Divergence in exercise-induced adaptive change in glucose tolerance between low and high responders to training

Lauren Clink
Medical University of Ohio

Follow this and additional works at: http://utdr.utoledo.edu/graduate-projects
Divergence in Exercise-induced Adaptive Change in Glucose Tolerance Between Low and High Responders to Training

Submitted by

Lauren Clink

In partial fulfillment of the requirements for the degree of Master of Science in Biomedical Sciences

Date of Presentation:

June 29, 2005

Academic Advisory Committee

Major Advisor
Abraham Lee, Ph.D.

Department Chairperson
Clayton Holmes, Ed.D., P.T.

Dean, College of Health Sciences
Christopher E. Bork, Ph.D., P.T.

Dean, College of Graduate Studies
Keith K. Schlender, Ph.D.
Divergence in Exercise-Induced Adaptive Change in Glucose Tolerance between Low and High Responders To Training.

Lauren Clink and Abraham D. Lee, Dept. of Physical Therapy, MUOT

Abstract

In a previous study, we found moderate heritability (25%) of a training-induced adaptive change in glucose tolerance and divergence between low and high responders of rats in the 1st generation from founding parents. **PURPOSE:** The purpose of this study was to test the hypotheses that 1) divergence in a training-induced change in glucose tolerance between the low and high responders would be maintained in a 2nd generation and 2) changes in insulin secretion and action would differ between the two lines of the responders after training. **SUBJECTS:** Seventy-one 2nd generation offspring of N/NIH strain of rats (40 in the low responding line and 31 in the high responding line) were used for the study. **METHODS:** All rats underwent an intraperitoneal glucose tolerance test before and after an 8-day intense intermittent swim training (8-10 bouts of 20-sec swim and 20-sec rest between bouts), carrying weight on the tail (14% body weight). Blood glucose was measured using a standard glucometer and the levels of plasma insulin and C-peptide were determined using radioimmunoassay kits from samples obtained before, and 30 and 60 minutes after a glucose injection (2g/kg body weight). **ANALYSIS:** The area under glucose curve (AUC) was calculated using a trapezoid rule. Improvement in glucose tolerance (= posttraining AUC - pretraining AUC) and changes in insulin secretion and sensitivity were analyzed using 2 x 2 ANOVA or MANOVA followed by t-test at a significant α-level of P ≤ 0.05. **RESULTS:** Improvement in glucose tolerance in the high line was significantly higher (12%, P<0.05) than that in the low line, showing the maintenance of divergence between the two lines. A significant improvement in insulin sensitivity of peripheral tissues after the training was found in the high line (42%, p<0.05) not in the low line. No difference in insulin secretion capacity between the two lines existed whereas a significant increase in hepatic insulin extraction occurred only in the low line (15%, P<0.05) after the training. **CONCLUSION:** These results demonstrate that a genetic animal model with a selective breeding for training-induced adaptive change in glucose tolerance is feasible and insulin action to peripheral tissue and insulin clearance by hepatic tissue may be responsible for a various extent of improvement in glucose tolerance after training. The finding of the maintained divergence in a training-induced change in glucose tolerance between the two lines in this study also confirms that the extent of change in glucose tolerance after training is a heritable trait.
Introduction

Diabetes, especially type 2 diabetes, is a significant public health problem resulting in substantial morbidity and mortality creating enormous economic consequences of medical expenditures for many countries. The number of adults with diabetes in the world will rise from 135 million in 1995 to 300 million in the year 2025 with the majority from developing countries (12). The polygenic metabolic syndrome is characterized by insulin resistance, hyperinsulinemia, glucose intolerance, obesity, dyslipidemia, and hypertension. Insulin plays an important role in maintaining the homeostasis of blood glucose by facilitating glucose entry into insulin-sensitive tissues such as skeletal muscles. In the presence of insulin resistance, the pancreas secretes insulin more than usual to compensate for the loss of insulin action and to maintain blood glucose within a normal limit, resulting in hyperinsulinemia. However, over time the pancreas fails in secreting insulin at a higher rate than usual, resulting in an impaired insulin secretion. Insulin resistance, impaired insulin secretion and compensatory hyperinsulinemia have been proposed as a causal link to the development of the diabetes.

One important factor in the management of Type 2 Diabetes is exercise. Several benefits of exercise training include: decreased blood glucose (14,4,21), improved glucose tolerance (14,4,21), increased insulin sensitivity (14,4,21,23,31), change in body composition (4), decreased hypertension (4), improved hepatic insulin sensitivity (36), decreased HbA1c (8), decreased blood triglycerides (4,22), increased HDL-cholesterol (4), decreased psychological stress and self-esteem (4). Many biochemical changes contributing to these benefits after exercise include: increased GLUT-4 expression, an insulin-induced glucose transporter (4,9), increased glycogen stores (4,20), increased muscle oxidative capacity (20), increased hepatic insulin signaling (36), increased enzyme activity of metabolic pathways such as AMP-activated protein kinase (AMPK) and calcineurin (4,9), citrate synthase and beta-hydroxyacyl-CoA dehydrogenase (11), decreased phosphofructokinase activity (11), increased PI3-kinase associated with IRS-1 and IRS-2 and increased Akt-1/PKB (15).

In addition to enzyme function, specific genes related to glucose metabolism have been identified. Genes such as IPF1, NEUROD1, PAX6, and MafA have been linked to individuals with diabetic phenotypes (18,30,19,27). Exercise-induced changes in insulin level and insulin action have also been linked to individual genotypes including PPARγ (32), β3AR (33,34), ACE (5,24,6) and uncoupling proteins (33). With the identification of genetic markers of diabetic individuals, scientists
have begun to demonstrate heritable correlations specifically for insulin sensitivity and glucose tolerance. Studies measuring insulin sensitivity at rest have estimated heritability between 30% and 40% (7,16,25,35), while another study showed 50% heritability for fasting glucose (26), suggesting that these phenotypes are significantly influenced by genetic factors. With metabolic syndrome traits being more prevalent in certain ethnicities, studies have been able to show stronger familial correlations. Hong et al. found 25% heritability of glucose tolerance among whites and 48% among blacks of the HERITAGE Family Study (10). Exercise-induced changes of glucose tolerance in relation to heritability have also been identified. Koch et al showed a higher divergence (70%) for aerobic capacity between high and low selected lines of a third generation of endurance trained rats (13). Lee et al. also showed 25% heritability and increased divergence (P<0.05) for improvements in glucose tolerance of a first generation of endurance-trained rats between a high low and line low of responders (14). However, it is not known if exercise induced improvements will continue in additional generations. Thus, the purpose of this study was to determine if 1) a divergence between selectively-bred high and low lines from the 1st generation in training-induced change in glucose tolerance would continue to the 2nd generation and 2) insulin secretion and action would differ between the two lines.

Research Design and Methods

Animals: Seventy-one rats of the second generation, 10-15 week old, (41=Low line, 30=High line) were used for this study. These rats were selectively bred from 3 families of the low line and 3 families of the high line of an N/NIH first generation, which were obtained from founding parents with heterogenetic backrounds. The high line demonstrates the greatest change in glucose tolerance in response to exercise whereas the low line demonstrates the least change in glucose tolerance in response to exercise. The rats were housed at a constant 22°C with a fixed 12-hour on, 12-hour off light/dark cycle and free access to food and water.

Intraperitoneal Glucose Tolerance Test (IPGTT): An IPGTT was performed on each rat after an overnight fast before and after exercise training according to the protocol used by Lee et al for the 1st generation (14). Rats were weighed, anaesthetized by intraperitoneal injection of pentobarbital (20-30 mg/kg body weight) and placed in a Plexiglas rat holder. The tail was warmed in a water bath maintained at 40°C for 5 minutes and a catheter was inserted into a tail vein for blood collection.
Glucose was injected intraperitoneally (2g/kg BW) 15 minutes after the first collection (0 min) and blood was collected again 30 and 60 minutes after glucose injection. Whole blood glucose concentration was immediately measured using an Accu-Chek Advantage automatic glucometer.

**Insulin and C-Peptide Assay:** Blood samples were centrifuged and plasma fractions were collected and stored at -80°C for later analysis. Insulin and C-peptide were determined using a radioimmunoassay kit (Linco Research Inc., St. Charles, MO).

**Exercise Training:** Swim training protocol was adapted from Nagasawa et al (23). Rats swam 15 minutes in a bucket filled with ~45cm of water at 35°C in order to acclimatize them to swimming prior to training. Rats swam 8 bouts (20 secs on/20 secs off) on days 1 and 2, and 10 bouts on days 3-8 while bearing weight equal to 14% of body weight at the base of the tail.

**Data Analysis:** All statistical analyses were performed using SPSS version 11.5 for Windows 98 (Statistical Package for Social Science, Inc., Chicago, IL) and data was expressed in mean ±SE. All statistical significant differences were determined at an α level of P<0.05 unless otherwise noted. Insulin sensitivity index (ISI) was determined using a formula from Matsuda et al: ISI=10,000/[(fasting glucose x fasting insulin) x (mean glucose x mean insulin)]^{1/2} (17). Insulinogenic Index (IGI) was calculated from a common formula: (insulin_{30 min} - insulin_{0 min}) / (glucose_{30 min} - glucose_{0 min}). Early phase C-peptide secretion was similarly calculated by dividing change in C-peptide with change in glucose during the 1st 30 min of IPGTT: (C-peptide_{30 min} - C-peptide_{0 min}) / (glucose_{30 min})-(glucose_{0 min}). Hepatic extraction, defined as 1- (Insulin_{30 min-0 min} / C-peptide_{30 min-0 min}), was compared to ISI using a regression line to find significance. To assess a change in glucose tolerance after training, total area under the glucose tolerance curve of (AUC) was calculated using trapezoid rule (29) and a change in glucose tolerance was determined by subtracting pre-training AUC from post-training AUC (Δ = post-training AUC – pre-training AUC) (26). A 2 x 2 ANOVA was used to determine if the pattern of change in glucose tolerance after training between the two lines would differ. This was followed by a paired or no-paired t-test if a significant difference was found. Changes in insulin and C-peptide after training were assessed in the similar way as changes in glucose tolerance using 2 x 2 MANOVA. C-peptide response to glucose, IGI, hepatic extraction and ISI also used a 2 x 2 MANOVA followed by a 2 x 2 ANOVA. Paired t-tests were performed if a significant difference was found. Independent t-tests
were also performed between high and low lines for each variable to determine further significance after training.

Results

**Reliability**: 10 random rat plasma samples were analyzed twice for insulin and c-peptide to see the reliability of analyses. There was no difference between the trials for insulin (P=0.94) and C-peptide (P=0.75). The coefficient of variation for insulin trial 1 was 15% and trial 2 was 17%. The coefficient of variation for C-peptide trial 1 was 23% and trial 2 was 21%.

**Glucose Tolerance**: The results of glucose tolerance are shown in Fig. 1, Fig. 2 and Fig. 3. The post-training value in the low line (Fig. 1) at 60 minutes was significantly lower (P<0.05) compared with pre-training value whereas in the high line post-training glucose values at all 3 time points were significantly lower than the pre-training values (P<0.05 at 0 and 30 min, P<0.01 at 60 min) (Fig. 2). No significant difference in AUC for glucose between pre- and post-training in the low line whereas there was a significant decrease (P<0.01) in AUC for glucose in the high line after training. (Fig. 3),

**Insulin and C-peptide Response and Hepatic Extraction of Insulin**: Insulin values were measured at rest and in response to a glucose load before and after training. The post exercise value in the low line (Fig. 4) at 60 minutes was significantly lower (P=0.005) compared to before training whereas no significance after training was shown in the high line (Fig. 5). There was a significant decrease in insulin AUC after training in the low line (P<0.04) however no significant change was shown in the high line (Fig. 6). To see whether or not changes in insulin secretion from the pancreas after training reflects the changes in insulin levels in the low and high lines, C-peptide was measured. The results are shown in Fig. 7 for the low line and in Fig. 8 for the high line. There was no significant change in any time point and the AUC (Fig. 9) in either the low or high line after training. On the other hand, there was a significant increase in hepatic extraction from 66% to 76% (P<0.01) in the low line after training without training effect in the high line (Fig. 10).

**Insulin Sensitivity**: Insulin sensitivity showed an increasing trend after training in the low line whereas significant improvement was shown in the high after training (P<0.05) (Fig. 11). There was a linear
relationship between insulin sensitivity and hepatic insulin extraction after training in both low 
\( r=0.59, \ P<0.001, \) Fig. 12) and high lines \( r=0.66, \ P<0.001, \) Fig. 13).

**Intrinsic Glucose Tolerance:** To evaluate if an intrinsic glucose tolerance influences training-induced 
 improvement in glucose tolerance, pre-training glucose AUC was plotted against post-training AUC. 
The results are shown in Fig. 14 for the low line and Fig. 15 for the high line. There was a significant 
correlation between the two variables in the low line \( r = 0.41, \ P<0.05 \) not in the high line \( r =0.25, \ P>0.05 \).

**Divergence in glucose tolerance between the two lines:** An improvement in glucose tolerance after the training was 185.25±382.78 mg/dl.min in the low line and 1600.16±548.95 mg/dl.min in the high line. 
The difference between the low and high lines was significant \( P<0.05, \) Fig. 16. There was no further 
significant improvement from generation 1 to generation 2 in the high line whereas the improvement in the generation 2 was significantly lower than that in the generation 1 in the low line \( P<0.05, \) Fig. 16.

**Discussion**

The purpose of this study was to determine if 1) a divergence in training-induced change in glucose tolerance between selectively-bred high and low lines found in the 1st generation would continue to the 2nd generation and 2) insulin secretion and action would differ between the two lines. 
Improvement (= posttraining AUC – pretraining AUC) in glucose tolerance after the training for the high line \(-1600.16 \pm 548.95 \) was significantly higher \( P<0.05 \) than that in the low line \(-185.25 \pm 382.78 \) mg/dl.min), showing a maintained divergence between the two lines. There was a further 
decrease \( P<0.05 \) in the low line while there was no change in the high line from the 1st generation.

The question is whether insulin sensitivity, insulin secretion, and hepatic extraction could help explain the maintained divergence between the two lines. Insulin sensitivity influences the magnitude of the excursion of glucose tolerance curve during a glucose tolerance test: less excursions in individuals with high insulin sensitivity and more excursions in individuals with insulin resistance from a base line \( (17) \). 
In this study there was a significant improvement in insulin sensitivity in the high line while there was 
no improvement in the low line. Thus, difference in improvement in glucose tolerance between the two 
lines can be explained partly. However, this may not be an only variable that accounts for the
difference between the two lines. Lee et al. found improvement in insulin sensitivity in both lines in spite of a large difference in improvement in glucose tolerance after the training between the two lines. A low capacity of the β-cells of the pancreas to secrete insulin is associated with a glucose intolerance in individuals with impaired glucose tolerance or type 2 diabetes mellitus (3). Thus, it is logical to see if or not there was a difference in insulin secretion between the two lines. As shown in Fig. 9, there was no difference for insulin secretion based on C-peptide AUC between the two lines. However there was a difference in hepatic insulin extraction between the two lines. There was a significant increase in hepatic insulin extraction in the low line whereas there was no change in the high line after the training during the first 30 min of glucose tolerance. This is reflected in a significant decrease in insulin AUC in the low line while there was no significant change in the high line after the training. Thus, it is possible that the combination of a significant decrease in insulin levels and no change in peripheral tissue insulin sensitivity in the low line after the training may result in less improvement in glucose tolerance compared with that in the high line.

In the literature it has been reported that several genotypes are associated with changes in insulin action after training. This includes PPARγ (32), β3AR (33,34), ACE (5,24,6) and uncoupling proteins (33). It is of interest to see if there are differences in the expression of these genotypes between the high and low lines in the future.

Summary

The purpose of this study was to determine 1) if there was a continued divergence in improvement in glucose tolerance in the 2nd generation and 2) whether there was a change in insulin action and insulin secretion after training between the low and high lines, which were selectively bred for training-induced improvement in glucose tolerance. A significant improvement in glucose tolerance was found after training in the high line whereas no improvement was observed in the low line. The difference in training-induced improvement in glucose tolerance between the two lines in the 2nd generation was found to be statistically significant as observed in the 1st generation. This difference was result from no further improvement in the high line and a significant decrease in improvement from the 1st generation in the low line. This result demonstrated a continuous divergence between the two lines in the 2nd generation.

An additional variable found to be significant after training in the high line was insulin sensitivity, suggesting a significant improvement in insulin sensitivity of peripheral tissues. There was
no significant improvement in insulin sensitivity in the low line. However, in the low line there was a significant decrease in insulin AUC and a significant improvement in hepatic extraction after the training. It appears that a lack of improvement in glucose tolerance in the low line results from the combination of lack of improvement in insulin sensitivity and an increased hepatic insulin extraction.

This suggests that the interaction between a pool of genes and the training in the high line is different from that in the low line reinforcing the theory that a wide variability exists for exercise-induced adaptive changes in glucose tolerance. According to the results, a genetic animal model with a selective breeding for training-induced adaptive change in glucose tolerance is feasible and insulin action to peripheral tissue and insulin clearance by hepatic tissue may be responsible for a various extent of improvement in glucose tolerance after training.

Currently, there is limited data that suggest physiological variables, which are responsible for difference magnitude improvement in glucose tolerance after training. It is hoped that questions related to various extent in training-induced improvement in glucose tolerance can be answered through the creation of the selective breeding model for glucose tolerance.
Figure Legend

Figure 1 Mean glucose values at rest and in response to a glucose load before and after exercise for the low line (n=40). A significant decrease was shown in glucose at 60 minutes post training (P<0.05, 181.25±7.56). Data expressed as means ± SE.

Figure 2 Mean glucose values at rest and in response to a glucose load before and after exercise for the high line (n=31). Significant improvement was shown before and after a glucose load after training [(0 min: P<0.05, 84.94±1.92), (30 min: P<0.05, 266.68±9.53), (60 min: P<0.01, 177.90±10.09)]. Data expressed as means ± SE.

Figure 3 Glucose area under the curve before and after training between the low (n=40) and high (n=31) line. A significant decrease or improvement in glucose tolerance was shown only in the high line after training (P<0.01, 11942.9±405.49). Data expressed as means ± SE.

Figure 4 Mean insulin values are shown at rest and in response to a glucose load before and after training for the low line (n=40). A significantly decreased amount of insulin was shown 60 minutes post training (P<0.01, 363.61±40.59) in response to a glucose load. Data expressed as means ± SE.

Figure 5 Mean insulin values are shown at rest and in response to a glucose load before and after training for the high line (n=31). No significance was shown after training in either line. Data expressed as means ± SE.

Figure 6 Insulin area under the curve before and after training for the low (n=40) and high (n=31) line. A significant decrease after training (P<0.04, 32816.1±4897.1) was shown only in the low line demonstrating the ability of the pancreas to secrete less insulin and for the liver to extract more insulin from the blood after training. Data expressed as means ± SE.

Figure 7 Mean C-peptide values at rest and in response to a glucose load before and after training for the low line (n=40). No significance was observed after training. Data expressed as means ± SE.

Figure 8 Mean C-peptide values at rest and in response to a glucose load before and after training for the high line (n=31). No significance was observed after training. Data expressed as means ± SE.

Figure 9 C-peptide area under the curve shows an accurate amount of insulin secreted from the pancreas before and after training in the low (n=40) and high (n=31) line. No significance was shown after training. Data expressed as means ± SE.

Figure 10. Amount of insulin extracted by the liver before and after training in the low (n=40) and high (n=31) line. A significant increase in hepatic extraction was shown only in the low line (P<0.01,
76%±2%). The high line also showed high extraction values (71% pre, 75% post) however there was no significance in response to training. Data expressed as means ± SE.

**Figure 11** Insulin sensitivity to skeletal muscle before and after training in the low (n=40) and high (n=31) line. Significant improvement was shown after training only in the high line (p<0.05, 3.54±0.50). Data expressed as means ± SE.

**Figure 12** Interaction between insulin sensitivity and hepatic insulin extraction after training for the low line (n=40). The regression equation, y=0.067x+0.521 (r=0.59, P<0.001), demonstrates a significant, positive relationship between ISI and hepatic insulin extraction in response to training. Data expressed as means ± SE.

**Figure 13** Interaction between insulin sensitivity and hepatic insulin extraction after exercise for the high line (n=31). The regression equation, (y=0.058x+0.551, r=0.66, P<0.001), demonstrates a significant, positive relationship between ISI and hepatic insulin extraction in response to training. Data expressed as means ± SE.

**Figures 14** The influence of intrinsic glucose on post exercise glucose tolerance in the low line (n=40) was demonstrated by an improvement in glucose tolerance (post AUC – pre AUC) or ideally a positive slope <1.0. Intrinsic glucose was shown to significantly influence glucose tolerance (y=0.4956x+6206, r = 0.41, P<0.05). Data expressed as means ± SE.

**Figure 15** The influence of intrinsic glucose on post exercise glucose tolerance in the high line (n=40) was demonstrated by an improvement in glucose tolerance (post AUC – pre AUC) or ideally a positive slope <1.0. No significance was shown between intrinsic glucose and glucose tolerance in response to training (y=0.2092x+9109, r =0.25, P>0.05). Data expressed as means ± SE.

**Figure 16** A divergence of exercise-induced changes in glucose tolerance over two generations in the low (n=40) and high (n=31) line. The second generation showed significant divergence between the high and low line (P<0.05).
References


**Fig. 1, P<0.05**  Glucose Response to a Glucose Load: Low Line

**Fig. 2, P<0.05**, **P<0.01**  Glucose Response to a Glucose Load: High Line
**Fig. 3, p<0.01 *** Glucose AUC**

**Fig. 4, p<0.01 *** Insulin Response to Glucose Load: Low Line**
Fig. 5  Insulin Response to Glucose Load: High Line

Fig. 6, p<0.05 **  Insulin AUC
Fig. 7  C-Peptide Response to Glucose Load in the Low Line

Fig. 8  C-Peptide Response to Glucose Load in the High Line
Fig. 9  Cpeptide AUC

Fig. 10, p<0.01 ***  Hepatic Extraction of Insulin
Fig. 11, p<0.05 ** Insulin Sensitivity Index

Fig. 12  Hepatic Extraction in Response to ISI: Low Line

$y = 0.0667x + 0.521, r = 0.59, p<0.001$
**Fig. 13** Hepatic Extraction in Response to ISI: High Line
\[ y = 0.058x + 0.551, \ r = 0.66, \ p < 0.001 \]

**Fig. 14** Intrinsic Glucose Response to Glucose Tolerance: Low Line
\[ y = 0.4956x + 6206, \ r = 0.41, \ p < 0.01 \]
Pre Training AUC, mg/dl - min

Post Training AUC, mg/dl - min

$y = 0.2092x + 9109, r = 0.25, p > 0.05$

**Fig. 15** Intrinsic Glucose Response to Glucose Tolerance: High Line

Training-induced improvement, (mg/dl).min

**Fig. 16** p<0.05 **  Divergent Response of Glucose Tolerance
Table 1—Determinants of Glucose Tolerance Divergence

<table>
<thead>
<tr>
<th></th>
<th>High Line Pre Training</th>
<th>High Line Post Training</th>
<th>High Line Δ Training</th>
<th>Low Line Pre Training</th>
<th>Low Line Post Training</th>
<th>Low Line Δ Training</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW, g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>262.16±11.43</td>
<td>266.61 ± 11.48</td>
<td>*4.45 ± 2.10</td>
<td>259.78 ± 9.40</td>
<td>262.70 ± 9.01</td>
<td>*2.93 ± 1.64</td>
</tr>
<tr>
<td>Glucose AUC, mg/dl.min</td>
<td>13543.07±</td>
<td>11942.90±</td>
<td>**-1600.16 ±</td>
<td>12672.00±</td>
<td>12486.75±</td>
<td>-185.25 ±</td>
</tr>
<tr>
<td></td>
<td>485.23</td>
<td>405.49</td>
<td>548.95</td>
<td>320.89</td>
<td>381.61</td>
<td>382.78</td>
</tr>
<tr>
<td>Insulin AUC, uU/ml.min</td>
<td>34008.93±</td>
<td>32816.14±</td>
<td>-1192.79 ±</td>
<td>38182.66±</td>
<td>30453.04±</td>
<td>*-7729.63 ±</td>
</tr>
<tr>
<td></td>
<td>4532.69</td>
<td>4897.06</td>
<td>3909.62</td>
<td>3786.87</td>
<td>2347.69</td>
<td>3531.56</td>
</tr>
<tr>
<td>Cpeptide AUC, pM.min</td>
<td>144273.02±</td>
<td>153159.81±</td>
<td>8886.79 ±</td>
<td>152890.68±</td>
<td>155123.15±</td>
<td>2232.47 ±</td>
</tr>
<tr>
<td></td>
<td>11545.67</td>
<td>1192.58</td>
<td>10069.35</td>
<td>8943.93</td>
<td>7771.01</td>
<td>8246.17</td>
</tr>
<tr>
<td>IGI, (uU/ml)/(mg/dl)</td>
<td>0.545± 0.10</td>
<td>0.543± 0.09</td>
<td>-0.002 ± 0.09</td>
<td>0.73± 0.10</td>
<td>0.60± 0.08</td>
<td>-0.14 ± 0.30</td>
</tr>
<tr>
<td>ISI</td>
<td>2.62± 0.34</td>
<td>3.54± 0.50</td>
<td>**0.91 ± 0.34</td>
<td>2.71± 0.32</td>
<td>3.01± 0.26</td>
<td>0.30 ± 0.11</td>
</tr>
<tr>
<td>C-peptide Response to Glucose (pM)/(mg/dl)</td>
<td>10.56± 1.49</td>
<td>13.60± 1.53</td>
<td>3.04 ± 1.61</td>
<td>12.81± 1.27</td>
<td>13.40± 1.09</td>
<td>0.59 ± 1.50</td>
</tr>
<tr>
<td>Hepatic Extraction</td>
<td>0.71± 0.04</td>
<td>0.75± 0.04</td>
<td>0.04 ± 0.05</td>
<td>0.66± 0.04</td>
<td>0.76± 0.02</td>
<td>**0.10 ± 0.04</td>
</tr>
</tbody>
</table>

High Line n=31, Low Line n=40
Values are expressed mean ± SE.  *P<0.05, **P<0.02