Insulin resistance and compensation in laminitis-predisposed ponies characterized by the Minimal Model

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Introduction

Laminitis occurs when laminae of the inner wall of the hoof separate leading to detachment of the pedal bone from the hoof wall and resulting in acute and sometimes irreversible hoof damage. In vitro studies have shown associations between failed glucose metabolism and hoof-wall separation (*Pass* et al. 1998, *French* and *Pollit* 2004). Few studies have considered glucose and insulin dynamics in laminitis-predisposed ponies (*Field* and *Jeffcott* 1989), and no studies have performed specific quantitative methods to characterize insulin resistance in these ponies.

Recently, proxies for insulin sensitivity (SI) and acute insulin response to glucose (AIRg) as assessed by the Minimal Model of glucose and insulin dynamics (*Treiber* et al. 2005a) indicated compensated insulin resistance in ponies with a previous history of laminitis compared to those never affected by the disease (*Treiber* et al. 2005b). To test the validity of these proxies and further characterize glucose metabolism in laminitis-disposed ponies we have applied the Minimal Model (*Hoffman* et al. 2003; *Treiber* et al. 2005c) to 14 ponies having either a history of recurrent laminitis on spring pasture (PL, n=7) or no history of laminitis (NL, n=7).

Materials and Methods

Fourteen Welsh and Dartmoor mares were maintained on pasture until the morning of the study, which was performed in the first week of March. Ponies were selected based on their individual history of laminitis as well as the occurrence of laminitis in members of their pedigree. Groups were matched for breed and body condition (*Henneke* et al. 1983). All ponies were considered overweight (BC 6-8). NL ponies were younger (median 4 y, range 4-6 y) than PL ponies (median 8 y, range 6-21 y). All ponies underwent a frequently sampled intravenous glucose tolerance tests (FSIGT) between 8:00 and 10:00 a.m., receiving 300 mg/kg BW glucose through a venous catheter at 0 min of the test and 20 mIU insulin/kg BW at 20 min of the test. The FSIGT began with a basal sample, followed by the glucose dose and sampling continued for four hours. The Minimal Model was used to calculate SI (L min^{-1} mU^{-1}), AIRg (mU/L min^{-1}), glucose effectiveness (SG, min^{-1}), and disposition index (DI, dimensionless ratio) (*Bergman* et al. 1997).

Results

The SI was lower (P=0.007) in PL ponies (0.08±0.03) compared to NL ponies (0.39±0.07). The AIRg was higher (P=0.045) in PL ponies (885±187) compared to NL ponies (405±65). The DI was significantly lower (P=0.037) in PL ponies (84.5±43.7) compared to NL ponies (172.7±48.5). There was no difference (P=0.61) in SG between PL and NL ponies. Age was not correlated to any parameters of the minimal model ($r<0.23$, $P>0.43$).

Discussion

These results indicate compensated insulin resistance in ponies predisposed to laminitis.

Insulin resistance in ponies may be the expression of a 'thrifty genotype' with insulin resistance being an adaptive strategy to conserve energy, particularly glucose (*Neel* 1962). Animals with the thrifty disposition would have a reduced tolerance for high dietary carbohydrates, and exposure could result in diseases associated with metabolic dysfunction such as hyperlipidemia and especially laminitis (*Jeffcott* and *Field* 1985). Certain populations and family-lines expressing this thrifty genotype, would therefore have an increased risk of developing laminitis on carbohydrate-rich spring and autumn pasture.

The present study is the first to characterize insulin resistance in laminitis-disposed ponies using a specific quantitative method. All ponies had insulin sensitivity in the lowest quintile of healthy horses (*Treiber* et al. 2005a), indicating a general degree of insulin resistance in these pony breeds perhaps related to the thrifty genotype. Ponies in the PL group, however, had only 1/5th the insulin sensitivity of NL ponies and this insulin resistance was not associated with age (P=0.43) or degree of obesity (P=0.67). Insulin resistance may decrease glucose availability to insulin-sensitive cells, such as laminar keratinocytes responsible for laminar tissue turnover or laminar basal cells (*Mobasheri* et al. 2004, *French* and *Pollit* 2004). Increased insulin resistance may also alter insulin-mediated affects on blood flow (*Coffman* and *Colles* 1983, *Field* and *Jeffcott* 1989, *Lind* et al. 2000).

Ponies in the NL group had an insulin secretory response similar to that previously reported in obese Thoroughbreds (*Hoffman* et al. 2003) while the secretory response was more than twofold higher in PL ponies. Increased insulin secretion compensates partially for decreased insulin efficiency and has been observed in Thoroughbreds, calves and humans (*Hoffman* et al. 2003, *Stanley* et al. 2002, *Welch* et al. 1990). However, insulin is also an important hormone in regulating fat metabolism, growth, and circulation. Compensatory hyperinsulinemia may therefore be another contributing factor to metabolic disorders such as hyperlipidemia, osteochondrosis and laminitis (*Jeffcott* and *Field* 1985, *Field* and *Jeffcott* 1989, *Ralston* 1996).

In some cases, compensation by increased insulin secretion may not be sufficient to overcome profound insulin resistance and hyperglycemia may result. None of the ponies in this study were hyperglycemic at baseline, however their tolerance of the glucose dose varied. The disposition index, DI, is the product of SI and AIRg and quantifies the effectiveness of an individual's insulin response relative to the insulin sensitivity of their tissue. As such, the DI is considered to be an indicator of the risk of developing hyperglycemia. Despite their greater insulin response, PL ponies had lower DI than NL ponies indicating an additional risk of potential disease. The DI in PL ponies was comparable to that observed in obese Thoroughbreds suggesting that the DI may be less differentiating in terms of the risk for laminitis than insulin sensitivity and compensatory hyperinsulinemia.

Conclusions

The present study characterizes insulin resistance in pony breeds, with extreme insulin resistance associated with a predisposition for laminitis. Insulin resistance may present an adaptive strategy in populations of equines, particularly pony breeds which evolved in nutritionally sparse environments. This predisposition may interact with an increasing starch intake from spring and autumn pasture, exacerbating insulin resistance and increasing the risk of laminitis. The present study with the Minimal Model also confirms previous results from proxies developed as a screening test to identify ponies in need of special management.

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