High-intensity training improves plasma glucose and acid-base regulation during intermittent maximal exercise in type 1 diabetes

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Running Title: Intense exercise training in type 1 diabetes

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In those without diabetes, high-intensity exercise (HIE) training may reduce (1) the characteristic post-exercise rise in plasma glucose with HIE (2–4); and reduces (5, 6) the marked acid-base balance perturbations (5–8). In type 1 diabetes, continuous HIE induces sustained hyperglycemia (9, 10); whilst very brief, intermittent HIE may reduce hyperglycemia (11). Acid-base disturbances during exercise may be heightened in type 1 diabetes (12–14). Effects of HIE training on glycaemia and acid-base balance during intermittent HIE in type 1 diabetes are unknown; thus, despite the potential clinical importance of such exercise, there is no evidence upon which to base patient guidelines. The aim of the present study was thus to investigate the effects of HIE training upon glycaemia and acid-base regulation during intermittent HIE in type 1 diabetes.

RESEARCH DESIGN AND METHODS - Eight subjects with type 1 diabetes (T1D group; duration of diabetes, 7.1 ± 4.0 yr) and seven subjects without diabetes (CON group), all of whom were healthy and took no medications (other than insulin in T1D), consented to participate. The study was approved by the Human Ethics Committees of The University of Sydney and the South Sydney West Area Health Service. CON subjects closely matched those with diabetes for age (T1D, 25 ±4; CON, 25 ±4 yr), BMI (T1D, 25.4±3.2; CON, 23.8±5.0 kg·m⁻²) and \( \text{VO}_{2\text{peak}} \) (T1D, 42.7±12.2; CON, 43.7±6.2 ml·kg⁻¹·min⁻¹); as detailed in a related paper that reported effects of sprint training on muscle sodium-potassium ATPase and on plasma potassium during maximal exercise (15). Testing was conducted after overnight fasting. T1D subjects delayed their morning insulin. Subjects completed four, 30-s maximal exercise bouts (EB1-4) (each separated by 4 min rest) on a cycle ergometer. Supervised high-intensity cycling training (5, 15, 16) was then conducted thrice-weekly for seven weeks. The number of cycle bouts per training session progressed from four in Week 1 to six in Week 2, eight in Week 3, and ten in Weeks 4-7. After training, EB1-4 were repeated, with power output set to be identical to the pre-training test. Arterialised blood was sampled at rest, before and in the final seconds of EB1-4, and during recovery. Blood gases, insulin, glucose, and HbA₁c were analysed as previously described (15). With the exception of lactate, which was analyzed using a standard enzymatic technique (17), plasma ions were analysed using an automated blood gas analyzer (Corning 865, Chiron Diagnostics Corporation, USA). The plasma strong ion difference was calculated (\( \text{SID} (\text{mmol}·\text{l}^{-1}) = ([\text{potassium}] + [\text{sodium}]) - ([\text{lactate}] + [\text{chloride}]) \)). Data were analyzed with repeated-measures ANOVA (SPSS 10.0 for Windows). When significance was detected, pair-wise comparison between means was performed by a contrast technique. Significance was accepted at \( P<0.05 \). Results are reported as mean ± SD.

RESULTS - Exercise training did not alter HbA₁c in T1D (Pre, 8.6±0.8; Post, 8.1±0.6%; \( P=0.09 \)). Resting [PG] was higher in T1D than in CON (13.3±5.3; 5.0±0.3 mmol·l⁻¹; respectively; \( P<0.001 \)), with no change after training. In T1D, exercise induced a sustained rise in [PG] from rest (\( \Delta[\text{PG}] \)) (Figure 1A). In CON, \( \Delta[\text{PG}] \) peaked at 4 min recovery, and did not fall significantly thereafter. After training, \( \Delta[\text{PG}] \) was marked attenuated in both groups (\( P=0.001 \; \text{ Figure 1A} \)). Insulin did not differ between groups at rest or after training, however, fell slightly during exercise in T1D, in contrast to the rise in
Plasma SID fell after EB1 and remained reduced throughout the remainder of the test (P<0.001), mainly due to the rise in plasma lactate, with no group differences. After training, SID was higher (P=0.001) in both groups (Figure 1B). SID was greater in T1D than CON across all times and both days (P<0.05), but within normal range. The dramatic rises in plasma [H+] and lactate during HIE (P<0.001; Figure 1C,D) were markedly attenuated after training (P<0.001), with no group differences. After training, bicarbonate fell less (P<0.001; Figure 1E) in both groups. Bicarbonate was greater (P<0.05) and chloride lesser (P<0.01) in T1D than CON across all times and both days, but both were within normal range. PO2 did not differ between days or groups. After training, PCO2 returned more rapidly towards resting values during recovery (P<0.01), with no group differences. PCO2 was greater across both days and all times in T1D than CON (P<0.01), however resting values were within normal range.

CONCLUSIONS - This is the first study to examine the effects of intermittent HIE and training on glycemia and acid-base regulation in type 1 diabetes. Hyperglycemia during and after HIE in T1D was likely due to a lack of physiological hyperinsulinemia (10). Interestingly, based upon findings in rodent muscle (18), the high plasma lactate in both groups may have induced acute insulin resistance. This may have further contributed to the hyperglycaemia in T1D; and likely explains the lack of fall in [PG] during recovery in CON, despite high insulin. After training, lower [PG] with similar insulin suggests less acute insulin resistance, improved clearance and/or lower catecholamine stimulation. Plasma lactate was considerably lower after training which may have lessened any acutely-induced insulin resistance. This, and effects of HIE training on GLUT4 content and catecholamines during repeated HIE in type 1 diabetes remain to be investigated.

Plasma acid-base status during HIE depends primarily upon the SID and PCO2: reduced SID and increased PCO2 will increase [H+] and reduce bicarbonate (19, 20). Less acid-base perturbation after training is consistent with the higher SID, due mainly to less rise in lactate; perhaps consequent to greater skeletal muscle oxidative metabolism (5). Plasma PCO2, SID and bicarbonate were greater, and chloride lesser in T1D than CON (though within normal range), whilst plasma [H+] did not differ between groups. The mechanism of greater PCO2 in T1D cannot be determined from this study, however higher PCO2 may have induced chloride movement into cells via the chloride/bicarbonate exchange (20). This is consistent with lower plasma chloride and hence greater SID in T1D, which likely explains the similar acidosis between groups.

HIE training did not improve HbA1c (however, this may reflect a type 2 error); but improved glycaemia and acid-base regulation during intermittent HIE in patients with type 1 diabetes.

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Figure 1. Effects of intermittent maximal exercise (hatched bars) before and after intense intermittent exercise training in the T1D group (white triangle = pre-training; black triangle = post-training) and CON group (white circle = pre-training; black circle = post-training) on: (A) the change (delta) in plasma glucose concentration; (B) plasma strong ion difference; (C) plasma hydrogen ion concentration; (D) plasma lactate concentration; and (E) plasma bicarbonate concentration. Data are mean ± SEM. For (A), *P<0.001, main effect of time; †P=0.001, main effect of training status, Pre>Post training; ‡P<0.001, training status-by-time interaction, Pre>Post; §P<0.001, time-by-group interaction, T1D>CON; and ¶P<0.001, T1D>CON. For (B), *P<0.001, main effect of time; †P=0.001, main effect of training status, Post>Pre training; ‡P<0.01, training status-by-time interaction, Post>Pre; and §P<0.05, T1D>CON. For (C) and (D), *P<0.001, main effect of time; †P<0.001, main effect of training status, Pre>Post training; and ‡P<0.001, training status-by-time interaction, Pre>Post. For (E), *P<0.001, main effect of time; †P<0.001, main effect of training status, Post>Pre training; ‡P<0.001, training status-by-time interaction, Post>Pre; and §P<0.05, T1D>CON.
Figure 1