

Extremely short duration high intensity training substantially improves insulin action
in young healthy males

Babraj JA*, Vollaard NBJ*, Keast C, Guppy FM, Cottrell G and Timmons JA

Translational Biomedicine, Heriot-Watt University, Edinburgh, Scotland

*These authors contributed equally to this work

E-mail addresses

JAB	j.babraj@hw.ac.uk
NBJV	n.vollaard@hw.ac.uk
CK	ck51@hw.ac.uk
FMG	fmg1@hw.ac.uk
GC	gc29@hw.ac.uk
JAT	jamie.timmons@gmail.com

Abstract

Background: Long duration aerobic exercise reduces cardiovascular and metabolic disease risk but involves a substantial time commitment. Extremely low volume high-intensity training (HIT) induces similar improvements to aerobic performance, but it has not been established whether HIT has the capacity to improve glycemic control.

Methods: 25 young men (21 ± 5 y) were randomly assigned to control (n=9) or HIT (n=16) groups. Subjects underwent an oral glucose tolerance test (OGTT) and a $VO_{2\text{peak}}$ test. The control group adhered to their normal routine for 2 weeks prior to a second OGTT. HIT comprised of 15 min exercise over 2 weeks, consisting of 4-6 x 30-second cycle-sprints per session. At 48 or 72 hr post training, subjects underwent a second OGTT and time trial.

Results: Following 2 weeks of HIT, the area under the plasma glucose, insulin and NEFA concentration-time curves were all reduced (12%, 37%, 26% respectively, all $P < 0.001$). Fasting plasma NEFA concentration was also reduced (pre: 350 ± 36 v post: $290 \pm 39 \mu\text{mol}\cdot\text{l}^{-1}$, $P < 0.05$) while fasting plasma insulin and glucose concentrations remained unchanged. Insulin sensitivity as measured by the Cederholm index was improved by 22.5% ($p < 0.01$). There were no changes in the control group.

Conclusions: The efficacy of HIT to rapidly improve insulin action is remarkable, indicating that this time-efficient training paradigm could be used as a novel strategy to improve insulin action in sedentary populations who otherwise would not adhere to a classic high volume, time consuming exercise regime.

Introduction

In 2007 the rapidly rising prevalence of type 2 diabetes (T2D) in the United States reached 17.5 million people [1]. Aside from the associated reduction in quality-of-life and the increase in morbidity and mortality for the affected individuals, the economic burden was estimated at \$116 billion in excess medical expenditures and \$58 billion in reduced productivity [1]. Similarly, the estimated direct and indirect economic costs of cardiovascular disease (CVD) in the US for 2008 are estimated at \$287 billion [2]. The risk of developing CVD and T2D can be modified by regular physical activity [3]. However, there is no consensus on the nature of exercise therapy required to provide adequate health benefits particularly with regard to the volume-intensity relationship. Furthermore, as we do not understand the precise mechanisms which link physical activity and a reduced risk of developing CVD or T2D the scientific basis for current health guides can be challenged[4] . For exercise guidelines to yield a positive economic benefit for society, as well as a health benefit for the individual, not only should the regime reliably modify key disease risk factors, it must also be plausible to implement.

Metabolic adaptations associated with traditional aerobic exercise training correlate with improved insulin action and glycemic control [5, 6]. These effects appear to be independent of changes in body composition [7] and more importantly aerobic training of higher intensity elicits greater improvements in insulin sensitivity than moderate intensity training [7-9]. Current recommendations for improving glycemic control involve performing moderate to vigorous intensity aerobic and resistance exercise for several hours per week [10, 11]. However, the general population fails to

follow such regimes due to lack of time, motivation and adherence [12]. This suggests that the current focus on time-consuming moderate intensity physical activity aimed at increasing total energy expenditure may not be optimal for reducing the risk of developing T2D. Recently an extremely low volume high-intensity training paradigm (HIT), consisting of no more than 7.5 minutes of exercise per week, has been proposed as a novel, time-efficient exercise regime for improving aerobic fitness [4, 13]. We speculated that it should be possible to substantially improve insulin action using HIT since despite a negligible contribution to total energy expenditure, this training model would acutely and rapidly deplete muscle glycogen stores. Compared to traditional strategies for reduction of risk factors of CVD and T2D, the extremely low volume of exercise required with HIT may promote adherence and thus represent a genuinely preventative public health strategy.

Methods

Subjects

Twenty-five young healthy sedentary or recreationally active men were recruited to participate in this study, with none engaged in a structured endurance training program. Subjects were randomly allocated to either a training group performing two weeks of HIT (n=16), or a control group asked to continue with their regular daily activities (n=9). There were no significant differences in baseline characteristics between the two groups (Table 1). The subjects were informed of the experimental protocol both verbally and in writing before giving informed consent. The study protocol was approved by the institutional Ethics Committee and conducted in accordance with the Helsinki Declaration.

Experimental procedures

Baseline aerobic performance and health parameters were determined over a 2-week period prior to commencement of the training program.

Oral glucose tolerance test (OGTT). Subjects refrained from performing any strenuous physical activity for 2 days prior to the OGTT, and attended the laboratory having fasted overnight. Venous blood samples were collected by venepuncture before, and 60, 90 and 120 min after ingestion of 75 g glucose (Fisher Scientific, Loughborough, UK) dissolved in 100 ml of water. Plasma was separated by centrifugation (10 min at 1600 g) and stored at -20°C until analysis of glucose, insulin and NEFA concentrations. Plasma glucose concentrations were measured using an automatic analyzer (YSI Stat2300, Yellow Spring Instruments, Yellow Spring, OH) and plasma insulin concentration was determined by ELISA (Invitrogen, UK). Plasma NEFA concentrations were determined by a colorimetric assay (Wako Chemicals, Germany) using a modified protocol. Briefly, 3.75 µl of plasma samples and standards of known concentration were pipetted into a 96-well plate. 75 µl of colour reagent A was added to each well and incubated at 37°C for 10 min. 150 µl of colour reagent B was added and incubated for a further 10 min at 37°C. The plate was then removed from the incubator and allowed to cool to room temperature prior to the absorbance being read at 550 nm.

VO₂peak test. On a separate occasion, subjects performed an exhaustive incremental cycling test (Lode Excalibur Sport, Groningen, the Netherlands) to determine maximal power output (W_{max}) and maximal oxygen uptake capacity (VO₂peak) using an online gas analysis system (SensorMedics, Bilthoven, the Netherlands).

After cycling at 30 W for 1 min, power output was increased by 30 W·min⁻¹ until volitional exhaustion. VO₂peak was determined as the highest value achieved over a 20-s period.

Time trials. Endurance performance was determined to provide an integrated physiological readout to facilitate comparison of the present study with previous studies which provided data from muscle biopsy samples. Subjects performed two self-paced cycling time trials in which 250 kJ of work had to be completed as fast as possible. The linear factor was chosen to produce a power output corresponding to 75% of W_{max} at a pedal rate of 90 rpm. No encouragement was given, and subjects were blinded from information on time, power output and pedal frequency. The amount of work (kJ) completed was called out every 25 kJ. Time trials were spaced at least two days apart. The fastest time achieved in the two trials was considered to be the pre-training performance level.

Sprint interval training

The sprint training protocol was similar to that used previously by Burgomaster *et al.* [4, 13]. Six sessions of sprint interval exercise were spread over 14 days, with 1 or 2 days of rest between each session. Each training session consisted of 4-6 repeated 30-s all-out cycling efforts (Wingate tests) with 4 min of recovery between sprints. During recovery, subjects remained on the bike and either rested or cycled at a low cadence without resistance. The number of sprints increased from 4 during the first two sessions, to 5 in the third and fourth sessions, and 6 in the last two sessions.

Post-training assessment

Subjects in the training group underwent a second OGTT either two or three days after completion of the last training session, followed one day later by a third cycling time trial. Subjects in the control group performed their second OGTT and third time trial approximately two weeks after completion of baseline testing.

Calculations and statistical analysis

Area under the plasma curve (AUC) was calculated using the conventional trapezoid rule. Cederholm index, which represents peripheral insulin sensitivity [14], was calculated using the formula:

$$ISI_{\text{Cederholm}} = 75000 + (G_0 - G_{120}) \times 1.15 \times 180 \times 0.19 \times BW / 120 \times G_{\text{mean}} \times \log(I_{\text{mean}})$$

Where BW is body weight, G_0 and G_{120} are plasma glucose concentration at 0 and 120 min ($\text{mmol}\cdot\text{l}^{-1}$), and I_{mean} and G_{mean} are the mean insulin ($\text{mU}\cdot\text{l}^{-1}$) and glucose ($\text{mmol}\cdot\text{l}^{-1}$) concentrations during the OGTT.

All data are presented as means \pm SEM. Plasma glucose, insulin, and NEFA responses to the baseline and post-intervention OGTTs were analyzed using repeated measures ANOVA with *post hoc* Student Newman-Keuls tests. Differences between baseline and post-intervention data for time trial performance and AUC for plasma glucose, insulin, and NEFA levels were analyzed using paired sample t-tests. Significance was accepted at $P < 0.05$.

Results

Glucose responses

In the pre-training OGTT, plasma glucose concentration was elevated 60 min after the 75 g glucose bolus (Figure 1A; 0 min: 5.0 ± 0.1 v 60 min: 6.5 ± 0.4 mmol·l⁻¹; $P < 0.001$), but not post HIT (Figure 1A; 0 min: 5.0 ± 0.1 v 60 min: 5.0 ± 0.2 mmol·l⁻¹). The plasma glucose area under the curve (AUC) was significantly reduced post training (Figure 1A: AUC pre 664 ± 103 v AUC post 585 ± 65 mmol·l⁻¹·min⁻¹; $P < 0.001$). Glucose response to the first and second OGTT did not differ in the control group (plasma glucose AUC: 671 ± 47 v 659 ± 40 mmol·l⁻¹·min⁻¹).

Insulin responses

In the pre training OGTT, plasma insulin concentration was elevated 60 min after the 75 g glucose bolus (Figure 1B; 0 min: 10.5 ± 1.6 v 60 min: 74.0 ± 8.9 mU·l⁻¹; $P < 0.001$). Post training this increase was significantly attenuated (Figure 1B; 0 min: 10.6 ± 1.6 v 60 min: 42.6 ± 6.0 mU·l⁻¹; $P < 0.001$). Plasma insulin remained elevated 90 min after the 75 g glucose bolus both pre and post training (pre: 38.8 ± 6.3 mU·l⁻¹, $P < 0.001$; post: 27.7 ± 2.7 mU·l⁻¹, $P < 0.05$). The plasma insulin AUC was significantly reduced post training (Figure 1B: AUC pre 4226 ± 1912 v AUC post 2654 ± 1252 mU·l⁻¹·min⁻¹; $P < 0.001$). Insulin sensitivity significantly improved following 2 weeks of HIT (Cederholm index: pre 80 ± 6 v post 98 ± 5 mg·l²·mmol⁻¹·mU⁻¹·min⁻¹, $P < 0.01$).

NEFA responses

HIT was associated with a significant decrease in baseline plasma NEFA concentration (Figure 1C; pre: 350 ± 36 v post: 290 ± 39 μmol·l⁻¹, $P < 0.05$). In the pre training OGTT, plasma NEFA concentration was decreased 60 min after the 75 g glucose bolus (Figure 1C; 60 min: 255 ± 48 μmol·l⁻¹; $P < 0.01$ v 0 min), and to a greater extent post HIT (Figure 1C; 60 min: 153 ± 17 μmol·l⁻¹; $P < 0.001$ v 0 min,

$P < 0.001$ pre v post). The plasma NEFA AUC was significantly reduced post training (Figure 1C: AUC pre 31584 ± 13205 v AUC post $23370 \pm 8630 \mu\text{mol}\cdot\text{l}^{-1}\cdot\text{min}^{-1}$; $P < 0.001$). Plasma NEFA response to the OGTTs did not change in the control group (AUC: 24035 ± 1611 v $22599 \pm 2544 \mu\text{mol}\cdot\text{l}^{-1}\cdot\text{min}^{-1}$).

Physiological considerations

To bench-mark our results with recently published studies, we determined the impact of HIT on performance. The 250 kJ time trial performance was significantly improved by an average of 6% following 2 weeks of HIT (mean difference: 75 s, 95% CI: 21-126 s; $P < 0.01$). Performance did not change significantly in the control group (pre: 1477 ± 214 v post: 1491 ± 245 s). At baseline, the only physiological parameter which related to a metabolic parameter, was aerobic capacity vs. NEFA response to the OGTT ($R^2=0.43$, $P < 0.001$). There was a modest correlation between changes in glucose and insulin AUC ($R^2=0.25$, $P < 0.05$). Changes in performance did not correlate with any of the other changes. We also considered whether the timing of the post-training assessment impacted on the observed metabolic changes. Improvements in glucose or NEFA responses were similar whether assessed two or three days following the final training session (mean improvement: glucose AUC, 2d post 12 ± 10 %, 3d post 19 ± 4 %; NEFA AUC, 2d post 23 ± 21 %, 3d post 27 ± 9 %).

Discussion

While exercise training represents one of the most powerful strategies to reduce future development of metabolic disease in healthy adults [15], most adults fail to meet current guidelines for participation [16]. These guidelines largely focus on the

accumulation of time spent carrying out moderately intense activity (or total energy expenditure) and ultimately require many hours of exercise each week. This is perceived as a major time commitment, driving or contributing to the low compliance. In the present study we demonstrate for the first time that only a few minutes of *high* intensity exercise performed over two weeks is required to substantially improve insulin action and glucose homeostasis in healthy men. This is both an important and useful finding, as preventative interventions should logically be implemented as early as possible to prevent age related development of cardiovascular disease.

Interestingly, despite employing long-term training interventions (2-16 months) the majority of studies investigating classic aerobic [9, 17-22] or strength training programs [23-25] have observed only a reduction in insulin area under the curve (AUC) in response to a glucose load following training, without a concomitant reduction in glucose AUC, indicating only a partial improvement in insulin action. The few longitudinal studies to have shown reductions in glucose AUC performed post-training OGTTs within 24 hours of the last exercise bout [26-28], therefore studying the combined impact of acute and chronic exercise [29]. In contrast, the low volume, but high intensity training utilized in the current study significantly reduced both glucose AUC (-12%) and insulin AUC (-37%), with a sustained benefit observed when OGTTs performed 2 or 3 days after the last exercise session. This was achieved without changes in body weight, and with a weekly energy-cost of training of just 45.2 ± 5.2 kcal during the first training week and 55.4 ± 5.2 kcal during the second training week (compared to ~ 2000 - 3000 kcal \cdot week $^{-1}$ in typical aerobic training programs [22, 30]). This implies that the mechanism underpinning the benefits we

observe with HIT, may be distinct from those responsible for the more modest improvements in insulin action with classic time consuming aerobic training.

Skeletal muscle is considered the major tissue responsible for the uptake of glucose following a glucose or insulin challenge [31] such that it is entirely reasonable to assume that muscle glucose uptake was substantially enhanced following HIT. The limiting step in glucose disposal is considered to be its transport into the skeletal muscle [6] and GLUT4 is the most abundant glucose transporter in skeletal muscle. Increased GLUT4 concentration with endurance training has been suggested to be an important factor regulating insulin sensitivity [6, 32]. Burgomaster *et al.* reported that skeletal muscle GLUT4 levels increase by ~20% after one week of HIT and remain elevated over 6 weeks of training and the subsequent 6 weeks of detraining [13]. Given the similarity in the aerobic performance improvements between our subjects and those involved in the Burgomaster studies, our studies should be comparable and thus an increase in GLUT4 may contribute to our findings. However, other mechanisms contribute to training-induced improvements in insulin sensitivity [32].

It has been demonstrated that key regulatory proteins in the insulin signalling pathway within skeletal muscle become more activated in response to insulin following aerobic training [33]. It has been shown that HIT produces similar changes in skeletal muscle markers of carbohydrate and lipid metabolism to aerobic training [34], so it should be investigated whether HIT produces similar adaptations of the insulin signalling pathway as seen following aerobic training [33]. Furthermore, a novel feature of HIT is the relatively large muscle mass is recruited during exercise, and this in turn would ensure glycogen breakdown and thus turnover occurs within a

greater proportion of fibres than classic aerobic training. Muscle contraction under condition of metabolic stress (such as that incurred during HIT) results in a very rapid depletion of glycogen degradation [35] and this would almost certainly acutely alter the binding of a variety of glycogen associated proteins [36, 37]. Improved whole body glucose disposal following training has been associated with an increase in insulin stimulated glycogen synthesis [38]. Therefore, remodelling of the glycogen pool, altering the molecules branching architecture [39], may well be important in regulating skeletal muscle insulin sensitivity following HIT.

Insulin sensitivity may also be regulated by plasma NEFA concentration. In lean and obese non-diabetic middle aged subjects, pharmacological lowering of plasma NEFA levels results in improved oral glucose tolerance with decreased plasma glucose and insulin AUC following an OGTT [40]. Conversely, raising plasma NEFA concentration through infusion of lipid emulsion results in a lower glucose infusion rate during peripheral insulinemia-euglycemia in young men [41]. In the present study, HIT was associated with a 17% decrease in fasting plasma NEFA concentration without a concomitant change in fasting insulin, as well as a 26% reduction in NEFA AUC following HIT despite a 37% reduction in the plasma insulin AUC. This is in contrast with studies in which 10 weeks of aerobic training failed to affect fasting plasma NEFA concentration [42], and only elicited a small effect on plasma NEFA AUC (2%) and plasma insulin AUC (5%) following a glucose load in young healthy subjects [43]. These data suggest that insulin was able to inhibit lipolysis to a greater extent, following HIT, consistent with the finding with traditional endurance training where a fall in interstitial glycerol concentration in adipose tissue can be observed [44].

Conclusion

In conclusion, we demonstrate for the first time that low volume high intensity exercise is sufficient for significant improvements in glycemic control in otherwise healthy young adults. Our findings warrant further studies investigating the effectiveness of HIT in improving glycemic control in individuals at risk of developing T2D.

Competing Interests

No authors report any competing interests

Author contribution

JB and NBJV participated in the study design, analysis, writing and editing of the manuscript, CK, FMG and GC participated in data generation and study analysis, JAT participated in the study design, writing and editing of the manuscript.

Acknowledgements

This work has been funded by Heriot-Watt University (L6004-JT). We would like to thank Martin J Gibala for his very useful comments during the preparation of this manuscript.

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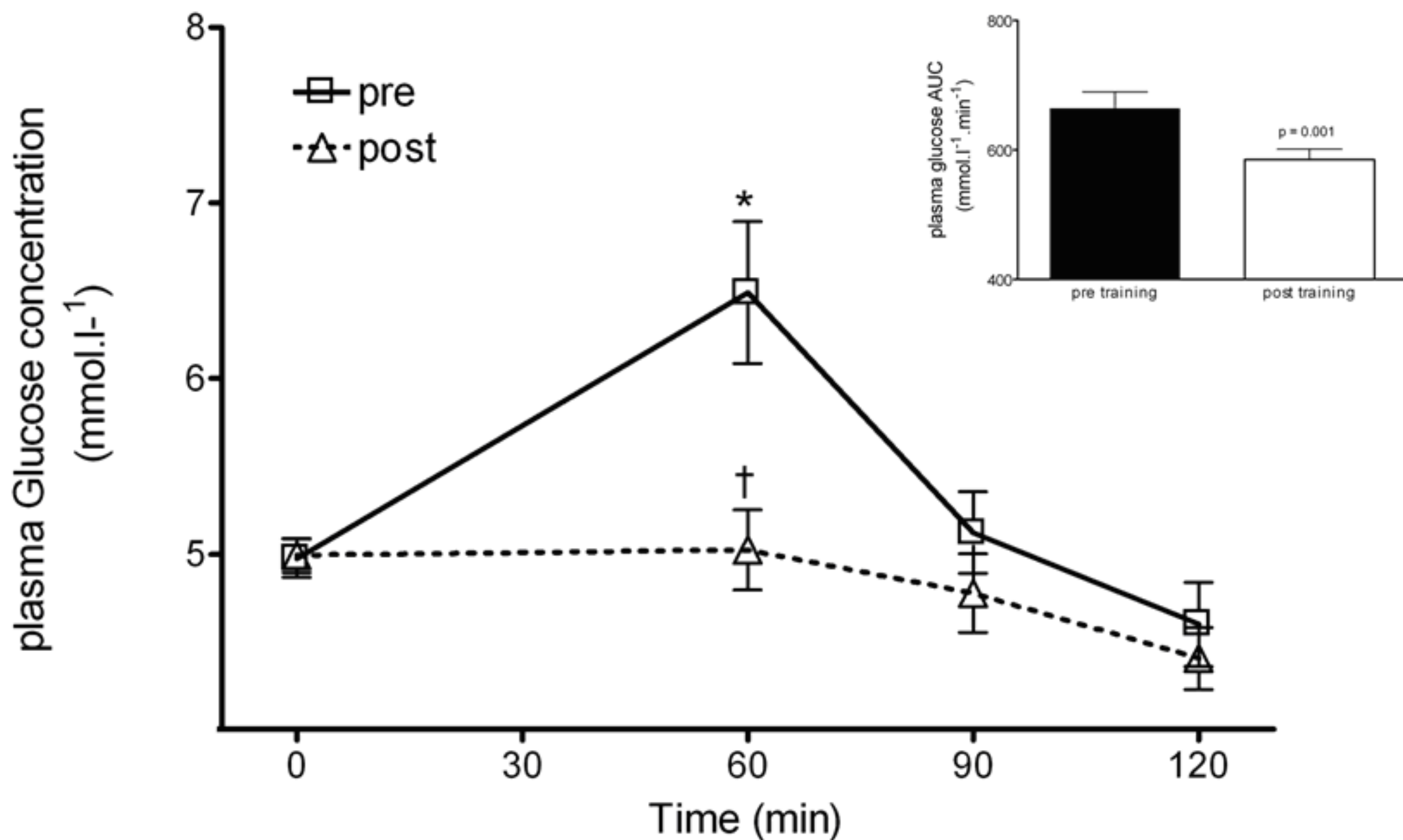
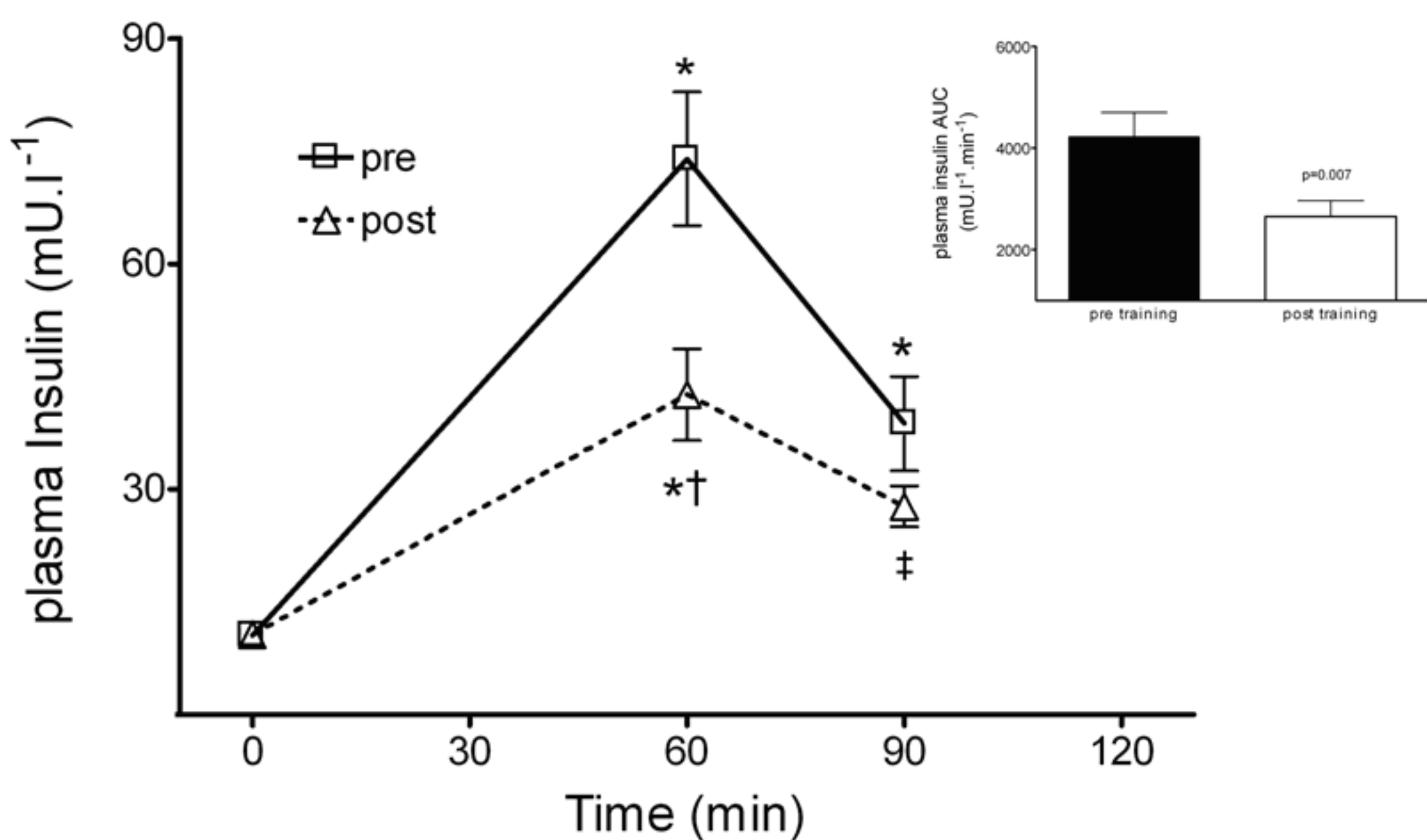
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Figure 1. Response to oral glucose load. A: plasma glucose concentration and AUC (* P<0.001 for pre 0 v pre 60 min; † P<0.001 for post 60 v pre 60 min); B: plasma insulin concentration and AUC (* P<0.001 v 0 min, ‡ P<0.05 v 0 min, † P<0.001 for post 60 v pre 60 min); C: plasma NEFA concentration and AUC (* P<0.001 v 0 min, ° P<0.01 v 0 min, ‡ P<0.05 post v pre 0 min, † P<0.001 post v pre 60 min).

Table 1. Subject characteristics at baseline

	Training group (n=16)	Control group (n=9)
Age (y)	21 ± 2	23 ± 8
Height (m)	1.3 ± 0.08	1.8 ± 0.09
Body-mass (kg)	82 ± 17	73 ± 9
BMI (kg·m ⁻²)	23.7 ± 3.1	23.0 ± 1.4
VO ₂ peak (ml·kg ⁻¹ ·min ⁻¹)	48 ± 9	47 ± 11
fasting glucose (mmol·l ⁻¹)	5.0 ± 0.4	4.9 ± 0.4
fasting NEFA (μmol·l ⁻¹)	350 ± 36	364 ± 13

Values shown are means ± SD

A**B****C**