Metabolic Syndrome in Healthy Ponies Facilitates Nutritional Countermeasures against Pasture Laminitis$^{1-3}$

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ABSTRACT Treatment of clinical laminitis usually fails to prevent some degree of persistent disability; thus, intervention should aim at avoiding risk factors and preventing the disease. Efficiency of intervention would be improved by identifying predisposed horses and ponies. A herd of 160 healthy ponies included 54 previously laminitic (PL) and 106 never laminitic (NL). Pedigree analysis was consistent with dominant inheritance partially suppressed in males. Blood analysis revealed higher plasma concentrations of insulin and triglycerides but not cortisol, glucose, or free fatty acids in the PL group. Proxies for insulin sensitivity and β-cell responsiveness, which were calculated from plasma insulin and glucose, indicated compensated insulin resistance in the PL group. A prelaminitic metabolic syndrome (PLMS) was derived statistically to have cut-off points for the 2 proxies, hypertriglyceridemia, and body condition score. It had a total predictive power of 78%. It identified 62 ponies with PLMS, and 98 as PLMS-free. Two months later, pasture starch concentration doubled, and 13 clinical cases of laminitis developed, 11 in the PLMS group and 2 in the PLMS-free group, giving an odds ratio of 10.4 ($P = 0.0006$). The PLMS can be used to identify predisposed ponies in need of special care; the efficiency of intervention would increase nearly 3-fold in the present case. It enables the design of new interventions suitable for testing. The PLMS also might influence market values. J. Nutr. 136: 2090S–2093S, 2006.

KEY WORDS: horses • metabolic syndrome • insulin resistance • dominant inheritance • pasture starch

Laminitis may involve insulin resistance in several ways (1–8). Insulin resistance refers to a reduced response of insulinsensitive cells, mainly in muscle, adipose tissue, and liver, to usual concentrations of circulating insulin (4). It has served as the central focus of a set of risk factors for certain diseases, originally called syndrome X (9), and subsequently termed metabolic syndrome (10,11). The critical hypothesis proposed by Reaven (9) was that a genetic predisposition for insulin resistance could be aggravated by a high-carbohydrate diet, leading to syndrome X in healthy individuals and making them prone to diseases such as diabetes mellitus type-2 (10) and coronary heart disease (11). This concept resonates in equids, because certain breeds, especially ponies, appear prone to laminitis (1), and because chronic adaptation to high-glycemic meals leads to compensated insulin resistance (12).

Laminitis literally means inflammation of the laminae, the interdigitating plates that lock the hoof wall to the third phalangeal bone (13–15). The lamellar structure confers weight-carrying strength through a combination of rigidity and resilience that enables it to act as a shock absorber. This unique structure differentiated as equine forebears evolved from 5 digits to a single toe. It is highly specialized, and it has become a vulnerable site for damage by many initially different causes (15,16). These converge into a common pattern of a complex disease that in its entirety involves much more than inflammation (13,15).

The main initiating causes of laminitis identified are pasture composition (mainly grass fructan and clover starch), which accounts for 54%; digestive problems, associated mainly with excessive grain intake, yield another 8% (16). Laminitis is reported by 13% of all horse operations annually, ~30% of large operations. It is the disease most in need of research according to a recent survey of equine veterinarians (17).

Laminitis is a form of lameness (16). It may be viewed as a systemic disease with its most severe manifestations in the foot. Its time course may be described in a series of stages (13,15): 1) Predisposition Stage (variable time): genetic, nutritional/metabolic, septic/inflammatory, mechanical/trauma are identified initiating causes. 2) Development Stage (hours, days): a) Rapid fermentation of soluble carbohydrates with release of trigger
factors by bacteria. b) Circulation of triggers for a clinically silent period of ~8–50 h, during which vasomotor, metabolic, and structural abnormalities are accumulating. 3) Acute Stage (days): a) Clinical signs of inflammation, such as pain, heat, reluctance to move, lameness, and characteristic posture. b) Demonstrable structural and metabolic lesions. c) Loosening of the connective tissue between the hoof wall and the pedal bone, which sinks and rotates to a variable degree in the foot, founder. Much pain and disableness are present. 4) Subacute Stage (weeks, months): less pain, lameness, and founder, with continuing damage varying with partial repair. 5) Chronic or Persistent Stage: repair of founder can never be complete, simply because of gravity; thus, some degree of disableness is persistent.

Our thesis

**Opportunities for successful intervention are confined to stages 1 and 2a above.** Once the pedal bone loosens from the hoof wall and starts to rotate or sink, the force of gravity will partially or completely impair restoration of the normal relation of the bone to the hoof wall, and the immediate disableness will persist to a variable extent. Euthanasia is an ever-present option to treatment because of extreme suffering in acute cases and residual chronic disability.

### Opportunities in the developmental phase

Before the acute phase of the disease, a developmental phase exists, during which *trigger factors* circulate in the blood for ~10–50 h (13–15). The main candidates are endotoxins, exotoxins, amines, and proinflammatory cytokines (15). Endotoxins, sepsis, and inflammation release cytokines. Circulating triggers presumably are doing harm that is not obvious, except for constriction of small blood vessels. Clearly, despite their subtle, silent nature, the triggers are damaging. Whether this trigger-circulating period offers an opportunity for treatment is now of major interest because it is clear that intervention during the acute phase is too late to avert persistent, albeit variable, lameness.

Endotoxins, exotoxins, and amines are released in the cecum, and perhaps to some extent in the stomach and small intestine, by bacteria feeding on lavish loads of soluble carbohydrates—sugars, starches, and fructans (15). Avoiding such loads and slowing down the bacteria offers opportunities for intervention that have to be tested. Once the triggers are released and start circulating to the foot, however, it may be too late.

### Opportunities involving predisposition

Proposals of inherited and metabolic predispositions to laminitis, especially in ponies, were considered moot for a century (1) with little support from relevant unambiguous data (18). An opportunity to study predispositions in ponies and risk factors in pasture became available through access to a local herd of Welsh and Dartmoor ponies.

**Genetics.** The 160 ponies had farm records of clinical laminitis, and 54 ponies had laminitis previously. Diagnosis was confirmed on those available by typical founder rings around the hoof walls. Prevalence was 34% overall, 50% in mares, and 6% in males. Pedigree analysis of each breed was consistent with a dominant mode of inheritance partially suppressed in males (3). Further suppression may reflect a gene–nutritional interaction, e.g., thresholds for intakes of soluble carbohydrates—starch, sugar, or fructan. Such an interaction could provide an opportunity for nutritional intervention. Whether this genetic predisposition has a beneficial effect on performance seems likely; otherwise, breeders would have bred out the laminitis tendency.

Generality comes into question when a study is made on a single inbred herd. The prospect of external validity is enhanced, however, by the finding of the same mode of inheritance in 2 breeds, Welsh and Dartmoor, instead of only one. The opportunity exists for molecular genetics to develop an exact 100% test for the presence of this predisposition in ponies.

**Prelaminitic metabolic syndrome.** Blood plasma analysis revealed that the 54 previously laminitic (PL)5 ponies had elevated insulin and triglycerides but not glucose, free fatty acids, or cortisol in March, 2004, compared with the 106 never laminitic (NL) ponies (6). The insulin and glucose data were used to calculate statistically derived proxies (7) for the 2 main parts of insulin resistance: insulin sensitivity was greatly decreased but this was compensated for by increased insulin secretion. Insulin resistance was suggested earlier but only on the basis of nonspecific evidence, and no previous report has demonstrated compensation.

Similar blood studies were conducted in May, this time with 13 ponies all from the PL group observed on d 1 or 2 of clinical laminitis (6). Plasma insulin was enormously increased in 9 clinical cases, and the proxies showed an exaggerated response of insulin from the pancreas. In the other 4 clinical cases, the insulin response was blunted according to the proxies.

Subsequently, the full frequent sampling i.v. glucose tolerance test was applied to the NL and PL groups, and the results confirm the findings with proxies (19). Moreover, applications of the minimal model to 2 clinical cases of a few days standing from local clinics (not our ponies) showed decompensation, with the supply of insulin failing, a diabetic-like condition (T. M. Hess, K. H. Treiber and D. S. Kronfeld, unpublished data).

We summarizing our findings on insulin resistance as follows: 1) No insulin resistance: 106 ponies with no history of laminitis. 2) Compensated insulin resistance: 54 ponies with a history of laminitis. 3) Exaggerated compensation: 9 clinical cases at 1 or 2 d. 4) De- or uncompensated insulin resistance: 4 clinical cases at 1 or 2 d. 5) De- or uncompensated insulin resistance: 2 clinical cases at ~5 d.

Our synthesis of these observations is that the predisposition of compensated insulin resistance is essentially physiological and health sustaining. About the time of emergence of clinical signs of laminitis, the insulin response becomes exaggerated, which leads to failure (exhaustion?) of pancreatic β-cells.

Statistical methods were applied to develop a prelaminitic metabolic syndrome [PLMS (6)]. The PLMS currently includes the 2 proxies, elevated triglycerides, and a higher body condition score. The PLMS based on the March data selected 11 of the 13 cases in May. The odds ratio for the incidence of cases developing in 2 mo was 10.4 (95% CI 2.2–48, P = 0.0006) for the PLMS group vs. the PLMS-free group. We are trying to improve the PLMS with measures of inflammation, oxidative stress, blood pressure, and the morphometrics of the neck (adipose tissue distribution).

The proxies correspond to insulin sensitivity and pancreatic β-cell response determined by the minimal model of glucose-insulin dynamics (7). They are derived statistically and reached a total predictive power of 78%. They are specific indicators of insulin resistance and should not be confused with nonspecific indications, such as fasting hyperinsulinemia and glucose intolerance (18).

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5 Abbreviations used: PL, previously laminitic; NL, never laminitic; PLMS, prelaminitic metabolic syndrome.
The PLMS is like the prediabetic and precoronary metabolic syndromes, which are sets of risk factors in apparently healthy people (10,11). The quantitative confirmation of insulin resistance (19), together with the hypertriglyceridemia and higher body condition score (6), fulfills the requirements of the diagnostic definition of the prediabetic metabolic syndrome (10).

The PLMS and the 2 human metabolic syndromes in healthy individuals are unlike the equine metabolic syndrome, which was proposed for sick horses affected by mild or moderate laminitis (3). Anecdotal claims of fasting hyperglycemia in all, and fasting hyperglycemia or obesity in most but not all affected horses (3), remain unsubstantiated by published data (18), and do not fulfill the criteria of the diagnostic definitions of the human metabolic syndromes (10,11).

**Pasture starch.** “Lush” is a word applied often as a warning about pasture (16), but lushness is not the sole nor is it a consistent predictor of fructan content in grass or starch content in clover. For example, frost-killed fescue is far from lush but has a high content of fructan (20).

In our pony study, pasture starch content increased from 4 to 8% of dry matter from March to May (6). Mean pasture height increased from ~5 to 15 cm. Clover proliferated, and it is consumed by ponies in preference to grass. It is likely, therefore, that starch intake increased much more than starch concentration, which doubled.

Large doses of starch (~4–8 times a large grain meal) were used experimentally to induce laminitis (21). The massive bolus-dose starch model (21), like the fructan model (14), revealed limited information about digestive changes, which are presumably much more subtle with the protracted nibbling of pasture, or further information about foot pathology in the acute separation phase, which is arguably too late for effective and lasting intervention.

**Predisposition facilitated countermeasures**

The PLMS identifies ponies in need of special care to avoid laminitis. In this case, intervention could have been confined to 62 PLMS ponies from a total of 160, an improvement of 2.6 in efficiency. The PLMS also should be useful for trading purposes.

The description of genetic and metabolic predispositions for laminitis enables the design of a rational intervention as follows: 1) Test all ponies (and possibly horses) at risk for PLMS. 2) Sample pastures, e.g., 1 time/wk, and analyze for starch, sugar, and fructan, beginning ~1 mo before laminitis is expected. In our case, that would have been late April. 3) When pasture concentrations of starch, sugar, or fructan rise, separate PLMS ponies onto dry-lots or into stalls. Feed mature hay that has been analyzed and found to have safe levels of starch, sugar, and fructan, perhaps supplemented with low glycemic feed.

This rational intervention must be tested empirically. The obvious weakness is the lack of statistically determined cut-off points for safe/unsafe concentrations of starch, sugar, and fructan in pasture and hay. In addition, to our knowledge, no commercial feed was shown to have a low glycemic effect. Low-starch feeds are not necessarily low glycemic; this poor predictability of glycemic effect from starch and sugar (available carbohydrate) contents was the reason for the development of the glycemic index.

Epigenetic nutritional thresholds for expression of the genetic predisposition for laminitis raises the possibility that a threshold may partially explain the difference between frequency of laminitis in pregnant mares (30%) and males (6%) at maintenance, a difference of only 20% daily digestible energy intake (22). This hypothesis could be tested by feeding a pasture supplement in which starch and sugar are replaced with fat and fiber to provide, e.g., 25–30% of the pregnant mare’s digestible energy. The damage here is that pony mares, unlike horse mares, may not cut back on their pasture intake when fed a supplement; hence, they become obese, thereby exacerbating their insulin resistance.

The characterization of insulin resistance by specific quantitative methods (18) in these studies of ponies (6,19) justifies rational intervention with measures known to improve insulin sensitivity in healthy horses and ponies, such as daily physical activity, reduction of body condition score (degree of fatness), avoidance of large meals of grain-molasses feeds, administration of antioxidants, and administration of (n-6) and (n-3) fatty acids (23). It should be noted, however, that no empirical evidence for the effectiveness of the above measures was demonstrated in laminic horses or ponies. Other common rational but untested countermeasures include avoidance of pastures likely to have high contents of fructan and starch (21,23–25). High fructan concentrations are expected in cool weather grasses during sunny days with cool nights. High starch contents may be expected when clover is growing in profusion.

The application of countermeasures against pasture laminitis is complicated by variation in the assays available from commercial laboratories (25). Starch is measured enzymatically in most laboratories with reasonably comparable results. “Sugar” as reported is true sugar from some laboratories but watersoluble carbohydrates (sugars plus fructans) from others. Assays of water-soluble carbohydrates and nonstructural carbohydrates are suitable physiologically for ruminants but not equids.

**Evidence-based medicine and nutrition**

Decision making about issues and questions of medicine and nutrition should weigh the strength of evidence in terms of the quality and quantity of observations (data) and the logic (mathematical and otherwise) of their relevance (26). The evidence required by the FDA for treatment or prevention is a randomized comparative, preferably placebo-controlled blind trial (27); to our knowledge, there is none for laminitis. The evidence required by the Surgeon-General for avoidance of nutritional risk factors is 2-fold (28): mechanism of causation plus epidemiological association.

Although their relevance to naturally occurring laminitis remains in question, the harsh starch and fructan models suggest mechanisms of causation (14,15). Rapid fermentation causes acidic conditions mainly in the cecum, with disruption of microbes and the cecal wall, and the release of triggers. These triggers initiate changes in the blood vessels and metabolism of the laminae—all likely mechanisms.

The relevance of the effects of a large bolus of fructan or starch to a nibbled, slower, and smaller intake is tenuous. Fructan concentrations in grass leaves under hot, bright sunny conditions in May in Wales were 14–30% dry matter from 0900 to 1500 and from 4 to 11% from 1500 to 2100 (21). Estimates of fructan intake based on such data cannot be precise; thus, a range should be considered, and different authors have arrived at different ranges. One estimate assumed pasture dry matter intakes ranging from 1.5 to 5.2% of body weight and daily mean fructan concentrations of 7.5–28%, hence a range of 0.6–7.3 kg/d fructan intake for a 500-kg horse (25). Our estimate of pasture dry matter intakes, ranging from 1.8 to 2.7% of body weight of pregnant mares, is based on data compiled by the NRC (23), and our range of estimated weighted average fructan contents of 6.5–12.5% of pasture dry matter (4) is based on the Welsh data (21), giving a range of fructan intake from 0.6 to 1.7 kg for a 500-kg horse over 24 h. The 2 low estimates are the
same, but the 2 high estimates, 1.7 and 7.3 kg/d, are far apart, a >4-fold difference. These high estimates should be compared with the oral dose of 3.75–6.25 kg of inulin (not the fructan in grass) given as a relatively rapid single bolus to a 500-kg horse, which causes severe yellow diarrhea before acute laminitis (14). In our view, the dosages in the fructan and starch models are close to 4 times higher than likely intakes from pasture and meals, respectively. The quality of data obtained with these experimental models of laminitis (14,22) is high, but the relevance of these observations is stronger for the later stages of the disease involving founder than for the earlier stages when effective intervention is more feasible.

Epidemiologic associations between pasture fructan and laminitis prevalence, the second type of evidence required by the Surgeon General (28), are lacking. The strongest argument is that climatic conditions that promote high pasture fructan also are associated with a high incidence of laminitis (15). Let’s examine the logic: A causes B, and A causes C, therefore B causes C?

Two pairs of numbers for laminitis prevalence and pasture starch content were reported (6); none such exist for fructan (14,15). Many pairs of laminitis prevalence and pasture concentrations of sugar, starch, or fructan would be required to calculate a conclusive correlation and to determine statistically the safe/unsafe cut-off points or gray zones. Collecting these necessary data is a daunting task. Instead we are observing changes in pasture composition and horse blood plasma throughout the day and night in 36-h studies. These observations may reveal nutritional correlations between pasture composition and equine metabolism that will suggest countermeasures suitable for testing.

LITERATURE CITED