A Ketone Ester Drink Increases Postexercise Muscle Glycogen Synthesis in Humans

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ABSTRACT

Introduction: Physical endurance can be limited by muscle glycogen stores, in that glycogen depletion markedly reduces external work. During carbohydrate restriction, the liver synthesises the ketone bodies, D-β-hydroxybutyrate and acetoacetate, from fatty acids. In animals and in the presence of glucose, D-β-hydroxybutyrate promotes insulin secretion and increases glycogen synthesis. Here we determined whether a dietary ketone ester, combined with plentiful glucose, can increase post-exercise glycogen synthesis in human skeletal muscle.

Methods: Following an interval-based glycogen-depletion exercise protocol, 12 well-trained male athletes completed a randomized, 3-arm, blinded crossover recovery study that consisted of consumption of either a taste-matched, zero-calorie control or a ketone monoester drink, followed by a 10 mM glucose clamp or saline infusion for two hours. The three post-exercise conditions were; control drink then saline infusion, control drink then hyperglycemic clamp or ketone ester drink then hyperglycemic clamp. Skeletal muscle glycogen content was determined in muscle biopsies of vastus lateralis taken before and after the two-hour clamps.

Results: The ketone ester drink increased blood D-β-hydroxybutyrate concentrations to a maximum of 5.3 vs. 0.7 mM for the control drink (p < 0.0001). During the two-hour glucose clamps, insulin levels were two-fold higher (31 vs. 16 mU/l, p < 0.01) and glucose uptake 32% faster (1.66 vs. 1.26 g/kg, p<0.001). The ketone drink increased by 61 g the total glucose infused over 2 h, from 197 g to 258 g, and muscle glycogen was 50% higher (246 vs.164 mmoles glycosyl units/kg dry weight, p < 0.05) than after the control drink.

Conclusion: In the presence of constant high glucose concentrations, a ketone ester drink increased endogenous insulin levels, glucose uptake and muscle glycogen synthesis.

Key Words: D-β-hydroxybutyrate, glucose clamp, glycogen repletion, hyperglycemia, insulin
INTRODUCTION

In a series of experiments showing that endurance correlated with initial muscle glycogen stores, Jonas Bergström and Eric Hultman (1966) demonstrated that muscle glycogen is the key determinant of endurance exercise capacity in man (5), and that glycogen exhaustion critically impairs the capacity for external muscular work (4, 6). The work prompted decades of investigation into the optimal dose and formulation of both carbohydrate and amino acid supplements to enhance muscle glycogen recovery. No oral, post-exercise regimen in humans seems superior to an intake of 1.0-1.2 g/kg/h carbohydrate over 4-6 hours (8, 34).

The ketone bodies, D-β-hydroxybutyrate and acetoacetate, are naturally-occurring four carbon substrates that are synthesized in the liver from circulating fatty acids under conditions of carbohydrate restriction. Ketone bodies supply fuel to the central nervous system (CNS) during periods of starvation (9, 31). The CNS has a constant, high energy demand and accounts for 20% of the body’s resting oxygen consumption (31). However, the brain is unable to oxidise fat, in which more than 99% of the body’s energy stores are to be found (11). Ketone bodies are water soluble, thermodynamically efficient substrates that connect the brain with its most abundant energy supply (24, 31, 35). In addition to providing an alternative to glucose for brain, skeletal muscle and cardiac metabolism (10), ketone bodies act as a powerful signal to conserve precious stores of carbohydrate with a switch to the more abundant energy source, fat (30).

Recently, a novel, safe, and orally-bioavailable ketone monoester ((R)-3-hydroxybutyl (R)-3-hydroxybutyrate) drink has been developed (13), which can elevate D-β-hydroxybutyrate to 5-6 mM (equivalent to approximately a week of total fasting) within 30 minutes of consuming a single drink (37). We have demonstrated that ketone bodies can alter fuel preference during exercise, away from carbohydrate and towards fat oxidation (14). Here we tested whether
elevated D-β-hydroxybutyrate influences fuel handling after exercise. Studies in animals have suggested that elevated ketone bodies, in the presence of abundant glucose, have the potential to increase glycogen synthesis (25, 28). However, no study has determined whether ketones alter fuel handling following exercise in human muscle. The purpose of the present study was to test the hypothesis that exogenous ketone supplementation can increase glycogen repletion in human skeletal muscle.

METHODS

Subjects

Twelve male, well-trained, athletes (mean ± SD: age, 33.0 ± 6.5 years; body weight, 75.8 ± 5.0 kg; height, 1.70 ± 0.10 m; \( \dot{V}O_{2\text{max}} \), 57.0 ± 4.8 ml/kg/min; peak power output, 316 ± 34 W) who trained for 6-8 hours per week, volunteered to take part in the study. Experimental procedures and potential side effects were explained and all participants gave written informed consent. Participants were instructed to refrain from alcohol and caffeine intake for 48 hours prior to study visits. None of the participants had a history of neuromuscular or metabolic illness and none were taking regular medication or dietary supplements. The study was conducted at the University of Oxford, was approved by the Ministry of Defence Research Ethics Committee (MODREC) and was conducted in accordance with the Declaration of Helsinki.

Measurement of maximal oxygen uptake

\( \dot{V}O_{2\text{max}} \) and peak power output (PPO) were determined in an incremental exercise protocol to volitional fatigue on an electrically-braked upright cycle ergometer (Ergoselect 100, Ergoline, Baden-Württemberg, Germany). The test commenced with a three-minute warm-up at 50 W, followed by 25 W increments in workload every three minutes. Breath-by-breath measurements
were performed using indirect calorimetry (Metalyser 3BR2Cortex Biophysik, Leipzig, Germany). A maximal test was defined by a respiratory exchange ratio exceeding 1.1 and/or a plateau in VO₂ despite increasing workload. All participants achieved a maximal test and reached, or exceeded, 90% of their age-predicted maximal heart rate.

**Glycogen depletion protocol**

Participants attended the laboratory following a 12-hour overnight fast. Glycogen depletion used the method described by van Loon and colleagues (39). Following a 10-minute warm-up at 50% VO₂max, participants commenced exercise at intermittent intensity for two-minute intervals, alternating 90% PPO efforts with 50% PPO recovery. When fatigued at this intensity, the upper interval workload was decreased progressively in 10% PPO increments. Exhaustion, and protocol completion, was defined by the inability to complete two minute at 60% PPO. Each participant’s heart rate was monitored throughout (Polar H7 heart rate monitor, Polar, Kempele, Finland) and water was consumed ad libitum.

**Ketone and control drinks**

After completion of glycogen depletion, participants consumed either a ketone drink, or an acaloric taste- and appearance-matched control drink of equal volume. The ketone drink, which had no side-effects, contained 0.573 ml/kg of the ketone ester, (R)-3-hydroxybutyl (R)-3-hydroxybutyrate (12, 13). The natural bitter taste was partially masked with citrus flavouring (Symrise, Holzminden, Germany) and proprietary sweetener (aspartame, NutraSweet™, Chicago, USA). The control drink contained the same citrus and sweetener components as the ketone drink. The bitter taste was matched with the addition of a weight-dosed commercial bitter agent (Symrise, Holzminden, Germany). The drinks were given immediately following the post-glycogen-depletion muscle biopsy and the clamps started 30 minutes following ingestion.
Hyperglycemic and saline clamps

The hyperglycemic clamp was conducted according to the method described by de Fronzo and colleagues (15). A clamp method of providing carbohydrate following exhaustive exercise was chosen for three reasons. First, the technique provided a way to standardize glucose available to skeletal muscle across different visits for the same participant, and between different individuals. Second, by delivering glucose intravenously, it is possible to avoid the variations in time and magnitude of glucose delivery caused by oral ingestion and enteral absorption. Third, it is possible to ensure that glucose delivery to the muscle is at least as high as would be provided by the recommended optimum post-exercise carbohydrate feeding of 1.0–1.2 g/kg/h over 4-6 hours (34). The selection of a supraphysiological target whole blood glucose of 10 mM was made so that, in the event that an increase in glucose uptake was evident following a ketone supplement, it would be likely to represent a biologically significant intervention, which would increase glucose uptake, and potentially glycogen storage, beyond that achieved by high-dose oral carbohydrate feeding alone.

Participants had two IV cannulae sited (Venflon™, Becton Dickinson, Plymouth, UK): one in the antecubital fossa (22 gauge), for infusion of 20% glucose (20% dextrose, Baxter Corporation, Staines, UK) and one in the dorsum of the contralateral hand (22 gauge) for sampling whole blood glucose at five minute intervals. The limb containing the sampling cannula was heated to 40-44 °C using two therapeutic heat pads (HK35 Beurer, Ulm, Germany) wrapped around the hand and forearm to cause maximal vasodilatation and generate a ‘pseudoarterialized’ blood sample. A priming dose of 240 mg/kg glucose was given over the first 15 minute of the clamp, after which the glucose infusion rate was adjusted to maintain a whole blood glucose of 10 mM (180 mg/dl), measured in the pseudoarterialized blood sample using a benchtop analyser.
(HemoCue 201+, Radiometer, Copenhagen, Denmark). At the end of the two-hour clamp, a second muscle biopsy was taken. The participant was then given a moderate glycemic index meal and the dextrose infusion rate was gradually lowered to zero. Participants were observed until euglycemia was maintained for a period of 30 minute after cessation of glucose infusion. For the saline clamp, all outward appearances and associated measurements were identical, but a 0.9% NaCl solution was infused instead of 20% glucose.

**Muscle Biopsies**

Muscle biopsies were taken under local anesthetic (2% lidocaine hydrochloride) injected subcutaneously and infiltrated up to 3 cm deep into underlying muscle. Biopsies were taken from lateral incisions (approximately 8 mm in length) 2-3 cm apart, over the distal third of the *vastus lateralis*. Sampling was performed using a Bard Monopty™ Core Biopsy Instrument, 12 French gauge, 10 cm long (Bard Biopsy Systems, Tempe, AZ, USA). Four passes were made with the biopsy instrument yielding approximately 100 mg of tissue per biopsy. Samples were immediately frozen in liquid nitrogen and then stored at -80 °C for later analysis.

**Blood analyses**

Peripheral blood samples were aspirated from the 22-gauge venous catheter inserted in the dorsum of the hand. Samples were collected in EDTA tubes and stored at 4 °C until centrifugation (1,500 g for 10 min at 4 °C). Multiple aliquots of plasma were stored at -80 °C until analysis. Samples were analyzed for glucose; lactate; non-esterified fatty acids (NEFA); and triglyceride, by automated benchtop analyser (ABX Pentra, Montpellier, France). D-β-hydroxybutyrate and acetoacetate were analyzed using commercially available colorimetric assays (Sigma-Aldrich, St Louis, USA). Insulin was measured using a commercial ELISA kit (Mercodia, Uppsala, Sweden).
**Glycogen Analysis**

Glycogen in muscle samples was determined according to the method described by van Loon and colleagues (39). 3-6 mg of freeze-dried skeletal muscle was powdered and hydrolyzed in 1M hydrochloric acid at 99 °C for four hours. Following passive cooling to room temperature, samples were neutralized using 250 μl of 0.12 mol/l Tris/2.1 mol/l potassium hydroxide saturated with potassium chloride. After centrifugation, 150 μl of supernatant was analyzed (in duplicate) for glucose using an automated benchtop analyser (ABX Pentra, Montpellier, France). Glycogen content was expressed as mmoles glycosyl units/kg dry weight of muscle.

**Study design**

The study was of a randomized, blinded, crossover design with three arms (Figure 1). Participants attended a baseline visit for familiarization with experimental conditions and to complete an incremental maximum exercise test, measuring maximum oxygen uptake (\(\dot{V}O_{2\text{max}}\)) and peak power output (PPO), to permit the prescription of the glycogen depletion protocol. Each study visit followed an overnight fast and commenced with a validated, exercise-interval protocol to deplete muscle glycogen (38, 39). Participants ingested a taste- and appearance-matched ketone or control drink prior to either a two hour hyperglycemic clamp with IV 20% glucose infusion to clamp whole blood glucose at 10 mM (180 mg/dl) or a sham clamp using a 0.9% saline infusion. The three recovery conditions used were: (i) control drink followed by saline clamp (control saline); (ii) control drink followed by hyperglycemic clamp (control glucose) and (iii) ketone ester drink ((R)-3-hydroxybutyl (R)-3-hydroxybutyrate at 0.573 ml/kg [615 mg/kg]) followed by hyperglycemic clamp (ketone glucose). Muscle samples were obtained from the vastus lateralis immediately following the glycogen depletion exercise and following the two-hour recovery period. Venous blood was sampled at five minute intervals for whole blood glucose and at regular intervals to measure substrate and insulin concentrations.
Statistical analysis

Statistical analysis was performed using GraphPad Prism (version 7, GraphPad Software Inc., California, USA). Energy substrate and insulin data were analyzed using a 2-way ANOVA, with time and recovery condition as factors. Comparisons included both substrate concentrations at pre-determined time intervals and area under the curve (AUC) measurements. Where significance of the recovery intervention or interaction of recovery intervention and time was detected, Tukey post-hoc corrections were made for multiple comparisons to identify specific significant differences. Results for substrates are presented as 2-way ANOVAs (AUC), followed by Tukey post-hoc comparisons of experimental conditions describing the mean difference and p value. Glycogen results were analyzed using Student’s paired t-test. All results are presented as means ± SEM. A p value ≤ 0.05 was taken to indicate statistical significance.

RESULTS

Physiological response to the glycogen depletion exercise

The time to exhaustion for all glycogen depletion protocols was 115 ± 2 minutes. The mean heart rate was 165 ± 0 bpm. The mean duration and heart rates were the same for the three recovery conditions.

Blood substrate concentrations

With control saline, blood D-β-hydroxybutyrate (βHB) concentrations rose steadily from 0.8 ± 0.1 mM at the start of the clamp to 1.6 ± 0.2 mM by the end (Figure 2A). With control glucose, βHB started at 0.7 ± 0.1 mM and fell to 0.15 ± 0.0 mM by the end of the clamp. Following the ketone ester drink, βHB rose to peak at 5.3 ± 0.5 mM and decreased to 3.3 ± 0.2 mM by the end of the clamp. The βHB areas under the curve from 0-120 minutes (AUC_{0-120}) for control saline, control glucose and ketone glucose were 190 ± 14, 97 ± 14 and 650 ± 38 mmol.min respectively (p < 0.0001 for comparison between each condition (Figure 2B)).
With control saline, the glucose at the start of the clamp was 4.5 ± 0.2 mM, and remained ≤ 4.6 ± 0.2 mM throughout (Figure 2A). Following both control glucose and ketone glucose the starting glucose, at ≤ 4.6 ± 0.2 mM, rose rapidly to a plateau between 9-12 mM throughout the 10 mM glucose clamp. There was no significant difference in glucose availability between control glucose and ketone glucose. The glucose AUC0-120 (Figure 2B) was the same for control glucose and ketone glucose, at 2,137 ± 43 and 1,927 ± 151 mmol.min, respectively.

For all conditions, NEFA was 0.42 ± 0.0 mM following the overnight fast (Figure 2A). During the glycogen depleting exercise, NEFA rose to 0.75 ± 0.1 mM, with no difference between groups prior to consuming the drinks. At the start of, and throughout the saline infusion, NEFA was elevated at ≥ 1.2 ± 0.2 mM. For control glucose, NEFA was 1.3 ± 0.2 mM at the start of the clamp, but fell rapidly to 0.6 ± 0.1 mM after 25 minutes. Following the ketone ester drink, NEFA was significantly lower than both control saline and control glucose at the start of the clamp, at 0.7 ± 0.1 mM (p < 0.0001). NEFA levels fell further, to 0.1 ± 0.0 mM, by one hour of the glucose clamp, and remained at this level for the following hour. The NEFA AUC0-120 (Figure 2B) for control saline, control glucose and ketone glucose were 272 ± 33, 165 ± 21 and 110 ± 13 mmol.min, respectively (p < 0.05 for comparisons between all conditions).

**Glucose uptake and endogenous insulin concentration**

During the 2-hour hyperglycemic clamp, glucose uptake was 32% higher following the ketone ester drink compared with the control drink (Figure 3, lower panel). Total glucose uptake was 1.26 ± 0.04 g/kg for control glucose and 1.66 ± 0.06 g/kg for ketone glucose, the difference being 0.4 ± 0.0 g/kg (p < 0.0001). Based on the mean body weight of the participants (75.8 kg), and two hours of clamping, this represents a 31% increase, from 197 g to 258 g, an additional 61
g or 340 mmoles of glucose. The greater glucose uptake was associated with a two-fold higher insulin concentration by the end of the clamp (Figure 3, upper panel), the insulin concentrations being 16 ± 3 mU/l for control glucose and 31 ± 6 mU/l for ketone glucose, with the mean difference being 15 ± 3 mU/l (p < 0.001).

Muscle glycogen

Muscle glycogen increased during the 2 h infusion following exercise under all conditions, but the levels following the ketone ester drink were 50% higher than those following the other two conditions. (Table 1 and Figure 4). During the saline infusion, glycogen synthesis was 70% lower than after the ketone drink plus 10 mM glucose clamp.

DISCUSSION

Here, under conditions of matched glucose availability, a ketone monoester drink allowed significantly greater endogenous insulin release, glucose uptake and muscle glycogen synthesis compared to hyperglycemic glucose alone. Richter and colleagues (1982) demonstrated that moderate intensity exercise causes both an increase in insulin sensitivity (defined as a left-shift of the glucose uptake vs. insulin concentration relationship) and insulin responsiveness (a state in which supra-physiological doses of insulin can effect a further increase in glycogen synthesis; defined as upward displacement of the glucose uptake vs. insulin concentration relationship) in rodents (32). Increases in both insulin sensitivity and insulin responsiveness enhance glycogen synthesis. Exercise alone can enhance insulin sensitivity, independent of glycogen depletion, but the increased insulin responsiveness is specifically mediated by glycogen depletion itself (41). AMPK activity has been implicated in the increased insulin sensitivity post-exercise (18) and ketone bodies may increase AMPK activity in rodents (40). AMPK activity is inversely
correlated with glycogen concentration and glycogen is thought to inhibit AMPK by binding to the carbohydrate-binding domain on its β-subunit (29). Taken together, these findings have led to speculation that increasing AMPK release from glycogen during exercise increases insulin sensitivity (23).

The close similarity between the additional amount of glucose taken up following the ketone ester and the additional amount of glycogen estimated to be stored in muscle, supports the argument that the infused glucose was stored as glycogen. The ketone ester increased whole body glucose uptake from 1.26 to 1.66 g/kg, equivalent to 340 mmoles of glucose. The ketone drink increased glycogen by 44 (from 70 to 114) mmoles glycosyl units/kg (dry weight of muscle). In a whole-body MRI study of 66 males aged 18-29, of a similar height and weight to our participants, Janssen et al. (2000) estimated the lower limb skeletal muscle mass to be 18.5 kg (22). Applying a wet:dry weight correction, based on a water content of 75% (36), 18.5 kg lower limb muscle mass would be equivalent to a dry weight of 4.4 kg in our participants. Assuming that trained individuals could recruit 90% of this muscle, then the increase seen in the glycogen content of our skeletal muscle biopsies following exogenous ketones would require an additional 352 mmoles glucose. Thus the fate of the additional infused glucose was probably incorporation into skeletal muscle glycogen, which is consistent with Maehlum et al (1978), who concluded that post-exercise, skeletal muscle glycogen synthesis takes precedence over hepatic glycogen synthesis (27).

It seems likely that elevated circulating D-β-hydroxybutyrate augmented insulin release from pancreatic beta cells, to double circulating insulin concentrations in response to 10 mM blood glucose, thereby explaining the 32% higher whole-body glucose uptake following a ketone ester vs. control drink. The first report of ketones causing endogenous insulin release was in 1964 in
dogs (26). Early studies in humans failed to demonstrate any increase in insulin secretion in response to ketone bodies (1, 2, 17). Subsequently, using catheters placed in the hepatic portal vein (for the purposes of hepatic imaging in two colorectal cancer patients), Balasse and colleagues (1970) identified an increase in hepatic portal vein insulin in response to acetoacetate infusion (3). However, the same group failed to reproduce the insulinotropic effect in the peripheral blood of obese subjects, admitted to hospital for therapeutic fasting, but their mean glucose concentration was low at 3.9 mM (~71 mg/dl). In all cases in which no increase in peripheral blood insulin was demonstrated, the blood glucose concentrations were 5 mM (90 mg/dl) or lower (1-3, 16, 17). It therefore appears likely that the augmentation of insulin release from beta cells in response to D-β-hydroxybutyrate requires a simultaneous presentation of high-normal, or frankly elevated, blood glucose. Here, increased insulin following ketone ester vs. control glucose was only observed following the start of glucose infusion and the rapid elevation of plasma glucose above the starting concentration of 4.6 mM.

D-β-hydroxybutyrate promotes insulin secretion from isolated rat pancreatic islets in the presence of 5 mM glucose, but is ineffective in the absence of glucose (7). Here, D-β-hydroxybutyrate did not increase insulin levels before the glucose infusion, when glucose concentrations were 4.6 mM (Figure 3), but it did lower circulating free fatty acid concentrations (Figure 2). Consequently, we do not know if D-β-hydroxybutyrate is utilised by the pancreatic beta cells for energy and thereby increases insulin release in proportion to the glucose taken up by tissues or if the D-β-hydroxybutyrate decreases free fatty acid concentrations, thereby stimulating glucose uptake into tissues (the “Randle effect”) or both.
The doubling of endogenous insulin release in response to elevated D-β-hydroxybutyrate concentrations has implications beyond enhanced glucose uptake and glycogen synthesis. Insulin has an anabolic action on skeletal muscle by inhibiting muscle catabolism that normally follows exercise (19, 20). Therefore, this large, sustained increase in insulin release with abundant carbohydrate supply immediately after exercise potentially preserves skeletal muscle. Speculation regarding the adaptive advantage of an insulinotropic effect of ketone bodies has centred on negative feedback mechanisms (33). Insulin inhibits peripheral lipolysis, thereby limiting the supply of circulating non-esterified fatty acids to the liver, and preventing uncontrolled ketogenesis. It is plausible that an insulinotropic action of ketones is an adaptation specifically to confer advantage at times of transition from the starved to the fed state. As glucose concentrations increase following a meal ending a prolonged fast, the enhanced insulin release in the presence of significant endogenous ketosis would serve both to protect the carbohydrate stores of the liver, by limiting hepatic glucose output, and to ensure maximal assimilation of the circulating glucose into body tissues in the form of glycogen.

**Limitations**

In this laboratory-based study, we used rigidly controlled, intravenous high-dose glucose delivery, aiming for constant 10 mM (180 mg/dL) whole blood glucose (the upper limit of glucose concentrations seen post-prandially). It is therefore necessary to investigate whether the findings of this study can be reproduced in athletes consuming a ketone ester drink in addition to recommended post-exercise dietary carbohydrate regimens. Not run was a fourth (control) protocol, a ketone drink plus saline infusion, which would presumably have resulted in low glycogen recovery, similar to that observed with the zero-calorie drink plus saline infusion, owing to the lack of exogenous glucose.
Given that low muscle glycogen stores impair both moderate and high intensity exercise (21), and that the exhaustion of glycogen reserves during exercise causes a marked reduction in external work (4, 6), any intervention that enhances glycogen synthesis is of potential benefit to human exercise performance. Here, we have shown that ketone and glucose together augment and accelerate glucose uptake, probably by elevating insulin, thereby hastening glycogen recovery.

**Acknowledgements**

The UK Defence Science and Technology Laboratories (DSTL) is gratefully acknowledged for funding this study. The authors declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation, and do not constitute endorsement by ACSM.

**Conflicts of Interest**

The intellectual property and patents covering the uses of ketone bodies and esters are owned by BTG Ltd, the University of Oxford, the NIH and TΔS® Ltd. Should royalties ever accrue from these patents, K.C., P.J.C. and D.A.H., as named inventors, may receive a share of royalties as determined by the terms of their respective institutions. KC is a director of TΔS®, a University of Oxford spin out company that aims to develop and commercialize products based on the ketone ester.
REFERENCES


FIGURE LEGENDS

Figure 1. Schematic of the study protocol.

Figure 2. D-β-hydroxybutyrate, glucose and non-esterified fatty acid (NEFA) concentrations during each study visit (Panel A). Area under the curve (AUC) measures of βHB, glucose and NEFA during the 2-hour recovery clamp (Panel B). * p < 0.05; ** p < 0.01; *** p < 0.001; **** p < 0.0001. Error bars are ± SEM.

Figure 3. Insulin concentration throughout the study visits and cumulative glucose uptake during the 2-hour recovery clamp. * p < 0.05; ** p < 0.01; *** p < 0.001; **** p < 0.0001. Error bars are ± SEM.

Figure 4. Skeletal muscle glycogen pre- and post- recovery period (Panel A). The increase in glycogen during 2 h infusion (Panel B). * p < 0.05; ** p < 0.01. Error bars are ± SEM.
Figure 1
Figure 2
Figure 3
Figure 4

**Glycogen**

- Saline
- Glucose
- Glu + Ket

* p < 0.05

**Delta Glycogen**

- Saline
- Glucose
- Glucose plus ketone

* p < 0.05

no significant baseline differences
### Table 1: Muscle glycogen concentrations before and following glucose/saline infusions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Post exercise glycogen (mmol/kg$_{DW}$)</th>
<th>Post-infusion glycogen (mmol/kg$_{DW}$)</th>
<th>Increase in glycogen (mmol/kg$_{DW}$/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control saline</td>
<td>134 ± 28</td>
<td>167 ± 34</td>
<td>35 ± 23</td>
</tr>
<tr>
<td>Control glucose</td>
<td>94 ± 15</td>
<td>164 ± 13</td>
<td>70 ± 13‡</td>
</tr>
<tr>
<td>Ketone glucose</td>
<td>132 ± 20</td>
<td>246 ± 32*†</td>
<td>114 ± 23*††</td>
</tr>
</tbody>
</table>

Values are means ± SEM. * = p < 0.05 for ketone glucose vs. control glucose; † = p < 0.05 for ketone glucose vs. control saline; †† = p < 0.01 for ketone glucose vs. control saline; ‡ = p < 0.05 for control glucose vs. saline.