Obesity and diet affect glucose dynamics and insulin sensitivity in Thoroughbred geldings
R. M. Hoffman, R. C. Boston, D. Stefanovski, D. S. Kronfeld and P. A. Harris

_J ANIM SCI_ 2003, 81:2333-2342.

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.journalofanimalscience.org/content/81/9/2333
Obesity and diet affect glucose dynamics and insulin sensitivity in Thoroughbred geldings

R. M. Hoffman, R. C. Boston, D. Stefanovski, D. S. Kronfeld, and P. A. Harris

ABSTRACT: Insulin resistance is considered a risk factor in obesity, laminitis, exertional rhabdomyolysis, and osteochondrosis. The objective was to use the minimal model to estimate glucose effectiveness (Sg) and insulin sensitivity (Si) in nonobese to obese horses initially adapted to forage only, then adapted to forage plus supplements rich in starch and sugar (SS) or fiber and fat (FF). Ten Thoroughbred geldings, with BCS of 5 (nonobese), 6 (moderately obese), and 7 to 8 (obese), were adapted to pasture and hay, allocated to two groups, and fed SS or FF in a switch-back design with 8 wk of adaptation. Modified frequent-sampling i.v. glucose tolerance tests were applied after adaptation to forage, SS, and FF. For the tolerance tests, horses were kept in stalls overnight and provided hay, and venous catheters were placed the next morning. Baseline samples were collected, 0.3 g of glucose/kg of BW was given i.v., and blood was sampled at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 19 min. At 20 min, 30 mU of insulin/kg of BW was given, followed by sampling at 22, 23, 24, 25, 27, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 150, and 180 min. Plasma was analyzed for glucose and insulin, and Si, Sg, acute insulin response to glucose, and the disposition index were calculated. Normality was tested using the Shapiro-Wilk statistic. Body condition effects were analyzed using a mixed model with repeated measures. Diet effects were analyzed using a Wilcoxon signed rank test. The Sg was higher in obese than nonobese (P = 0.003) and moderately obese (P = 0.007) horses; Si was lower in obese than nonobese (P = 0.008) horses, and acute insulin response to glucose was higher in obese than nonobese (P = 0.039) horses. Effects of diet were likely confounded by body condition, but horses had lower Si (P = 0.066) when fed SS compared with FF, especially when nonobese. In conclusion, the minimal model effectively estimated Sg, Si, acute insulin response to glucose, and disposition index in horses. Obese geldings were insulin-resistant and seemed to rely primarily on Sg for glucose disposal. Feeding a diet rich in sugar and starch decreased insulin sensitivity of horses. Maintenance of body condition and avoidance of grain-based meals rich in sugar and starch would be beneficial to decrease the risk of developing insulin resistance and associated metabolic syndromes in horses, especially for horses at risk for these syndromes.

Key Words: Glucose, Glucose Tolerance, Horses, Insulin, Obesity

©2003 American Society of Animal Science. All rights reserved.

Introduction

Insulin resistance has been generally defined as a state in which normal concentrations of insulin fail to elicit a normal physiological response (Kahn, 1978). Insulin resistance is fundamental in the pathology of type II diabetes and has been identified as a risk factor in obesity, cardiovascular disease, hypertension, and cancer in humans (Reaven, 1988; Kim, 1998; Frayn, 2001). Diets rich in simple sugars have been associated with insulin resistance in several animal and human studies (Storlien et al., 2000; Bessesen, 2001), so the common management practice of feeding starch-rich cereal grains in two meals a day may promote insulin resistance in horses. Insulin resistance in horses has been associated with obesity and laminitis (Jeffcott et al., 1986; Pass et al., 1998), and may play a role in colic (Hudson et al., 2001), exertional rhabdomyolysis (Valentine et al., 2001), and osteochondrosis (Ralston, 1996).
Glucose dynamics are described by the minimal model, a mathematical construct that partitions glucose disposal into glucose effectiveness, or the capacity of glucose to mediate its own disposal independent of plasma insulin, and insulin sensitivity, or the capacity of insulin to promote glucose disposal (Bergman et al., 1979; Ward et al., 1991; Bergman, 1997). The minimal model of glucose dynamics has been used primarily in the study of human diabetes.

The objective of this study was to use the minimal model to estimate glucose effectiveness and insulin sensitivity in horses, to test the effects of body condition (nonobese to obese), and to test effects of dietary adaptation to forage only, and then adaptation to forage plus supplements rich in starch and sugar or fiber and fat. The hypothesis was that insulin sensitivity would be lower in obese vs. nonobese horses, and insulin sensitivity would be lower with adaptation to twice-daily meals rich in starch and sugar compared with fiber and fat.

### Materials and Methods

#### Horses and Diets

The research was conducted at the Middleburg Agricultural Research and Extension (MARE) Center. The protocol was approved by the Institution’s Animal Care and Use Committee.

Ten Thoroughbred geldings (Table 1) aged 12 ± 3 yr (SD) and with BCS (Henneke et al., 1983) ranging from 5 to 8 were used. Body condition was recorded at the beginning of each of three periods and averaged across the study. Average BCS of 5 to 5.9 were denoted as “nonobese” (n = 4), 6 to 6.9 as “moderately obese” (n = 3), and 7 to 9 as “obese” (n = 3).

The geldings were maintained in two groups on 12-ha mixed grass/legume pastures. Previous nutrient analysis (Hoffman et al., 2003) of these pastures through different seasons indicated no difference (P > 0.10) between pastures in nutrient composition of DM, CP, ADF, NDF, fat, nonfiber carbohydrate, and non-structural carbohydrate. Representative forage samples were collected by gathering random clippings from all areas of each pasture, beginning before the onset of the study and continuing on a monthly basis until the study was complete (including a total of seven samples from each pasture).

Two pasture supplements (Hoffman et al., 2001) were formulated to be isocaloric and isonitrogenous, with mineral contents balanced to complement the pasture and meet or exceed current recommendations (NRC, 1989). One supplement was rich in sugar and starch (SS) and the other in fiber and fat (FF). A pilot study indicated that the glycemic index of the SS supplement was higher (P = 0.001) than FF, with glucose area under the curve at 143.9 ± 4.1 and 11.4 ± 5.4 g-min-L⁻¹ for SS and FF, respectively.

When appropriate for the study design, the supplements were fed to the geldings at a rate of 6.2 kg/d per horse, divided into two meals. The goal was approximately a 2:3 supplement:forage ratio (Kronfeld, 1998) and maintenance of BCS (Henneke et al., 1983). Although the geldings were maintained in groups, the supplements were fed to each gelding individually, with the measured amount distributed to each in a pan. The pans were placed in a circular pattern on the ground with a distance of approximately 6 m between pans to minimize dominant/submissive behavioral effects during feed ingestion. The geldings were observed carefully at each meal to ensure each consumed their allotted supplement.

The study was divided into three 8-wk periods with a modified frequent sampling i.v. glucose tolerance test (FSIGT; Caumo et al., 2000) administered at the end of each period. Previous equine studies indicated effects of diet on glucose metabolism after 27 to 29 d (Sticker et al., 1995; Powell et al., 2002) and 6 wk (Freestone et al., 1992), so 8 wk was considered sufficient to allow for dietary adaptation.

During Period 1, geldings were adapted to pasture only. After completion of the Period 1 FSIGT, the geldings were randomly assigned to one of two groups of

### Table 1. Clinical characteristics of Thoroughbred geldings used

<table>
<thead>
<tr>
<th>Horse</th>
<th>Age, yr</th>
<th>BWa, kg</th>
<th>Body conditionb</th>
<th>Obesity groupc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>756 ± 10.4</td>
<td>8 ± 0</td>
<td>Obese</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>588 ± 5.2</td>
<td>6 ± 0</td>
<td>Moderately obese</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>629 ± 2.6</td>
<td>5.3 ± 0.3</td>
<td>Nonobese</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>573 ± 9.3</td>
<td>7 ± 0</td>
<td>Obese</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>545 ± 10.4</td>
<td>5.3 ± 0.3</td>
<td>Nonobese</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>537 ± 8.5</td>
<td>5.6 ± 0.3</td>
<td>Nonobese</td>
</tr>
<tr>
<td>7</td>
<td>17</td>
<td>588 ± 5.7</td>
<td>6 ± 0</td>
<td>Moderately obese</td>
</tr>
<tr>
<td>8</td>
<td>11</td>
<td>608 ± 9.4</td>
<td>7.3 ± 0.3</td>
<td>Obese</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>640 ± 12.7</td>
<td>6.3 ± 0.3</td>
<td>Moderately obese</td>
</tr>
<tr>
<td>10</td>
<td>12</td>
<td>559 ± 11.1</td>
<td>5 ± 0</td>
<td>Nonobese</td>
</tr>
</tbody>
</table>

aBody weight and body condition data are shown as the mean ± SE of three observations across the duration of the study.

bBody condition score was assigned on a scale of 1 to 9 (Henneke et al., 1983).

cBody condition scores of 5 to 5.9 were denoted as “nonobese,” BCS of 6 to 6.9 were “moderately obese,” and those of 7 to 9 were “obese.” Body condition groups were not different (P = 0.30) in body weight.
Glucose-insulin dynamics in horses

The geldings were moved from pastures into stalls 15 to 18 h before the onset of each FSIGT. Geldings from the same groups were housed in adjacent stalls so they could see each other in order to avoid social dislocative stress. Because fasting has been shown to reduce tissue sensitivity to the glucoregulatory action of insulin in equids (Forhead and Dobson, 1997), the geldings were allowed ad libitum access to grass hay and water in order to mimic the nonfasted, grazing state on pasture. The grass hay offered was harvested from pastures on site. A core sampler was used to collect hay samples, each being a composite of 10 bales.

On the morning of the FSIGT, geldings were weighed using an electronic scale (TYREL Platform, model TC-10S, Allweights Hamilton Scale Corp., Richmond, VA). Catheters were placed in jugular veins, and after an adjustment period of approximately 1 h, baseline blood samples were collected. Glucose tolerance was shown to have a diurnal variation in humans (Lee et al., 1992) and appears to have a diurnal variation in horses (Staninar, 2002), so the modified FSIGT were initiated at approximately the same time each morning (0857 with SD of 23 min).

A glucose bolus (dextrose solution 50%, Phoenix Pharmaceutical, Inc., St. Joseph, MO) of 0.3 g/kg of BW was administered through the catheterer over a period of 2.4 min with a SD of 0.5 min. This dose was similar to other i.v. glucose doses used previously in horses (Giraudet et al., 1994; Sticker et al., 1995; De La Corte et al., 1999), as well as other FSIGT in humans (Caumo et al., 2000).

At 20 min after the glucose dosing, an insulin bolus (Humulin R, Eli Lilly and Co., Indianapolis, IN) of 30 mU/kg of BW was administered through the catheter. Human insulin varies from horse insulin by two amino acids—serine instead of glycine on the A-chain (position A-9) and threonine instead of alanine on the B-chain (position B-30). In a previous report, administration of human insulin induced acute hypoglycemia in horses (De La Corte et al., 1999), as well as other FSIGT in humans (Caumo et al., 2000).

During the 3-h duration of the FSIGT, 30 venous samples were collected, at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 150, and 180 min after the glucose administration. The blood samples were immediately placed in heparinized sample tubes (Vacutainer, Fisher Health Care, Chicago, IL) and kept in ice water until centrifuged; plasma was removed within 10 to 20 min of collection (Ferrante and Kronfeld, 1994). Plasma was frozen at −4°C pending analysis of glucose and insulin concentrations.

Analyses and Calculations

Samples of the SS and FF supplements, pastures and hay were weighed, dried for 24 h at 100°C, and DM was calculated. Dry samples were ground using a Thomas-Wiley Laboratory Mill (model 4, Thomas Scientific, Swedesboro, NJ) with a 1-mm screen. Ground samples were submitted for proximate and mineral analysis by a commercial laboratory (Table 2; Dairy One DHIA Forage Testing Laboratory, Ithaca, NY).

Plasma concentrations of glucose were determined by colorimetric assay (Glucose Procedure #16-UV, Sigma Diagnostics, St. Louis, MO), and insulin concentrations were determined by radioimmunoassay (IRI Procedure #16-B, Sigma Diagnostics, St. Louis, MO).
Glucose effectiveness (min⁻¹) of decline of insulin action; X(t) is insulin action (min⁻¹) (i.e., the acceleration of glucose disposal at time t associated with insulin concentration above basal); parameter p₂ represents the rate (min⁻¹) of introduction of insulin into the interstitial space; I(t) represents the insulin concentration (mU/L) at time t; and Ib represents basal insulin concentration (mU/L). Assumptions were X(0) = 0 and |I(t) - Ib| = 0 if I(t) < Ib.

Acute insulin response to glucose (mU·min⁻¹·L⁻¹), which quantifies endogenous insulin secretion in response to the glucose dose, was calculated using the following equation:

\[
\text{AIRg} = \int [(I(t) - Ib) \times dt] \tag{4}
\]

where I(t) represents the insulin concentration at time t and Ib represents basal insulin concentration. The equation was integrated from 0 ≤ t ≤ 10 min in accordance with the definition of AIRg (Bergman, 1997).

The disposition index, an index that describes β-cell responsiveness and accounts for the influence of both endogenous insulin secretion (AIRg) and Si, was calculated as follows:

\[
\text{DI} = \text{AIRg} \times \text{Si} \tag{5}
\]

Statistics

Normality was tested using the Shapiro-Wilk statistic. The pasture samples were compared using an ANOVA mixed model with repeated measures, with individual pasture samples corresponding to study period as fixed effects (SAS Inst., Inc., Cary, NC). Effects of body condition were analyzed using the mixed model with repeated measures, with sources of variation including body condition, diet, horse within diet, horse within body condition, and the residual error horse × body condition × diet. Horse within body condition was used as the error term to test effects of body condition, and means were compared using the Tukey test. Effects of diet (overall and within body condition) were ana-

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>SS (n = 4)</th>
<th>FF (n = 4)</th>
<th>Pasture (n = 14)</th>
<th>Hay (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM, %</td>
<td>88.2 ± 0.3b</td>
<td>91.9 ± 0.3a</td>
<td>45.9 ± 5.8d</td>
<td>87.6 ± 11.5c</td>
</tr>
<tr>
<td>DE, Mcal/kg⁵</td>
<td>3.10 ± 0.05</td>
<td>2.95 ± 0.07</td>
<td>2.17 ± 0.05</td>
<td>1.97 ± 0.04</td>
</tr>
<tr>
<td>CP, %</td>
<td>15.5 ± 0.3</td>
<td>14.3 ± 0.4</td>
<td>14.7 ± 0.6</td>
<td>13.7 ± 1.3</td>
</tr>
<tr>
<td>ADF, %</td>
<td>13.6 ± 1.4a</td>
<td>28.4 ± 1.7a</td>
<td>37.3 ± 0.5</td>
<td>39.4 ± 1.0</td>
</tr>
<tr>
<td>NDF, %</td>
<td>23.1 ± 1.3a</td>
<td>42.1 ± 1.5a</td>
<td>64.3 ± 1.3</td>
<td>64.1 ± 2.8</td>
</tr>
<tr>
<td>NFC, %</td>
<td>52.1 ± 0.8a</td>
<td>26.2 ± 0.9a</td>
<td>14.9 ± 1.0</td>
<td>17.1 ± 2.2</td>
</tr>
<tr>
<td>NSC, %</td>
<td>46.2 ± 0.7a</td>
<td>14.0 ± 0.8a</td>
<td>8.1 ± 1.0</td>
<td>6.9 ± 2.1</td>
</tr>
<tr>
<td>Fat, %</td>
<td>3.1 ± 0.7b</td>
<td>13.1 ± 0.8a</td>
<td>2.9 ± 0.2</td>
<td>2.3 ± 0.5</td>
</tr>
</tbody>
</table>

Supplement (formulated to be rich in starch and sugar [SS] or fiber and fat [FF]) means differ (P < 0.05).

Pasture and hay means differ (P < 0.05).

Calculated using NRC (1989) tables.


Nonstructural carbohydrate.

were determined using a RIA (Coat-A-Count Insulin, Diagnostic Products, Los Angeles, CA) previously validated for equine insulin (Freestone et al., 1991). Duplicate assays completed for each sample had an intraassay CV of <1% for glucose, and 5% for insulin. The interassay CV was 2% for glucose and 5.5% for insulin.

A diagram of the minimal model (Bergman et al., 1981) used to interpret the modified FSIGT is shown in Figure 1. Glucose effectiveness (Sg), insulin sensitivity (Si), acute insulin response to glucose (AIRg), and the disposition index (DI) were calculated using MinMod Millennium (Ver. 5.10, BeBoS Assoc., 2001) and WinSAAM (Ver. 3.0.1, Greif and Boston, 1997) software and five equations (Bergman et al., 1979; Bergman, 1997).

Glucose effectiveness (min⁻¹)—the capacity of glucose to mediate its own disposal independent of a change in plasma insulin—was calculated using the following equation:

\[
G'(t) = -(X + Sg) \times G(t) + (Sg \times Gb) \tag{1}
\]

where G(t) represents the rate (min⁻¹) of glucose clearance from plasma; X represents insulin action (i.e. the acceleration [min⁻¹] of glucose disposal associated with insulin concentration above basal); G(t) represents plasma glucose concentration (mg/dL) at time t, with G(0) being the theoretical glucose concentration at time 0, as calculated using the minimal model (Bergman et al., 1979); and Gb represents basal glucose concentration (mg/dL) maintained by hepatic production.

Insulin sensitivity (L·mU⁻¹·min⁻¹)—the capacity of insulin to promote glucose disposal—was calculated using the following equations:

\[
X'(t) = -p_2 \times X(t) + (p_3 \times [I(t) - Ib]) \tag{2}
\]

\[
Si = p_3/p_2 \tag{3}
\]

where X′(t) (min⁻²) represents the change in insulin action over time; parameter p₂ represents the rate

\[}
analyzed using a Wilcoxon signed rank test, with comparisons of pasture and hay only vs. SS, pasture and hay only vs. FF, and SS vs. FF. Results were considered statistically significant at $P < 0.05$, with a tendency towards statistical significance at $0.05 < P < 0.10$ (Rosner, 1995).

**Results**

Nutrient analysis of the supplements, pastures, and hay are shown in Table 2. There were no differences ($P > 0.42$) in DM, DE, CP, ADF, NDF, nonfiber carbohydrate, nonstructural carbohydrate, or fat between individual pastures, so data from both pastures were combined. The hay fed during the FSIGT differed from the pastures only in DM. Compared to FF, the SS supplement had higher nonfiber carbohydrate ($P = 0.001$) and nonstructural carbohydrate ($P = 0.001$), and lower fat ($P = 0.001$), ADF ($P = 0.001$), and NDF ($P = 0.001$).

One obese gelding (Horse 8) was profoundly insulin resistant and had an undetectable response to the insulin dose, regardless of diet fed. This lack of response drove the estimation of Si below the sensitivity of the software. The estimated Si of this gelding had a mean fractional SD of 360%. In comparison, the mean fractional SD of Si in the remaining horses was 8.3%. The Sg of this gelding had a range of 0.019 to 0.029 min$^{-1}$.

The mean BW was 598, 599, and 613 kg, and mean BCS was 5.8, 6.1, and 6.4 after Periods 1, 2, and 3, respectively, with no difference in BW ($P = 0.86$) or condition ($P = 0.33$) over the duration of the study. There was no difference ($P = 0.11$) in BW between the groups of obese, moderately obese, or nonobese horses. The effects of body condition and diet on glucose and insulin concentrations during the modified FSIGT are shown in Figures 2 and 3, respectively. Basal glucose concentration was 101 $\pm$ 2.9 mg/dL and peak glucose concentration was 358 $\pm$ 11.4 mg/dL. Basal insulin concentration was 16.7 $\pm$ 3.2 mU/L and was not influenced by diet or body condition. The endogenous insulin response to glucose administration before insulin injection at 20 min had a mean plateau of 39.0 $\pm$ 0.37 mU·L$^{-1}$ with a range of 16.2 to 82.4 mU·L$^{-1}$. The effects of diet and body condition on the endogenous insulin response to glucose are shown in Figure 4. Diet had no influence ($P = 0.65$), but plateau insulin concentrations were higher ($P = 0.001$) in obese than nonobese or moderately obese horses. Peak insulin concentration after the insulin injection was 556 $\pm$ 61 mU/L and was not influenced by diet ($P = 0.85$) but was higher ($P = 0.013$) in obese than nonobese horses.

For all horses across the study, mean Sg was 2.06 $\pm$ 0.14 $\times 10^{-2}$ min$^{-1}$, with a range of 0.72 to 3.42 $\times 10^{-2}$ min$^{-1}$. Mean Si was 1.28 $\pm$ 0.21 $\times 10^{-4}$, with a range of 0.07 to 3.32 $\times 10^{-4}$ L·mU$^{-1}$·min$^{-1}$. Mean AIRg was 241 $\pm$ 22, with a range of 101 to 483 mU·min·L$^{-1}$. Mean DI was 2.89 $\pm$ 0.60 $\times 10^{-2}$, with a range of 0.26 to 11.1 $\times 10^{-2}$.

The effects of body condition on Sg, Si, AIRg, and DI are shown in Table 3. Glucose effectiveness was higher in obese vs. nonobese ($P = 0.003$) or moderately obese ($P = 0.007$) horses. Insulin sensitivity was lower ($P = 0.008$) in obese vs. nonobese horses and tended to be...
lower ($P = 0.051$) in obese vs. moderately obese horses. Acute insulin response to glucose was higher ($P = 0.039$) in obese vs. nonobese horses and tended to be higher ($P = 0.058$) in obese vs. moderately obese horses. There was no effect ($P = 0.23$) of body condition on DI.

The effects of diet on $S_g$, $S_i$, $AIR_g$, and $DI$ are shown in Table 4. There were no effects of diet on $S_g$ ($P = 0.31$). Insulin sensitivity ($P = 0.066$), $AIR_g$ ($P = 0.051$), and $DI$ ($P = 0.051$) were lower when horses were fed SS compared with FF. Within the horses of nonobese body condition, $S_i$ was lower ($P = 0.062$) when horses were fed SS ($0.73 \pm 0.05 \times 10^{-4}$ L·mU$^{-1}$·min$^{-1}$), compared to FF ($2.59 \pm 0.05 \times 10^{-4}$ L·mU$^{-1}$·min$^{-1}$). There were no other effects of diet on $S_g$, $S_i$, $AIR_g$, or $DI$ within body condition groups.

**Discussion**

**Application of the Minimal Model of Glucose Dynamics in the Horse**

The results of this study demonstrate that the insulin-modified FSIGT and application of the minimal model commonly used for human investigations is a useful tool to examine glucose-insulin dynamics in horses, especially because it provides a quantitative
measure of insulin sensitivity. The terms “insulin resistance” and “insulin sensitivity” have been used rather loosely in equine literature, with insulin resistance or reduced insulin sensitivity used interchangeably, indicating comparatively elevated glucose tolerance, a greater insulin requirement to clear blood glucose, or the failure of exogenous insulin to suppress blood glucose (Jeffcott and Field, 1985; Jeffcott et al., 1986; Free- stone et al., 1992).

Similarly, in human literature, insulin resistance has been considered a generic term, generally defined as a state when normal concentrations of insulin fail to elicit a normal physiological response (Kahn, 1978). Since the first clear differentiation between the concepts of insulin secretion and insulin sensitivity in diabetes (Himsworth, 1936), most reports evaluating insulin resistance have compared the effects of insulin on glucose metabolism (i.e., the stimulation of peripheral glucose disposal and suppression of hepatic production, rather than quantifying insulin resistance or insulin sensitivity per se) (Reaven, 1988; Frayn, 2001).

The evaluation of insulin sensitivity was much improved by the development of the glucose clamp technique, which stabilizes blood glucose concentration after an insulin injection using variable glucose infusion (Sherwin et al., 1974; DeFronzo et al., 1979). Insulin sensitivity may be calculated by dividing the glucose infusion rate by the product of the clamped glucose concentration, body weight, and change in insulin above basal (Finegood et al., 1984). Alternatively, applying the glucose clamp procedure at two different stable insulin concentrations allows estimation of Si by dividing the difference in maintenance glucose clearance rates by the difference in insulin concentrations (Beard et al., 1986). The glucose clamp technique has been applied successfully in the horse (Powell et al., 2002), but rather than quantifying Si, the authors reported effects on insulin sensitivity based on changes in glucose infusion rate.

The FSIGT and application of the minimal model (Bergman et al., 1979) provided a quantification of insulin sensitivity with a test less invasive and less complex to execute than the glucose clamp. An Si of 1.28 × 10^{-4} L-mU^{-1}-min^{-1}, found as the mean for all horses on this study, implies that for each 1 mU-L^{-1} increase in plasma insulin, there was an increase of 0.0128% per minute of fractional glucose disappearance. Although previous equine studies have evaluated insulin sensitivity on a relative basis through i.v. or oral glucose tolerance tests or glucose clamp techniques, this is the first quantitative estimation of Sg and Si.

Glucose tolerance and minimal model analysis has been used primarily to elucidate etiologies of diabetes in humans and other species. Additionally, analysis of i.v. glucose tolerance test data has been used in the dairy industry to select young bulls for breeding purposes, with positive associations between glucose clearance and pedigree breeding value, and EBV of the progeny (Panicke et al., 2002). From another perspective, Si estimated using the minimal model was positively

### Table 3. Effects of body condition (mean ± SE) on glucose effectiveness (Sg), insulin sensitivity (Si), acute insulin response to glucose (AIRg), and disposition index (DI) across diet in mature Thoroughbred geldings

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonobesea</th>
<th>Moderately obesea</th>
<th>Obesea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sg, × 10^{-2}/min</td>
<td>1.43 ± 0.16b</td>
<td>1.59 ± 0.19c</td>
<td>3.02 ± 0.22b</td>
</tr>
<tr>
<td>Si, × 10^{-4} L-mU^{-1}-min^{-1}</td>
<td>1.94 ± 0.19b</td>
<td>1.47 ± 0.23bc</td>
<td>0.370 ± 0.27c</td>
</tr>
<tr>
<td>AIRg, mU-min-L^{-1}</td>
<td>211 ± 34.7c</td>
<td>221 ± 40.1d</td>
<td>408 ± 49.1d</td>
</tr>
<tr>
<td>DI, × 10^{-2}</td>
<td>1.22 ± 0.64</td>
<td>2.68 ± 0.77</td>
<td>0.494 ± 0.90</td>
</tr>
</tbody>
</table>

aBody condition scores (Henneke et al., 1983) of 5 to 5.9 were denoted as “nonobese,” 6 to 6.9 as “moderately obese,” and 7 to 9 as “obese.” Observations included four nonobese, three moderately obese, and three obese horses.

b,cMeans in rows with different superscripts differ, P < 0.01.

dMeans in rows with different superscripts differ, P < 0.05.

### Table 4. The effects of diet (mean ± SE) on glucose effectiveness (Sg), insulin sensitivity (Si), acute insulin response to glucose (AIRg), and disposition index (DI) across diet in mature Thoroughbred geldings fed pasture and hay only (PH), or pasture plus supplements rich in starch and sugar (SS) or fiber and fat (FF)

<table>
<thead>
<tr>
<th>Variable</th>
<th>PHa</th>
<th>SSA</th>
<th>FFa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sg, × 10^{-2}/min</td>
<td>2.21 ± 0.24</td>
<td>1.82 ± 0.20</td>
<td>2.15 ± 0.29</td>
</tr>
<tr>
<td>Si, × 10^{-4} L-mU^{-1}-min^{-1}</td>
<td>1.20 ± 0.37bc</td>
<td>1.00 ± 0.27c</td>
<td>1.62 ± 0.41b</td>
</tr>
<tr>
<td>AIRg, mU-min-L^{-1}</td>
<td>241 ± 46de</td>
<td>220 ± 34e</td>
<td>261 ± 36d</td>
</tr>
<tr>
<td>DI, × 10^{-2}</td>
<td>2.84 ± 0.12de</td>
<td>1.88 ± 0.52c</td>
<td>3.95 ± 0.12d</td>
</tr>
</tbody>
</table>

aDiets were fed to 10 horses in a switch-back design with an 8-wk adaptation period.

b,cMeans in rows with different superscripts differ (P = 0.066).

dMeans in rows with different superscripts differ (P = 0.051).
correlated with maximal aerobic capacity (VO$_{2\text{max}}$) and proportion of type-I muscle fibers in humans (Goedecke et al., 2001). Hence, application of the minimal model should be further explored to determine its use as a tool to evaluate reproductive or athletic potential in horses.

**Obesity**

In this study, insulin sensitivity was approximately 80% lower in obese horses than in nonobese horses, an effect similar to a reported 76% reduction in insulin sensitivity in obese vs. normal-weight humans (Lee et al., 1992). Compared with lean mares, obese mares had lower insulin sensitivity, and both obese and lean mares had improved insulin sensitivity after 7 d of moderate exercise training (Powell et al., 2002). Insulin resistance, or reduced insulin sensitivity, in horses has been associated with obesity and laminitis (Jeffcott et al., 1986; Pass et al., 1998), some forms of exertional rhabdomyolysis (Valentine et al., 2001), and has been suggested to play a role in osteochondrosis (Ralston, 1996).

Given the lower Si and higher Sg found in the obese vs. nonobese horses in this study, it appears that obese geldings rely primarily on glucose-mediated glucose disposal. The higher AIRg and correspondingly higher endogenous insulin plateau in obese vs. nonobese or moderately obese horses suggest an enhancement of the equine insulin system to sustain glucose clearance through the secretion of higher amounts of insulin in compensation for its limited effectiveness. The low Si in obese horses should not imply noninsulin dependent diabetes mellitus because the lack of difference in DI between horses of different body condition suggests an adequate capacity of AIRg to compensate for limited Si.

**Diet**

The lack of a distinct effect of diet may be due to confounding by effects of body condition. Effects of a high sucrose diet on insulin action were less evident in obese rats that those that were insulin resistant before dietary modification (Pagliassotti et al., 2000).

The higher Si in all horses, especially those of nonobese body condition when fed FF vs. SS, may reflect adaptation to diets with widely different glycemic indices. Compared with FF, the SS diet had approximately three times more nonstructural carbohydrate, one-fourth the fat, and one-half the NDF. The glycemic index of the feeds was approximately 12 times higher in SS than FF. In humans, consumption of a diet with a low glycemic index appeared to elevate insulin sensitivity in heart disease patients (Frost et al., 1996). Consumption of another low glycemic index diet resulted in a higher disposition index and tended to improve insulin sensitivity in humans with insulin resistance (Wolever and Mehling, 2002). Horses fed grain meals rich in starch with a high glycemic index may have a higher risk of developing insulin resistance.

In spite of the lower Si, the horses had lower AIRg and lower DI when fed SS compared with FF. It would be expected that lower Si would be compensated by higher AIRg and hence no change in DI, but this was not the case. The lower AIRg occurring when horses were fed SS points to the horses being less sensitive to stimulation by the i.v. glucose load. The DI is considered an index of the ability of the β-cell to compensate for reduced Si by increasing endogenous insulin secretion (Chen et al., 1988), so the lower DI when horses were fed SS vs. FF suggests less β-cell responsiveness. Thus, when horses were adapted to SS, the twice-daily glucose and insulin perturbations associated with meal feeding affected glucose metabolism, as suggested by the lower Si, AIRg, and DI.

**Comparative Aspects**

The pattern of glucose response to the FSIGT in the horse was similar to that found in studies of other species (Finegood et al., 1984; Bergman, 1997; Feldhahn et al., 1999). The glucose response initially exhibited an abrupt decline due to mixing of glucose in the distribution space, followed by a phase of glucose-mediated glucose disposal and accelerated glucose disappearance mediated by exogenous insulin, followed by a period in which the glucose concentration fell below baseline and then rebounded to basal concentrations (Bergman, 1997).

The endogenous insulin secretion in response to i.v. glucose increased and then plateaued at 1 min after i.v. glucose infusion and remained at this concentration until the exogenous injection of insulin at 20 min. The rapid arrival and persistence of endogenous insulin secretion to a plateau implies that equine insulin secretion is matched by disposal during the first phase of the FSIGT. The pattern of endogenous insulin response to i.v. glucose was similar to that previously reported in horses (Giraudet et al., 1994) but different from that in humans (Bergman et al., 1981; Wolever and Mehling, 2002) and sheep (Francis et al., 1999). Compared to an endogenous insulin plateau in horses, the endogenous insulin response in humans and sheep reached a peak within minutes after i.v. glucose infusion and then declined as plasma glucose decreased.

Endogenous secretion of insulin in response to glucose stimulation in humans and other species appears to be mainly a result of punctuated secretory bursts of insulin (Pørksen et al., 1997; Pørksen, 2002). Preliminary work in our laboratory suggests that a similar pattern of punctuated secretion of insulin may be present in the horse in order to maintain endogenous insulin response at the plateau found in this study, but further research would be required for verification.

In comparison to Sg and Si derived using the minimal model in other species, Si (Table 5) was lower in horses than in nondiabetic humans (Beard et al., 1986; Caumo et al., 2000), dogs (Finegood et al., 1984), cats (Feldhahn et al., 1999), calves (Stanley et al., 2002), and sheep (Williams et al., 2002). Insulin sensitivity was lower in noninsulin-dependent diabetic humans (Welch et al.,
1990) and diabetic cats (Feldhahn et al., 1999) than in nonobese horses but was similar to that of obese horses. Compared with Si, there was less variation in Sg between species, obesity, or disease state, suggesting that Sg is a principal mechanism for glucose disposal, especially in obesity or noninsulin-dependent diabetes mellitus when insulin-dependent glucose uptake mechanisms are sluggish or dysfunctional.

**Implications**

The application of the minimal model of glucose dynamics commonly used for human investigations is a useful tool to examine glucose metabolism and insulin sensitivity in horses. Obese horses have decreased insulin sensitivity and seem to rely on glucose-mediated disposal of glucose. Horses have an increased risk of developing insulin resistance when fed grain-based meals that are rich in sugar and starch. Decreased insulin sensitivity (or insulin resistance) has previously been associated with obesity, laminitis, exertional rhabdomyolysis, and osteochondrosis in horses. Maintenance of optimal body condition and avoidance of grain-based meals rich in sugar and starch should be beneficial for all horses to decrease the risk of developing insulin resistance and associated metabolic syndromes, but especially those horses at greater risk for these syndromes.

**Literature Cited**


---

**Table 5. A comparison of glucose effectiveness (Sg) and insulin sensitivity (Si) from horses in this study to reported values derived from minimal model analysis of modified frequent sampling i.v. glucose tolerance tests in other species**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sg, x 10⁻²/min</th>
<th>Si, x 10⁻⁴ L·mU⁻¹·min⁻¹</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humans, nonobese</td>
<td>1.7 ± 0.03</td>
<td>6.7 ± 1.1</td>
<td>Beard et al. (1986)</td>
</tr>
<tr>
<td>Humans, obese</td>
<td>2.4 ± 0.3</td>
<td>2.3 ± 0.2</td>
<td>Bergman (1989)</td>
</tr>
<tr>
<td>Humans, NIDDM</td>
<td>1.4 ± 0.2</td>
<td>0.61 ± 0.16</td>
<td>Welch et al. (1990)</td>
</tr>
<tr>
<td>Dogs, nonobese</td>
<td>4.3 ± 0.5</td>
<td>4.3 ± 0.7</td>
<td>Finegood et al. (1984)</td>
</tr>
<tr>
<td>Cats, nondiabetic</td>
<td>3.0 ± 0.3</td>
<td>3.22 ± 0.37</td>
<td>Feldhahn et al. (1999)</td>
</tr>
<tr>
<td>Cats, diabetic</td>
<td>1.4 ± 0.3</td>
<td>0.58 ± 0.16</td>
<td></td>
</tr>
<tr>
<td>Sheep, early lactation</td>
<td>1.34 ± 1.24</td>
<td>5.42 ± 0.93</td>
<td>Williams et al. (2002)</td>
</tr>
<tr>
<td>Calves, 6 wk old</td>
<td>2.4 ± 0.3</td>
<td>10.5 ± 1.5</td>
<td>Stanley et al. (2002)</td>
</tr>
<tr>
<td>Horses, all</td>
<td>2.06 ± 0.14</td>
<td>1.28 ± 0.21</td>
<td>This study</td>
</tr>
<tr>
<td>Horses, nonobese</td>
<td>1.43 ± 0.16</td>
<td>1.94 ± 0.19</td>
<td></td>
</tr>
<tr>
<td>Horses, obese</td>
<td>3.02 ± 0.22</td>
<td>0.37 ± 0.27</td>
<td></td>
</tr>
</tbody>
</table>

*NIDDM = noninsulin-dependent diabetes mellitus.*