med* 27: 9–18, 2006. doi:10.1055/s-2005-837505.
19. **Derosa G, Salvadeo SA, Mereu R, D'Angelo A, Ciccarelli L, Piccinni MN, Ferrari I, Gravina A, Maffioli P, Tinelli C.** Continuous glucose monitoring system in free-living healthy subjects: results from a pilot study. *Diabetes Technol Ther* 11: 159–169, 2009. doi:10.1089/dia.2008.0101.
20. **Fanelli C, Pampanelli S, Epifano L, Rambotti AM, Ciofetta M, Modarelli F, Di Vincenzo A, Annibale B, Lepore M, Lalli C, Del Sindaco P, Brunetti P, Bolli GB.** Relative roles of insulin and hypoglycaemia on induction of neuroendocrine responses to, symptoms of, and deterioration of cognitive function in hypoglycaemia in male and female humans. *Diabetologia* 37: 797–807, 1994. doi:10.1007/BF00404337.
21. **Franchini E, Brito CJ, Artioli GG.** Weight loss in combat sports: physiological, psychological and performance effects. *J Int Soc Sports Nutr* 9: 52, 2012. doi:10.1186/1550-2783-9-52.
22. Friedl KE, Moore RJ, Hoyt RW, Marchitelli LJ, Martinez-Lopez LE, Askew EW. Endocrine markers of semistarvation in healthy lean men in a multistressor environment. J Appl Physiol (1985) 88: 1820–1830, 2000.10797147
23. **Gerich JE.** Physiology of glucose homeostasis. *Diabetes Obes Metab* 2: 345–350, 2000. doi:10.1046/j.1463-1326.2000.00085.x.
24. **Guezennec CY, Satabin P, Legrand H, Bigard AX.** Physical performance and metabolic changes induced by combined prolonged exercise and different energy intakes in humans. *Eur J Appl Physiol Occup Physiol* 68: 525–530, 1994. doi:10.1007/BF00599524.
25. **Henry CJ, Lightowler HJ, Tydeman EA, Skeath R.** Use of low-glycaemic index bread to reduce 24-h blood glucose: implications for dietary advice to non-diabetic and diabetic subjects. *Int J Food Sci Nutr* 57: 273–278, 2006. doi:10.1080/09637480600931626.
26. **Hofeldt FD, Dippe S, Forsham PH.** Diagnosis and classification of reactive hypoglycemia based on hormonal changes in response to oral and intravenous glucose administration. *Am J Clin Nutr* 25: 1193–1201, 1972.
27. **Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Fox LA, Beck RW, Xing D;.** Variation of interstitial glucose measurements assessed by continuous glucose monitors in healthy, nondiabetic individuals. *Diabetes Care* 33: 1297–1299, 2010. doi:10.2337/dc09-1971.
28. **Karl JP, Smith TJ, Wilson MA, Bukhari AS, Pasiakos SM, McClung HL, McClung JP, Lieberman HR.** Altered metabolic homeostasis is associated with appetite regulation during and following 48-h of severe energy deprivation in adults. *Metabolism* 65: 416–427, 2016. doi:10.1016/j.metabol.2015.11.001.

28a. **Lieberman HR, Bukhari A, Caldwell J, Wilson MA, Mahoney CR, Pasiakos SM, McClung JP, Smith TJ.** Two days of calorie deprivation induced by underfeeding and aerobic exercise degrades mood and lowers interstitial glucose but does not impair cognitive function in young adults. *J Nutr*, in press.

29. **Lieberman HR, Caruso CM, Niro PJ, Adam GE, Kellogg MD, Nindl BC, Kramer FM.** A double-blind, placebo-controlled test of 2 d of calorie deprivation: effects on cognition, activity, sleep, and interstitial glucose concentrations. *Am J Clin Nutr* 88: 667–676, 2008.
30. **Loy SF, Conlee RK, Winder WW, Nelson AG, Arnall DA, Fisher AG.** Effects of 24-hour fast on cycling endurance time at two different intensities. *J Appl Physiol (1985)* 61: 654–659, 1986.
31. **Margolis LM, Crombie AP, McClung HL, McGraw SM, Rood JC, Montain SJ, Young AJ.** Energy requirements of US Army Special Operation Forces during military training. *Nutrients* 6: 1945–1955, 2014. doi:10.3390/nu6051945.
32. **Margolis LM, Murphy NE, Martini S, Spitz MG, Thrane I, McGraw SM, Blatny JM, Castellani JW, Rood JC, Young AJ, Montain SJ, Gundersen Y, Pasiakos SM.** Effects of winter military training on energy balance, whole-body protein balance, muscle damage, soreness, and physical performance. *Appl Physiol Nutr Metab* 39: 1395–1401, 2014. doi:10.1139/apnm-2014-0212.
33. **Marics G, Koncz L, Körner A, Mikos B, Tóth-Heyn P.** [Role of continuous subcutaneous glucose monitoring in intensive care]. *Orv Hetil* 154: 1043–1048, 2013. doi:10.1556/OH.2013.29662.
34. **Marniemi J, Vuori I, Kinnunen V, Rahkila P, Vainikka M, Peltonen P.** Metabolic changes induced by combined prolonged exercise and low-calorie intake in man. *Eur J Appl Physiol Occup Physiol* 53: 121–127, 1984. doi:10.1007/BF00422574.
35. **Melki V, Ayon F, Fernandez M, Hanaire-Broutin H.** Value and limitations of the Continuous Glucose Monitoring System in the management of type 1 diabetes. *Diabetes Metab* 32: 123–129, 2006. doi:10.1016/S1262-3636(07)70258-6.
36. **Mitrakou A, Ryan C, Veneman T, Mokan M, Jenssen T, Kiss I, Durrant J, Cryer P, Gerich J.** Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. *Am J Physiol* 260: E67–E74, 1991.
37. **Moore RJ, Friedl KE, Kramer TR, Martinez-Lopez LE, Hoyt RW, Tulley RE, DeLany JP, Askew EW, Vogel JA.** *Changes in Soldier Nutritional Status & Immune Function During the Ranger Training Course. T13–92*. Natick, MA: US Army Research Institute of Environmental Medicine, 1992.
38. **Nielsen JK, Djurhuus CB, Gravholt CH, Carus AC, Granild-Jensen J, Orskov H, Christiansen JS.** Continuous glucose monitoring in interstitial subcutaneous adipose tissue and skeletal muscle reflects excursions in cerebral cortex. *Diabetes* 54: 1635–1639, 2005. doi:10.2337/diabetes.54.6.1635.
39. **Nindl BC, Barnes BR, Alemany JA, Frykman PN, Shippee RL, Friedl KE.** Physiological consequences of U.S. Army Ranger training. *Med Sci Sports Exerc* 39: 1380–1387, 2007. doi:10.1249/MSS.0b013e318067e2f7.
40. **Nindl BC, Friedl KE, Frykman PN, Marchitelli LJ, Shippee RL, Patton JF.** Physical performance and metabolic recovery among lean, healthy men following a prolonged energy deficit. *Int J Sports Med* 18: 317–324, 1997. doi:10.1055/s-2007-972640.
41. **O'Connor KL, Scisco JL, Smith TJ, Young AJ, Montain SJ, Price LL, Lieberman HR, Karl JP.** Altered appetite-mediating hormone concentrations precede compensatory overeating after severe, short-term energy deprivation in healthy adults. *J Nutr* 146: 209–217, 2016. doi:10.3945/jn.115.217976.
42. **Opstad PK.** Androgenic hormones during prolonged physical stress, sleep, and energy deficiency. *J Clin Endocrinol Metab* 74: 1176–1183, 1992.
43. **Owen OE, Reichard GA Jr, Patel MS, Boden G.** Energy metabolism in feasting and fasting. *Adv Exp Med Biol* 111: 169–188, 1979. doi:10.1007/978-1-4757-0734-2_8.
44. **Pasiakos SM, Caruso CM, Kellogg MD, Kramer FM, Lieberman HR.** Appetite and endocrine regulators of energy balance after 2 days of energy restriction: insulin, leptin, ghrelin, and DHEA-S. *Obesity (Silver Spring)* 19: 1124–1130, 2011. doi:10.1038/oby.2010.316.
45. **Pettersson S, Ekström MP, Berg CM.** Practices of weight regulation among elite athletes in combat sports: a matter of mental advantage? *J Athl Train* 48: 99–108, 2013.
46. **Pittas AG, Hariharan R, Stark PC, Hajduk CL, Greenberg AS, Roberts SB.** Interstitial glucose level is a significant predictor of energy intake in free-living women with healthy body weight. *J Nutr* 135: 1070–1074, 2005.
47. **Roach PJ.** Glycogen and its metabolism. *Curr Mol Med* 2: 101–120, 2002. doi:10.2174/1566524024605761.
48. **Rostami E, Bellander BM.** Monitoring of glucose in brain, adipose tissue, and peripheral blood in patients with traumatic brain injury: a microdialysis study. *J Diabetes Sci Technol* 5: 596–604, 2011. doi:10.1177/193229681100500314.

Downloaded from journals.physiology.org/journal/jappl (151.186.191.116) on July 29, 2026.

49. **Schwartz NS, Clutter WE, Shah SD, Cryer PE.** Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. *J Clin Invest* 79: 777–781, 1987. doi:10.1172/JCI112884.
50. **Siesjö BK.** Brain energy metabolism and catecholaminergic activity in hypoxia, hypercapnia and ischemia. *J Neural Transm Suppl* 14: 17–22, 1978.
51. **Smid HG, Trümper BG, Pottag G, Wagner K, Lobmann R, Scheich H, Lehnert H, Heinze HJ.** Differentiation of hypoglycaemia induced cognitive impairments. An electrophysiological approach. *Brain* 120: 1041–1056, 1997. doi:10.1093/brain/120.6.1041.
52. **Southgate DA.** Digestion and metabolism of sugars. *Am J Clin Nutr* 62, *Suppl*: 203S–210S, 1995.
53. **Swan DC, Davidson P, Albrink MJ.** Effect of simple and complex carbohydrates on plasma non-esterified fatty acids, plasma-sugar, and plasma-insulin during oral carbohydrate tolerance tests. *Lancet* 1: 60–63, 1966. doi:10.1016/S0140-6736(66)92357-9.
54. **Tarnopolsky MA, Cipriano N, Woodcroft C, Pulkkinen WJ, Robinson DC, Henderson JM, MacDougall JD.** Effects of rapid weight loss and wrestling on muscle glycogen concentration. *Clin J Sport Med* 6: 78–84, 1996. doi:10.1097/00042752-199604000-00003.
55. **Terada T, Loehr S, Guigard E, McCargar LJ, Bell GJ, Senior P, Boulé NG.** Test-retest reliability of a continuous glucose monitoring system in individuals with type 2 diabetes. *Diabetes Technol Ther* 16: 491–498, 2014. doi:10.1089/dia.2013.0355.
56. **Tharion WJ, Lieberman HR, Montain SJ, Young AJ, Baker-Fulco CJ, Delany JP, Hoyt RW.** Energy requirements of military personnel. *Appetite* 44: 47–65, 2005. doi:10.1016/j.appet.2003.11.010.
57. **Towler DA, Havlin CE, Craft S, Cryer P.** Mechanism of awareness of hypoglycemia. Perception of neurogenic (predominantly cholinergic) rather than neuroglycopenic symptoms. *Diabetes* 42: 1791–1798, 1993. doi:10.2337/diab.42.12.1791.
58. **Weiss V.** From memory span and mental speed toward the quantum mechanics of intelligence. *Pers Individ Dif* 7: 737–749, 1986. doi:10.1016/0191-8869(86)90045-0.
59. **Yu M, Zhou J, Xiang KS, Lu HJ, Ma XJ, Lu W.** [The glycemic excursions in normal glucose tolerance individuals revealed by continuous glucose monitoring system]. *Zhonghua Yi Xue Za Zhi* 84: 1788–1790, 2004.



Downloaded from journals.physiology.org/journal/jappl (151.186.191.116) on July 29, 2026.