Title

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Insulin Resistance as a Result of Body Condition Categorized as Thin, Moderate, and Obese in Domesticated U.S. Donkeys (*Equus asinus*)

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ABSTRACT

Donkeys are often kept, especially in industrialized countries, as companion animals. Donkeys have greater digestive efficiency and tend to expend less energy than horses or ponies, which contributes to obesity in nonworking donkeys. Obesity in all equine species increases risk of chronic health conditions such as laminitis and insulin resistance. Previous studies in horses and ponies have documented obesity's potential effects on glucose-insulin dynamics with lower insulin sensitivity and higher insulin responses to glucose. However, limited studies on obesity and its health impacts in donkeys exist, so these effects on glucose-insulin dynamics have not been fully studied. Twenty-four donkeys were selected according to initial body condition score (BCS) and divided into three categories with eight donkeys in each: thin, moderate, and obese. A frequently sampled glucose-insulin tolerance test was performed with subsequent MINMOD analysis to determine the effects of BCS on glucose-insulin dynamics. Basal insulin was highest in obese donkeys when compared with moderate and thin donkeys ($P = .02$ and $P = .01$, respectively). There was an overall trend across groups for BCS to lower insulin sensitivity ($P = .06$). No other effect was found. Body condition score seems to affect donkeys in a similar manner to horses and ponies as higher BCS was associated with higher basal insulin and may lower insulin sensitivity. Higher basal insulin concentrations in obese donkeys could negatively influence health and contribute to serious, chronic conditions.

1. Introduction

As a separate species, donkeys have unique morphological and physiological differences from horses and ponies. Likely due to domestication in desert regions, donkeys tolerate greater water losses than horses or ponies and are well adapted to eating poor-quality forage [1]. Donkeys have enhanced digestive efficiency for fiber with improved dry matter digestibility and longer retention times to use full hindgut capacity [2,3]. In spite of this efficiency, donkeys expend less energy during work [1,4], making management of donkeys challenging. Donkeys typically lead sedentary lives when kept at maintenance, and well-meaning owners have a tendency to overfeed their animals [5,6], contributing to their obesity. In one survey in the United Kingdom, over one third of their donkeys were reported as overweight or obese [7]. Obesity contributes to lifelong health problems in horses and ponies, including laminitis and insulin resistance [8–11], and it has been associated with similar metabolic problems in donkeys [12]. Previous studies have compared glucose tolerance across species [13] and shown a negative association between body condition and insulin sensitivity (Si) in horses and ponies [8,14–17]. In addition to body condition score (BCS), prior research has also found a correlation between increased regional adiposity in the neck, the "Cresty Neck Score," and hyperinsulinemia in ponies [18]. Donkeys typically deposit more fat in the neck than over their whole bodies like horses and ponies [19], which, given the previous findings in

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ponies, could predispose donkeys to insulin regulation problems. In some studies, lower Si associated with obesity was improved when horses and ponies lost weight and returned to moderate body condition [9,14]. Prior research in donkeys only found a difference between sexes with female donkeys having lower Si than males [20]. However, this previous study was unable to confirm the negative association between body condition and Si in donkeys. The present study hypothesizes that donkeys with BCS above moderate values (>6) will have lower Si when compared with donkeys with thin or moderate BCS (≤6).

2. Materials and Methods

2.1. Animals

The study was approved by the Michigan State University Institutional Animal Care and Use Committee. Twenty-four standard donkeys, ranging in height at the withers from 102 to 142 cm and age from 1 to 20 years, were acquired from various sources specifically for the study over the course of two years, twelve per year. Each donkey was chosen according to BCS based on specific guidelines for body condition scoring donkeys on a scale of 1–9 [21] and was not fed to achieve a certain BCS. Eight donkeys were acquired for each of the three groups according to their initial BCS averaged from four trained observers: thin (BCS 2–3.5), moderate (BCS 4–6), and obese (BCS 6.5–9). These divisions among BCS categories were chosen so that no donkey could be placed into two categories at once. Body weights (BWs) were calculated using a previously published method for the estimation of live weight in donkeys [21]. The donkeys were acclimated to an *ad libitum*, moderate-quality pasture for a three-week period before a frequently sampled intravenous glucose-insulin tolerance test (FSIGT) was performed. No changes in BW were noted over this three-week period as more emphasis was placed on the donkeys' BCS rather than BW. The donkeys were removed from pasture 14–16 hours before testing and individually placed in stalls. During testing, donkeys were offered *ad libitum* access to grass hay and water.

2.2. FSIGT Sampling Protocol

Jugular catheters were placed in each donkey an hour before taking the initial baseline sample, and sampling was conducted using a previously established method in horses [9]. During the 5 hours of FSIGT, 35 venous samples were collected and immediately placed into heparinized tubes. At −60, −45, and 0 minutes, baseline samples were taken and then 300 mg per kg BW glucose (Dextrose Solution 50%, Butler Animal Health Supply Co, Dublin, OH) was quickly given intravenously. Blood was sampled again at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 19 minutes after glucose bolus according to previously established methods in horses and ponies [9,14,22]. At 20 minutes, 0.4 mU per kg BW of insulin (Humulin R, Eli Lilly and Co, Indianapolis, IN) was rapidly administered intravenously. This dose was chosen as it was used in a previous study on exogenous insulin administration in donkeys [23], and literature is limited on this species. Although the previous study was an insulin-only protocol in fasted animals, this was considered a safe dose to use for donkeys in the present study. Subsequent sampling occurred at 22, 23, 24, 25, 27, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 150, 180, 210, and 240 minutes. Catheters were flushed with 10 mL heparinized saline after each sampling. Plasma for glucose and insulin analysis was removed immediately after centrifugation and frozen at −4°C. Blood glucose during sampling was monitored using a hand-held glucometer (MediSense Precision Xtra; Abbott Laboratories, Alameda, CA). Plasma glucose was analyzed by enzymatic assay (Autokit Glucose; Wako Diagnostics, Richmond, VA), and insulin was determined using a radioimmunoassay (Coat-A-Count Insulin; Diagnostic Products Corp, Los Angeles, CA).

2.3. Minimal Model Analyses and Calculations

The minimal model (MINMOD) analysis determined glucose and insulin dynamics as demonstrated in previous studies [9,24]. Insulin sensitivity and endogenous β-cell responsiveness, represented by acute insulin response to glucose (AIRg), were calculated with equations using basal glucose (Gb) and basal insulin (Ib) as defined below. Other parameters determined by MINMOD analysis were glucose effectiveness (Sg), the capacity of the cells to take up glucose without insulin mediation, and disposition index (DI), a measurement of the influence of both AIRg and Si. All the equations used to calculate various parameters have been previously validated in humans and equines [9,24,25].

Glucose effectiveness (min^{-1}) was calculated by the following equation:

$$G'(t) = -(X + Sg) \times G(t) + (Sg \times Gb)$$

In this equation, G′(t) is the net rate (min^{-1}) of change in plasma glucose at time (t), X is insulin action, and Gb ($mg \cdot dL^{-1}$) represents itself.

Insulin sensitivity was calculated using two equations:

$$X'(t) = -p2 \times X(t) + (p3 \times [I(t) - Ib])$$

$$Si = p3/p2$$

X′(t) (min^{-2}) was defined as insulin action change over time, where X (t) (min^{-1}) was insulin action at time (t). The variables p2 and p3 (min^{-1}) described the disposal of insulin from and the delivery of insulin to the interstitial space, respectively. I(t) served as insulin concentration ($mU \cdot L^{-1}$) at time (t) while Ib ($mU \cdot L^{-1}$) represents itself.

Acute response of insulin to glucose ($mU \cdot L^{-1} \cdot min^{-1}$), which represents the increase in plasma insulin above basal concentrations, was calculated using an integral equation:

$$AIRg = \int_0^{10} [I(t) - Ib] \times dt$$

Using insulin at time (t) and Ib, this equation was integrated from 0 to 10 minutes after the glucose bolus was administered.

Disposition index was calculated from AIRg and Si with the following equation:

$$DI = AIRg \times Si$$

2.4. Statistical Analysis

Statistical analyses (SAS 9.0, SAS Inst., Inc, Cary, NC) were conducted using a one-way ANOVA in the mixed procedure to evaluate BCS and its interactions with Si, Ib, AIRg, DI, Sg, and Gb. There was no effect of year on any variables, so data from both years were pooled. Effect of sex and interactions with BCS were also evaluated. Tukey's adjustment was used when evaluating effect of sex due to unequal distribution of sexes in the second year. Significance was determined when $P < .05$ and trends were considered when $.05 < P < .10$.

3. Results

The mean ± SE of BW and BCS as well as the age range of each group are presented in Table 1. There was no difference among groups in age ($P = .3$). Throughout the FSIGT, obese donkeys maintained higher mean insulin concentrations at the majority

Table 1
Mean ± SE of BW and BCS as well as age range of thin (BCS 2–3.5), moderate (BCS 4–6), and obese (BCS 6.5–9) donkeys.

Variable	Obese	Moderate	Thin
BW, kg	219 ± 12	188 ± 7	163 ± 12
BCS	7.9 ± 0.2	5.1 ± 0.2	3.0 ± 0.3
Age, yr	4 to 16	2 to 10	1 to 20

Abbreviations: BW, body weight; BCS, body condition score.

sampling points than moderate or thin donkeys ($P < .05$, Fig. 1). Moderate and thin donkeys had almost no differences in mean insulin concentrations during this protocol ($P > .10$). From the MINMOD analysis, basal insulin was highest in obese donkeys when compared with moderate and thin ($P = .02$ and $P = .01$, respectively). There was an overall trend across groups for BCS to lower Si ($P = .06$). Obese donkeys tended have lower Si than thin donkeys ($-4.2 \pm 1.6 \times 10^{-4}$ L·mU^{-1}·min^{-1}, $P = .02$), but this difference was not observed between obese and moderate or moderate and thin donkeys ($P = .1$ and $P = .4$, respectively). No effect of BCS on Sg, AIRg, Gb, or DI was found (Table 2). Sex also had no effect on Ib ($P = .8$), Si ($P = .5$), or any other variable.

4. Discussion

Body condition score serves as a simple and practical management tool for owners to determine fat deposition and potential risk of obesity, and obese, nonworking donkeys are potentially at increased risk of chronic disease, negatively impacting their overall welfare. This study examined the effect of BCS on glucose-insulin dynamics in donkeys. Although obese donkeys (BCS > 6) had higher mean insulin concentrations during a FSIGT and higher Ib when compared with moderate or thin donkeys (BCS ≤ 6), BCS did not appear to affect other variables. Insulin sensitivity may have been influenced by BCS, as indicated by the overall trend for obese donkeys to have lower Si than thin donkeys. However, this hypothesis of the present study was not borne out by the results.

Although Gb was not different among BCS groups, Ib was highest in obese donkeys when compared with the other two groups. Overall, Ib in these donkeys was similar to previous values reported in overweight and obese horses and ponies [26]. One study compared glucose tolerance across horses, ponies, and donkeys by measuring glycemic response after nasogastric administration of a glucose solution [13]. This previous study found no difference in resting insulin among horses, ponies, and donkeys, but donkeys did have higher insulin concentrations after 6 hours than either horses or ponies. Body condition was not reported, so it may be hard to determine if the results occurred because of a difference in glucose-insulin dynamics in donkeys or because of the effects of body condition on these dynamics. However, given the results of the present study, donkeys appear to follow similar patterns in resting insulin concentrations as horses and ponies, namely that, concentrations may increase with increasing adiposity.

High insulin concentrations are tied to obesity and insulin resistance in other species [27–29], although researchers are not certain if this link is causal [27]. Nevertheless, hyperinsulinemia is a trademark of impaired glucose tolerance and insulin resistance that eventually leads to type II diabetes in humans [28]. Chronic consumption of excess energy, the leading cause of obesity, is also believed to promote high Ib secretion in humans without glucose stimulation [28]. However, in horses and ponies, obesity itself does not appear to cause insulin resistance or hyperinsulinemia as it does in humans. Insulin is recognized as an adipogenic hormone through its effects stimulating fatty acid uptake by adipocytes and preventing lipolysis by blocking the enzyme hormone-sensitive lipase [30]. Given donkeys' evolved ability for lower required

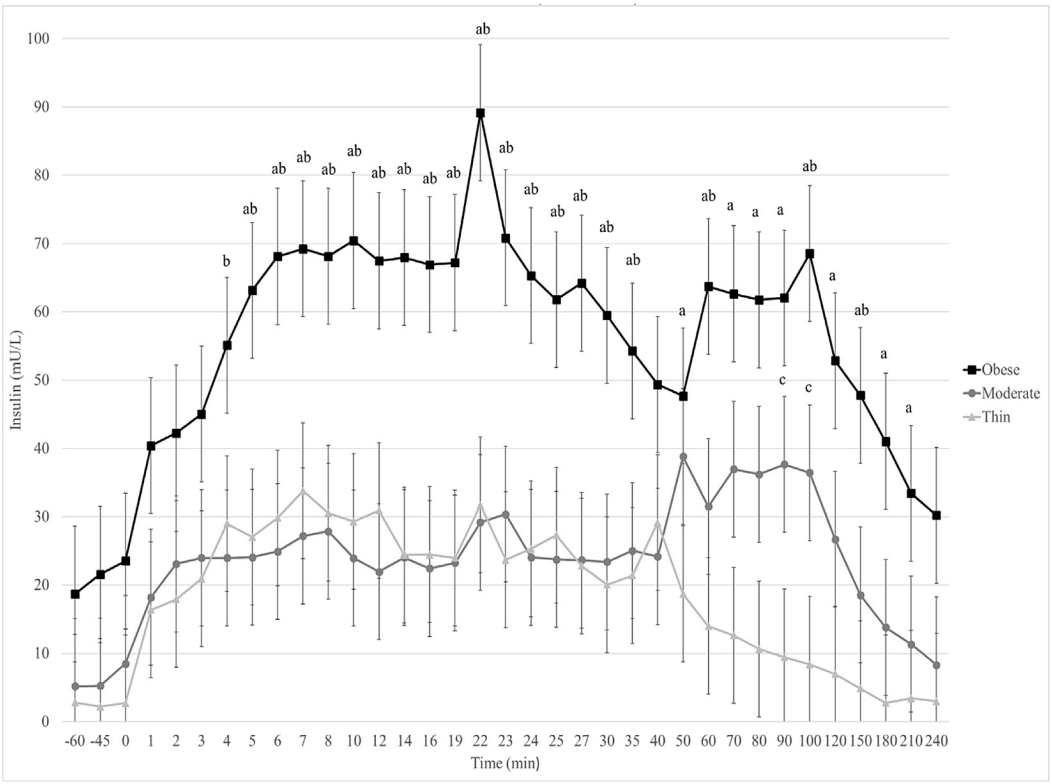

Fig. 1. Mean insulin concentrations (±SE) over time in response to glucose (0 minutes) and insulin injection (20 minutes) in donkeys of various body conditions. [a]Denotes difference between obese and thin ($P < .05$). [b]Denotes difference between obese and moderate ($P < .05$). [c]Denotes difference between moderate and thin ($P < .05$).

Table 2
Glucose effectiveness, insulin sensitivity, acute insulin response to glucose, disposition index, basal glucose, and basal insulin reported as arithmetic means (±SE) in donkeys of various body conditions.

Variable	Obese (BCS 6.5–9)	Moderate (BCS 4–6)	Thin (BCS 2–3.5)
Si, $\times 10^{-4}$ L·mU^{-1}·min^{-1}	0.77 ± 1.15[a]	3.43 ± 1.15[ab]	4.97 ± 1.15[b]
Ib, mU·L^{-1}	22.3 ± 4.6[a]	6.0 ± 4.6[b]	2.7 ± 4.6[b]
AIRg, mU·L^{-1}·min^{-1}	344 ± 83	168 ± 83	222 ± 83
DI	303 ± 117	400 ± 117	584 ± 117
Sg, min^{-1}	0.016 ± 0.003	0.013 ± 0.003	0.019 ± 0.003
Gb, mg·dL^{-1}	104 ± 6	89 ± 6	90 ± 6

Abbreviations: BCS, body condition score; Si, insulin sensitivity; Ib, basal insulin; AIRg, acute insulin response to glucose; DI, disposition index; Sg, glucose effectiveness; Gb, basal glucose.
[abc]Numbers lacking a common superscript within a row differ.

energy and greater digestive efficiency [1], well-meaning owners may contribute to obesity, and subsequently potentially hyperinsulinemia, in donkeys through overfeeding. Once adipose tissue starts to accumulate, these problems may be exacerbated by weight loss resistance due to donkeys' metabolic efficiency [1]. Over time, this hyperinsulinemia may lead to insulin resistance and impaired glucose tolerance, which could further put donkeys at risk for many other health problems. The association between high Ib and BCS in this study is troubling and may follow the same pathology as in other species [27–29], showing the need for further research on donkeys to improve welfare and health care.

There was an overall trend ($P = .06$) for BCS to affect Si in this study. Obese donkeys tended to have lower Si than thin donkeys, but there was no difference between obese and moderate or moderate and thin groups. Overall, values for Si in donkeys were similar to those previously reported in sedentary or obese horses and ponies [8,9,14,22]. Although previous studies have documented the negative association between obesity and Si in horses [8,9,14], this was not fully corroborated in this study. In obese ponies, improvements in Si could be seen after weight loss of 10–15% BW [15] so that the ponies were in moderate condition, but this effect was not seen in the present study. However, one previous study found that the degree of insulin-induced hypoglycemia in response to exogenous insulin decreased after longer bouts of fasting, ranging from overnight to three days, in donkeys [23]. Although this previous study used rate of plasma glucose uptake as a proxy for peripheral Si instead of MINMOD analysis, these results could explain the lack of significant difference in the present study. Another possibility may be that donkeys may be less sensitive to insulin than horses or ponies. A previous study found that donkeys maintained higher blood glucose while also maintaining higher amounts of insulin than horses or ponies [13]. No explanation for this difference was offered, but a shifted glucose curve for donkeys has been adopted to inform clinical setting [12]. More studies are needed to determine if the lack of sensitivity in this study and others is a species-specific mechanism to improve donkey care and welfare in places of overabundant nutrition.

Another possibility for this lack of difference in Si was probably the low insulin dosage used in this study. Previous studies in horses and ponies used 10–30 mU per kg BW of insulin in the FSIGT [9,14,16,17,22], whereas this study only used 0.4 mU per kg BW. Because donkey physiology and metabolism differ from horses and ponies with their own unique problems [4,12], there was some concern that using an equivalent dose would cause severe hypoglycemia and create acute health problems. A previous study used this lower dose in donkeys fasted either overnight or for three days and noted that one donkey did present with negative clinical effects after insulin injection [23]. Because the donkeys in the present study were not fasted, the probability of negative effects after insulin bolus was likely low, but given the thin donkeys and limited literature, the possibility for hypoglycemia and other negative health effects remained. Rather than risk the donkeys becoming hypoglycemic and negatively impact their health, the low dose of 0.4 mU per kg BW was used in the present study. However, because the insulin peak caused by the administration of exogenous insulin was very low in these animals, it was primarily the rise and fall of the endogenous insulin, in response to the administered glucose that was fitted in the MINMOD analysis. This may have influenced the Si values and their direct comparison with previous studies in ponies and horses.

Potentially, this low insulin dosage could have impacted other variables in the MINMOD analysis as well, and previous studies using MINMOD analysis in horses and ponies have associated lower Si with possible compensatory mechanisms in other variables. Higher AIRg values have been reported in obese horses with lower Si [9,14] and insulin resistant (IR) horses and ponies [22,31], indicating increased insulin secretion in response to glucose (AIRg) to maintain glucose homeostasis. Obese horses with lower Si may also have higher Sg to facilitate glucose clearance when Si is reduced [9]. Obese horses and IR ponies may have lower DI values as well [9,22] because this variable is a product of Si and AIRg, but results remain mixed [14,31]. Without an appropriate insulin challenge in the present study, variations in glucose and insulin data from the FSIGT protocol remained large and could have masked potential differences in MINMOD variables among groups as demonstrated by previous research. Possible compensatory mechanisms to cope with higher Ib in obese donkeys in the present study could not be determined, potentially due to this low insulin dose.

Debate remains whether high-fat or high-starch diets promote IR in equines [9,17,32]. Previous research has shown that feeding above energy requirements in general will contribute to obesity and therefore lower Si [9,14–17]. Although donkeys have higher energy requirements than ponies of a similar size, they expend less energy and have enhanced digestive efficiency [4], making appropriate energy balance difficult to achieve in nonworking donkeys. Obese donkeys in the present study could only have achieved such a BCS by eating above their energy requirements, and while lower Si was only a trend, high Ib was present, possibly predisposing them to insulin resistance and other health problems. Obesity can affect horse health due to increased risk of and poorer prognosis for recovery from laminitis [11,33,34], greater production of inflammatory cytokines [8,35], altered estrous cycles in mares [36], and impaired heat and exercise tolerance. Although these conditions have not been well studied in donkeys, these kinds of welfare concerns may still be present in the donkey population. In addition, obese horses, ponies, and donkeys may have increased risk of hyperlipemia and hyperlipidemia [12,37], although only one study has documented the range of blood lipids in healthy donkeys [38]. A multivariate analysis on risk factors of hyperlipemia in donkeys found that higher BCS, and therefore obesity, increased hazard ratios and had a negative effect on survival when compared with lower to normal BCS [39]. Although hyperlipemia and

hyperlipidemia are likely a result of stress and periods of severe energy restriction [40], maintaining a normal BCS may reduce this risk or improve survival outcomes. As with horses, obesity presents a range of health and welfare issues in donkeys, and using BCS as an indicator of increased fat deposition could serve as a useful tool for owners and managers to avoid these problems.

5. Conclusion

Body condition affects donkeys in a similar manner to horses and ponies with increasing adiposity contributing to higher insulin concentrations and potentially lowered Si. Obese donkeys have higher basal insulin concentrations than moderate or thin donkeys, and this difference could contribute to potentially lower Si over time through a number of mechanisms discussed earlier. However, no other connection between body condition and glucose-insulin dynamics has been corroborated in this study. The negative association between body condition and Si found in horses and ponies was only a trend in donkeys in the present study. This trend could be due to an insufficient amount of insulin used in the FSIGT protocol due to concerns over donkey health. Further research is needed to determine if this lack of association is from species differences or experimental design. However, given that high circulating insulin interferes with cellular mechanisms in glucose-insulin dynamics, excess weight gain and obesity should be strongly discouraged in donkeys. Appropriate management strategies should consider the physiological differences of donkeys and be used before donkeys become obese, especially when it comes to overfeeding and excess energy intake. Using BCS as an easy, external measure for energy balance would be helpful in determining if a donkey was at risk for high insulin concentrations and potentially insulin resistance.

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