Hyperglycemia blunts the therapeutic effect of exercise on glycemic control in patients with type 2 diabetes

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Keywords

TO THE EDITOR

Randomized controlled trials show that aerobic exercise training improves glycemic control in type 2 diabetics [1]. However, inter-individual variability is large[2]. This may be explained by genetic variability[3], but ambient hyperglycemia[4] and pancreatic beta-cell function[5] may also contribute. We examined whether changes in glycemic control following a 12-16-week aerobic exercise training intervention were influenced by the pre-training glycemic state in 105 individuals with impaired glucose tolerance or type 2 diabetes.

Methods

Before and following a 12-16 week period of aerobic exercise training, body composition, aerobic fitness (VO_2max), and glycemic control (hemoglobin [Hb]A_{1c}, fasting glucose, and oral glucose tolerance test [OGTT]) were determined in a total of 105 older (61±1 years; mean±S.E.M.), overweight/obese (33±1 kg/m^2) subjects with impaired glucose tolerance (N=56) or type 2 diabetes (N=49; diagnosed 4.8±0.9 years prior and not insulin-treated). Relationships between pre-intervention variables and intervention-induced changes in variables were assessed by linear and non-linear regression. The study was approved by our institutional review board and subjects provided informed-consent. See **eMethods** (http://archinte.jamanetwork.com) for full details of the study design.

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Results

Body weight (-4.6 ± 0.5 kg), whole-body adiposity ($-1.9\pm0.3\%$), VO_2max ($+0.23\pm0.03$ L/min), fasting plasma glucose (-0.35 ± 0.08 mmol/L), and 2-hour OGTT glucose (-0.8 ± 0.2 mmol/L) were significantly improved following exercise training (full data is shown in **eTable 1**). Pre-training fasting plasma glucose did not influence exercise-induced changes in glycemic control. However, there was a non-linear quadratic relationship between pre-training 2-hour OGTT glucose and exercise-induced changes in the 2-hour glucose response ($r^2=0.26$, P=0.06; **Fig. A**). Subjects with a pre-training 2-hour OGTT glucose of less than 13.1 mM showed greater exercise-induced decreases in 2-hour glucose (r=-0.44, P<0.001); while subjects with a pre-training 2-hour OGTT glucose of greater than 13.1 mM had smaller improvements in 2-hour glucose (r=0.29, P=0.07). The same non-linear quadratic relationship existed between pre-training HbA_{1c} and exercise-induced changes in HbA_{1c} ($r^2=0.33$, P<0.05; **Fig. B**); where subjects with pre-training HbA_{1c} less than 6.2% had an exercise-induced decrease in HbA_{1c} (r=-0.55, P<0.01), while subjects with pre-training HbA_{1c} greater than 6.2% had smaller exercise-induced improvements in HbA_{1c} (r=0.38, P<0.05). Furthermore, pre-training HbA_{1c} was linearly and inversely related to the exercise-induced change in VO_2max, such that high pre-training HbA_{1c} predicted smaller exercise-induced increases in VO_2max (r=-0.38, P<0.01; **Fig. C**).

COMMENT

These findings emphasize that exercise-induced improvements in glycemic control are dependent on the pre-training glycemic level. We demonstrate that although moderate-intensity aerobic exercise can improve glycemic control, individuals with ambient hyperglycemia are the most likely to be non-responders. Our key observation is that pre-training hyperglycemia predicts exercise-induced improvements in glycemic control: for every 1 mM rise in pre-training 2-hour OGTT glucose above 13.1 mM (the curve inflection point in **Fig. A**) we predict a 0.2 mM loss of improvement in 2-hour OGTT glucose following exercise. Accordingly, for every 1% point increase in pre-training HbA_{1c} above 6.2% (the curve inflection point in **Fig. B**), we predict a 0.2% point loss of improvement in HbA_{1c} following exercise. Pre-training hyperglycemia also predicted the exercise-induced increment in aerobic fitness: for a 1% increase in pre-training HbA_{1c} we predict a 0.11 L/min loss of improvement in VO_2max following exercise.

Prior work shows that diabetes remission following exercise and diet intervention is more likely in individuals with a shorter disease history and lower HbA_{1c}[6]. Here we show that aerobic exercise-induced improvements in glycemic control are blunted by ambient hyperglycemia, particularly in subjects with type 2 diabetes. Mechanistic studies are required to help us understand this phenomenon, but underlying impairments in beta-cell function are likely to be very important[5]. That hyperglycemia blunted the cardiovascular adaptations to exercise (VO_2max) is in agreement with some prior reports[7] and may be explained by the causal association between chronic hyperglycemia and micro- and macrovascular dysfunction[8].

The clinical relevance of these new findings is paramount as they highlight the need to understand the metabolic "non-responder". Because chronic hyperglycemia (>6.2% HbA_{1c}; >13.1 mM glucose) potentially predicts a poor therapeutic effect of aerobic exercise upon glycemic control and fitness, using exercise to treat patients with poorly-controlled type 2 diabetes may have limited chances of a successful outcome.

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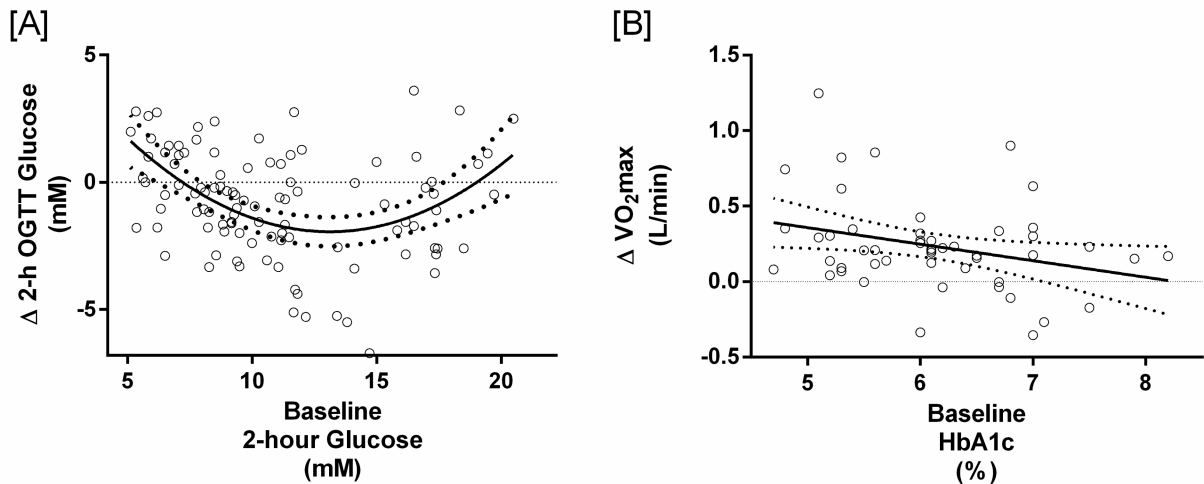
Fig 1.
Subjects with impaired glucose tolerance or type 2 diabetes underwent 12-16 weeks of moderate-intensity exercise training, 5 d/wk, 60 min/d. Individual subject data points are plotted on both panels; the X-axis represents the pre-training variable and the Y-axis indicates the exercise-induced change such that data points above the axis indicate an exercise-induced increase, and vice versa. Open circles (   ) represent impaired glucose tolerant subjects; open triangles (   ) represent subjects with type 2 diabetes. The solid line represents the regression curve; the dotted line represents the 95% confidence interval. [**A**] There was a non-linear quadratic relationship between pre-training 2-hour OGTT glucose and the training-induced change in 2-hour OGTT glucose ($y=0.06x^2-1.5x+7.6$; $r^2=0.26$, P=0.06; N=105). For every 1 mM increase in pre-training 2-hour glucose above 13.1 mM (the inflection point of the curve), there was a 0.2 mM loss of improvement in 2-hour glucose following exercise. [**B**] There was also a non-linear quadratic relationship between pre-training HbA_{1c} and the training-induced change in HbA_{1c} ($y=0.31x^2-3.8x+11.7$; $r^2=0.33$, P<0.05; N=52). For every 1% point increase in pre-training HbA_{1c} above 6.2% (the inflection point of the curve), there was a 0.2% point loss of improvement in HbA_{1c} following exercise. [**C**] An inverse linear relationship between pre-training HbA_{1c} and the training-induced change in aerobic fitness was found ($y=-0.11x+0.91$; r=−0.38, P=0.006; N=52). For every 1% increase in pre-training HbA_{1c}, there was 0.11 L/min loss of improvement in VO_2max following exercise training.