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Insulin resistance in the horse: Definition, detection, and dietetics^{1,2}

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ABSTRACT: Specific quantitative methods for determining insulin resistance have been applied to obesity, activity/inactivity, reproductive efficiency, and exercise in horses, but only nonspecific indications have implicated insulin resistance as a risk factor or component of equine diseases. Insulin resistance derives from insulin insensitivity at the cell surface, which regulates glucose availability inside the cell, or from insulin ineffectiveness due to disruption of glucose metabolism inside the cell. Interplay of insensitivity and ineffectiveness should be considered in regard to patterns of disease, such as laminitis. Detection of insulin insensitivity is made weakly on the basis of fasting hyperinsulinemia, more strongly with a statistically validated surrogate, such as the logarithm of the reciprocal of basal insulinemia, or best by a specific quantitative method. Subjects found to be at risk can be managed to improve their insulin sensitivity by dietetics. Claims for dietetic prevention of a disease should be distinguished from claims for avoidance of a dietary risk factor. The evidence required for a claim of prevention is a controlled intervention trial as for a therapeutic drug, according to the U.S. FDA. In contrast, the evidence required for a claim

of avoidance is association revealed by population studies plus causation shown by mechanistic experiments, as formulated in the Surgeon General of the Public Health Office's (1988) Report on Nutrition and Health. In this view, no appropriate evidence is available for the prevention or treatment of insulin resistance in an equine disease. Evidence is available, however, to justify avoidance of high-glycemic feeds, such as high starch intakes in grains, clover, and alfalfa, and high fructan intakes in grasses, to decrease the risk of acute digestive disturbances associated with rapid fermentation, and chronic metabolic disorders associated with insulin resistance. During submaximal exercise, high-glycemic meals have been shown to increase glucose utilization immediately. On the other hand, chronic adaptation to feeds that exchange corn oil and fiber sources for sources of sugar and starch confers benefits to athletic performance that may be due to several aspects of fat adaptation, including the regulation of insulin sensitivity, as well as glycolysis and lipid oxidation by signals from insulin receptors. Information regarding insulin resistance suggests methods for protecting health and promoting horse performance.

Key Words: Fructan, Glycemic Index, Insulin Sensitivity, Laminitis, Starch

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Introduction

Insulin resistance (**IR**) has been implicated in the pathogenesis of equine diseases, such as laminitis, pituitary adenoma, hyperlipidemia, and osteochondritis desiccans (Coffman and Coles, 1983; Jeffcott and Field, 1985; Garcia and Beech, 1986; Ralston 1996). It is affected by fatness/leanness, inactivity/activity, diet, and

endotoxin administration (Jeffcott et al., 1986; Freestone et al., 1992; Powell et al., 2002; Hoffman et al., 2003; Fitzgerald, 2004; Treiber et al., 2004a). It also influences reproductive efficiency (Fitzgerald and McManus, 2000; Sessions et al., 2004) and probably exercise (Jose-Cunilleras et al., 2002; Sloet van Oldruitenborgh-Oosterbaan et al., 2002).

The field was initiated by Himsworth (1935), who observed that insulin administration depressed the oral glucose tolerance curve in some diabetic patients (insulin sensitive), but not others (insulin insensitive). It expanded substantially when IR was found to be a risk factor for several human diseases, for example, coronary heart disease, hypertension, and polycystic ovarian syndrome, in addition to diabetes mellitus type 2 (Reaven, 1988).

A provocative hypothesis is that genetic predisposition to IR is aggravated by a higher-carbohydrate diet in

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humans (Reaven, 1988). The primary target was the high-carbohydrate diet promoted as heart-protective by public health advocates. The hypothesis resonates in the horse because an increased risk of several digestive and metabolic disorders has been associated with feeding meals of grain and molasses (Kronfeld and Harris, 2003). Thus, the safe use or avoidance of rapidly digested, high-carbohydrate meals, which induce insulin insensitivity (Hoffman et al., 2003; Treiber et al., 2004a), offers management opportunities with regard to avoiding certain diseases and promoting performance.

Definition

Insulin resistance alludes to insensitivity at the cell surface and to several disorders inside the insulin-sensitive cells, notably in muscle, adipose tissue, and liver. An oft-cited definition was proposed by Kahn (1978): "Insulin resistance [exists] whenever normal concentrations of hormone produce a less than normal biologic response." He proposed that IR could occur at any of three levels: before the cell receptor, at the cell receptor, and distal to the cell receptor.

Prior diminution of response could be due to rapid insulin degradation or to neutralization by antibodies. Interference at the cell surface could occur at the insulin receptor (a glycoprotein associated with receptor tyrosine kinases), at several connectors with the glucose transporters (GLUT4 in muscle cells), or in the translocation of these glucose transporters to the cell surface.

From studies of insulin's "bioeffects" on isolated cells, a sigmoidal dose response curve was proposed by Kahn (1978). Decreased insulin sensitivity would move the curve to the right, apparently increasing the K_m by analogy with enzyme kinetics, and decreased responsiveness would diminish the upper asymptotic value or V_{max} (Figure 1). Only approximately 5% of receptors were occupied when insulin-induced glucose oxidation by adipocytes was maximal; this situation was regarded as insulin sensitive. In contrast, approximately 100% of receptors were occupied when insulin-induced α -aminoisobutyric acid transport by thymocytes was maximal; this situation was regarded as insulin insensitive. Reduction in the number of insulin receptors of adipocytes by trypsin was regarded as a model of unresponsiveness, a lowering of V_{max} .

This use of "responsiveness" conflicts with a common use in this field relating to pancreatic β -cell response. In addition, the sigmoidal curves as used by Kahn (1978) do not readily apply to the intact animal. We propose a modified use of these curves, which we expect will facilitate understanding of the roles of IR in various diseases. The shift to the right will continue to represent decreased sensitivity, and hence refers to glucose transport into the cell. On the other hand, the depressed asymptote (V_{max}) is taken in this view to indicate disruption of glucose metabolism inside the cell at hexokinase and beyond, hence, a loss of the cell's metabolic capability,

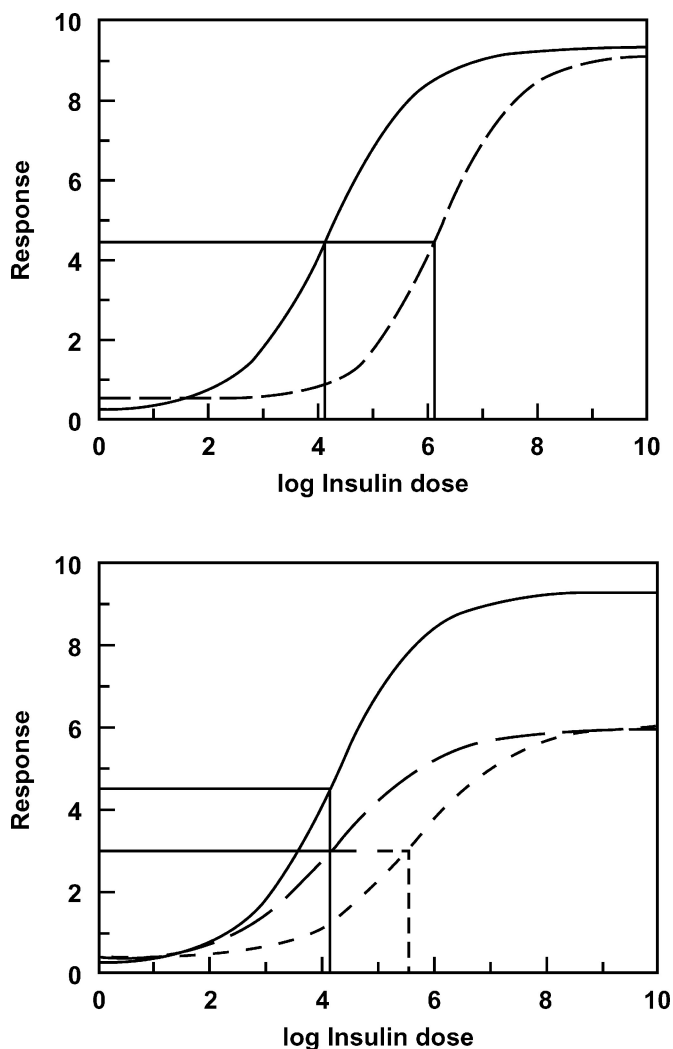


Figure 1. Insulin resistance in isolated adipocytes has a sigmoidal dose-response curve. It can be separated into two components. One is insulin insensitivity, which affects glucose transporters at the cell surface and moves the curve to the right (upper figure). The other is insulin ineffectiveness due to disruption of glucose metabolism inside the cell, which depresses the upper asymptote (lower figure). These two forms of insulin resistance may interact in various disease patterns (modified from Kahn, 1978).

and we propose to differentiate this loss of response as "insulin ineffectiveness."

Insulin signaling involves numerous substances and affects both transport and subsequent utilization of glucose, especially in relation to hexokinase, glycogen synthase, and other key enzymes in glucose and lipid metabolism (Saltiel and Kahn, 2001). The main insulin receptor in the cell membrane involves tyrosine kinase. Its activation leads to translocation of a glucose transporter, mainly GLUT4 in muscle, from the interior to the cell surface. Two main chains of proteins link the tyrosine kinase receptor to the GLUT4 transporters. Other insulin receptor signals affect enzymes involved in glucose

and lipid metabolism inside the cell. Thus, the insulin receptor itself is capable of integrating insulin sensitivity and effectiveness (i.e., glucose transport into the cell and its subsequent intracellular utilization), especially in relation to lipid metabolism. An example that places the sigmoidal curve to the far left and the asymptotic value to a maximum (Figure 1, upper) is the enhanced metabolic regulation of horses fed a diet containing 10% vegetable oil (discussed below). On the contrary, insulin receptor modulation or dysfunction may contribute to both insulin insensitivity (causing decreased glucose transport into the cell) and insulin ineffectiveness (due to altered glucose metabolism inside the cell).

Intracellular disruption of glucose metabolism would result, in this view, in insulin ineffectiveness. Intracellular changes are the rate-controlling steps or primary alterations in some disorders (Shulman, 2000). For example, hexokinase or glycogen synthase may be inhibited during inflammation and sepsis (Perseghin et al., 2003). Mitochondrial degradation of fatty acids may lead to accumulation of fatty acid metabolites following fat-loading in susceptible species (Kim et al., 2004). Inducible nitric oxide synthase, accumulation of reactive oxygen species, and oxidative stress play a critical role in vasoendothelial damage (Schulz et al., 2004). Critical thinking is needed to identify similarities and dissimilarities between different intracellular disorders associated with IR. In common, however, is a decrease in the intracellular capacity to utilize glucose, regardless of glucose transport and availability, so that insulin becomes partially or completely ineffective.

The sigmoidal dose-response proposed for insulin sensitivity (Figure 1) is in keeping with the general nonlinear nature of regulatory processes. In contrast, decreases in the asymptotic value representing a diminished capacity of intracellular glucose metabolism and insulin ineffectiveness, as indicated in the preceding paragraph, may represent partial or complete failure of signaling by the insulin receptor, and hence may be nonlinear or due to a primary disruption of intracellular glucose metabolism that is not regulated and more likely to be linear down to a state of complete disruption.

A metaphor of trains in a railway yard was used by Kahn (1978). In this tradition, we offer as a pattern for disease another metaphor. The insulin receptor and glucose transporter are represented by the accelerator (throttle), especially the modern electronic "drive-by-wire" type that delivers fuel to the engine. The enzymatic machinery inside the cell (hexokinase and beyond) is represented by the engine. Many things can go wrong with the engine, and they may interact with the fuel supply in several ways. Some may be helped by an abundant fuel supply, with insulin remaining partially effective, others not, with insulin becoming totally ineffective.

We will present one example of interplay between insulin insensitivity and ineffectiveness: a hypothetical disease pattern involving IR in alimentary metabolic laminitis. We assume that genetic predisposition in healthy ponies is revealed by obesity (and fat distribu-

tion), hyperinsulinemia, and hypertriglyceridemia, which are commonly associated with chronic, compensated insulin insensitivity. If such ponies ingest a sufficient load of starch or fructan, rapid fermentation lyses bacteria with a release of toxins that may superimpose acute insensitivity on the preexisting chronic condition. The combined insensitivity impairs the vasodilatory effect of the hyperinsulinemia, which releases endothelin and cause vasoconstriction. Ischemia-reperfusion and IR combine to cause oxidative stress and vasoendothelial damage. Bacterial exotoxins also activate collagenase in the hoof laminae and connective tissue (Pollitt et al., 2003). Loosening of the fibrous anchors allows the hoof wall to move relative to the underlying coffin bone. Let us say that ATP provided by glucose metabolism is needed to deactivate the collagenase, but glucose is unavailable due to insulin insensitivity. Is acute insulin insensitivity accentuated by the pain and release of cytokines by counterregulatory hormones, such as epinephrine and cortisol, imbalancing activation/deactivation? Do other toxins and cytokines disrupt intracellular glucose metabolism, and so induce insulin ineffectiveness regardless of the glucose supply? To think clearly about such disease patterns, we should discriminate between insulin insensitivity (cell surface and glucose supply) and insulin ineffectiveness (intracellular glucose utilization), and the interplay between the two.

The above discussion has focused on glucose entry into cells and its subsequent utilization. Insulin sensitivity as it is usually measured also includes the sensitivity of the liver and hepatic glucose production. Feeding fat to dogs, for example, induces predominant hepatic insulin resistance, a failure to suppress glucose production, with only modest peripheral insulin resistance (Kim et al., 2003).

Compensation for insulin insensitivity may be achieved in two ways. The first is an increase in pancreatic β -cell release and secretion of insulin, which is a regulated and nonlinear process that maintains insulin-mediated glucose uptake. The second is an increase in glucose-mediated glucose uptake in a linear relationship to increasing concentration of plasma and extracellular glucose. All of these variables are calculated by the minimal model of glucose insulin regulation (Bergman et al., 1979).

Detection

In people, IR has been implicated in many metabolic conditions and diseases by evidence demonstrated by specific, quantitative methods, namely the euglycemic-hyperinsulinemic clamp and the minimal model (Bergman et al., 1979; DeFronzo et al., 1979). In the horse, however, IR has been implicated in several metabolic conditions and diseases by weak evidence, indications that are nonquantitative and nonspecific, such as hyperinsulinemia, hyperglycemia, glucose intolerance (oral or intravenous), insulin tolerance, hyperlipidemia, and obesity (Kronfeld et al., 2005). The clamp has been applied

to inactivity/activity and to reproductive efficiency by Fitzgerald and associates (Powell et al., 2002; Sessions et al., 2004). The minimal model has been applied to obesity and diet (Hoffman et al., 2003; Treiber et al., 2004a). We have found only one refereed article regarding insulin sensitivity demonstrated by a specific quantitative method in an equine disease (Annandale et al., 2004), and we suggest that the time has come for more frequent application of the clamp and the minimal model to sick horses.

The euglycemic-hyperinsulinemic clamp measures insulin-mediated glucose disposal (i.e., insulin sensitivity) only. The minimal model determines insulin sensitivity plus glucose-mediated glucose disposal and pancreatic β -cell response, which enables the assessment of compensation/decompensation. The clamp and the minimal model are technically demanding and expensive, however, and therefore unsuitable for situations calling for multiple observations, such as population studies or daily monitoring of a case. Consequently, simple surrogates have been sought for human studies. We have found satisfactory surrogates for insulin sensitivity and β -cell responsiveness (Treiber et al., 2004b). As one example, insulin sensitivity is predicted approximately 27% better by the log of the reciprocal of fasting insulinemia than by the insulinemia itself. More important, the combined use of surrogates for insulin sensitivity and pancreatic β -cell responsiveness enables differentiation between compensation in apparently healthy individuals that have a high risk of disease, and eventual decompensation as secretion subsides and disease ensues. Thus, studies of IR in horses can use either the full quantitative methods or the statistically validated surrogates, whichever is more appropriate to the experimental design or clinical situation.

Dietetics

Dietetics is the design of diets and feeding management for specified purposes, such as the avoidance or prevention of disease, or the promotion of performance. Avoidance and prevention have similar common meanings, but different official meanings in public health. The claim of prevention of a disease is like treatment, and a specific diet or nutrient assumes the role of a drug, according to the FDA (1997). Prevention must be demonstrated by a controlled trial designed to test the efficacy of the specific claim. It also must be demonstrated to be safe, following the same general protocols used for all drugs.

The concept of avoidance in dietetics was developed in the 1980s, and it took form in the Surgeon General of the Public Health Office's (1988) Report on Nutrition and Health. Two types of evidence were required for avoidance: associations established by population studies and causation indicated by mechanistic research. Three examples were offered: avoidance of excessive fat, especially saturated fat, to reduce the risk of heart disease; avoidance of excessive salt to reduce the risk of

hypertension and stroke; and avoidance of excessive sugar to reduce the risk of dental caries.

Equine Grain-Associated Disorders

In the same way (Kronfeld and Harris, 2003), avoidance of rapid and excessive meals of grain and molasses (starch and sugar) has been suggested to decrease the risk of acute digestive disturbances due to rapid fermentation in the stomach (ulcers) and the cecum (some forms of diarrhea, colic, and laminitis), and the risk of chronic metabolic disorders associated with alterations in insulin sensitivity (such as some forms of laminitis, dyschondroplasia, and exertional rhabdomyolysis). Supporting population studies and digestive and metabolic experiments were offered as evidence. Suggested ways to avoid excessive rapid intake of grain and molasses were discussed in detail by Kronfeld and Harris (2003), and are summarized here. Grain and molasses concentrates have 25 to 50% more DE than the same amount of forage, and hence can promote and sustain a higher level of energy output and performance. If a high intake of grain is desired to enable higher performance, more frequent meals rather than larger meals are indicated. Grain intake should be safe if nibbled rather than fed as meals of more than approximately 0.2 to 0.4% of BW, or 1.4 to 2.3 kg for a 500-kg horse. The recommended upper limits of meal size were based on fistula studies that showed appreciable amounts of starch reaching the distal ileum or cecum (Potter et al., 1992; Mayer et al., 1995). These limits are one-eighth or less of the starch overload that has been widely used as a model of alimentary metabolic laminitis (Garner et al., 1975). Although adaptation to grain and molasses feeds reduces insulin sensitivity, the condition is well compensated by pancreatic β -cell secretion (Hoffman et al., 2003; Treiber et al., 2004a).

Fats or oils have more than twice the energy density of grain, and their inclusion in a ration promotes efficiency of utilization (Kronfeld, 1996). The most palatable are corn oil and rice bran. Vegetable oils and animal fats should be introduced gradually to avoid shiny, greasy, or loose feces. Prudent use of these largely "empty calories" should be limited to a few weeks to avoid multiple incipient deficiencies, although relevant data are lacking for the horse.

High-fat feeds, if properly fortified with essential nutrients would overcome the potential difficulties of using straight fat or oil. The higher energy density calls for a smaller daily intake of fat-fortified supplement and a corresponding increase in forage to prevent fattening.

Fat and fiber feeds, such as those under development at Virginia Tech (Kronfeld et al., 1996), have enough fiber to be fed exclusively as complete feeds, and enough fat to be used as typical concentrate feeds. They all contain approximately 12% vegetable oils, rich in omega-6 fatty acids, but they vary in carbohydrate profiles for specific purposes: for example, repeated sprints or pasture supplementation for growth (Hoffman and Kronfeld, 1999; Graham-Thiers et al., 2001). Compared with

a typical sweet feed, one of our fat and fiber feeds has lowered the glycemic response by 40% and the insulimic response by 85% (Williams et al., 2001). It also avoided the insulin insensitivity that develops during chronic adaptation to sweet feed (Hoffman et al., 2003; Treiber et al., 2004a).

In many species, insulin sensitivity has been decreased by feeding saturated fat but has been increased by feeding polyunsaturated, omega-6 fatty acids (Storlien et al., 2000). The omega-3 fatty acids also improve insulin sensitivity in rats but not humans (Revillese and Lilli, 2003). Administration of omega-3 fatty acids has been claimed to prevent starch-induced laminitis in horses (Neeley and Herthel, 1997). Menhaden oil modulates leukotriene synthesis in horses and may influence inflammatory conditions (Hall et al., 2004), including the inflammatory component of insulin resistance (Fitzgerald, 2004).

Pasture Starch and Fructan

Safe concentrations of starch and fructan in pastures and hays have not been well established. Extensive information is available about environmental factors that affect pasture contents of starch and fructan (Longland et al., 1999; Watts and Chatterton, 2004), but this type of information has yet to be associated closely with disease incidence.

Fructan concentrations in grass leaves under hot, bright, sunny conditions in May in Wales, U.K., were 14 to 30% DM from 0900 to 1500 and from 4 to 11% from 1500 to 2100 (Longland et al., 1999). Estimates of fructan intake based on these data cannot be precise. A 500-kg horse consuming 16.4 Mcal of DE over 24 h (NRC, 1989), or approximately 8 kg of DM of pasture, could ingest from 0.5 to 1.0 kg of fructan based on estimated weighted average fructan contents of 6.5 (low) or 12.5% (high). An oral dose of 3.75 to 6.25 kg of inulin (not the fructan in grass) given as a relatively rapid single bolus to a 500-kg horse has caused severe diarrhea and acute laminitis but not colic (Pollitt et al., 2003).

In our experience with a herd of 170 ponies in north-central Virginia, no cases of laminitis were present when pasture starch was about 4% DM in March, 2004, and 12 cases were present at the end of May, when pasture starch was approximately 8% (our unpublished data). This increase in starch was consistent with a rich growth of red and white clover in May.

On the other hand, pasture hydrolyzable carbohydrate (mainly starch) concentrations of 8 to 11% were found in March, April, June, September, October, and November of 1996 in north-central Virginia, and the water-soluble, rapidly fermentable carbohydrate fraction, which contained fructan, was 5 to 6% in April, October, and November (Hoffman et al., 2001). No cases of laminitis occurred in 100 to 125 Thoroughbreds, which suggests a lack of genetic predisposition compared with the nearby ponies. Thus, it is important to identify apparently healthy horses and ponies at risk (those in which

insulin insensitivity is present but currently compensated for by pancreatic insulin secretion) on the basis of previous history and the detection of a genuine "prelaminitic metabolic syndrome" (Treiber et al., 2004b), so that special precautions regarding pasture management can be given to these animals.

The word "sugar" is being used in two ways (Kronfeld et al., 2004). Some commercial forage laboratories use an 80 or 90% ethanolic solution that extracts only mono- and disaccharides, so they report true sugar. Others extract with water and therefore measure water-soluble carbohydrates, which contain the true sugars plus fructan (oligo- and polyfructosyl sucrose), and report this fraction as "sugar" (a misnomer).

Starch assays available from commercial forage laboratories are for total hydrolyzable carbohydrate. For the present purpose, the rapidly digestible, slowly digestible, and resistant fractions should be determined (Englyst et al., 1999). Resistant starch is rapidly fermentable and, hence, potentially conducive to colic, diarrhea, and laminitis (Kronfeld and Harris, 2003). Rapidly available glucose (rapidly digestible starch plus glucose free and from disaccharides) has been shown to determine the glycemic response in humans (Englyst et al., 1999, 2003). It can be used to calculate the ratio of glycemic energy to total energy, a parameter that might supersede the glycemic index (Kronfeld et al., 2004).

Glycemic Index

Originally, this index compared the glycemic effect of 50 g of "available carbohydrate" in a food with that of 50 g of glucose in humans (Jenkins et al., 1981). At that time, proximate carbohydrate analysis could not predict glycemic effects. A high-carbohydrate, low-fat diet was being recommended to decrease the risk of heart disease in the whole American human population. It was unsuitable, however, for people who had compromised glucose homeostasis, such as the 11% who had diabetes and a similar number of prediabetics. Today, the prevalence of human prediabetic metabolic syndrome is approximately 25% (Ford and Giles, 2003). What was desired in the 1970s was a high-carbohydrate, low-glycemic diet.

The glycemic index is no longer needed in human dietetics because the *in vitro* enzymatic method of measuring rapidly digestible starch, combined with glucose from sugars, accurately predicts glycemic effects (Englyst et al., 1999, 2003). The glycemic index has other practical and theoretical difficulties (Pi-Sunyer, 2002; Monro, 2003). Its estimates have large errors (Figure 2). It is better based on available energy than on available carbohydrate in a dietetic system that aims to provide an ideal energy intake (Kronfeld et al., 2004).

The glycemic effect of the food becomes identical with the glycemic response of the subject, which depends on rates of ingestion, gastric emptying, digestion, and absorption, then rates of removal from blood that are glucose-mediated or insulin-mediated. All of these rate processes are regulated, and regulated systems are nonlin-

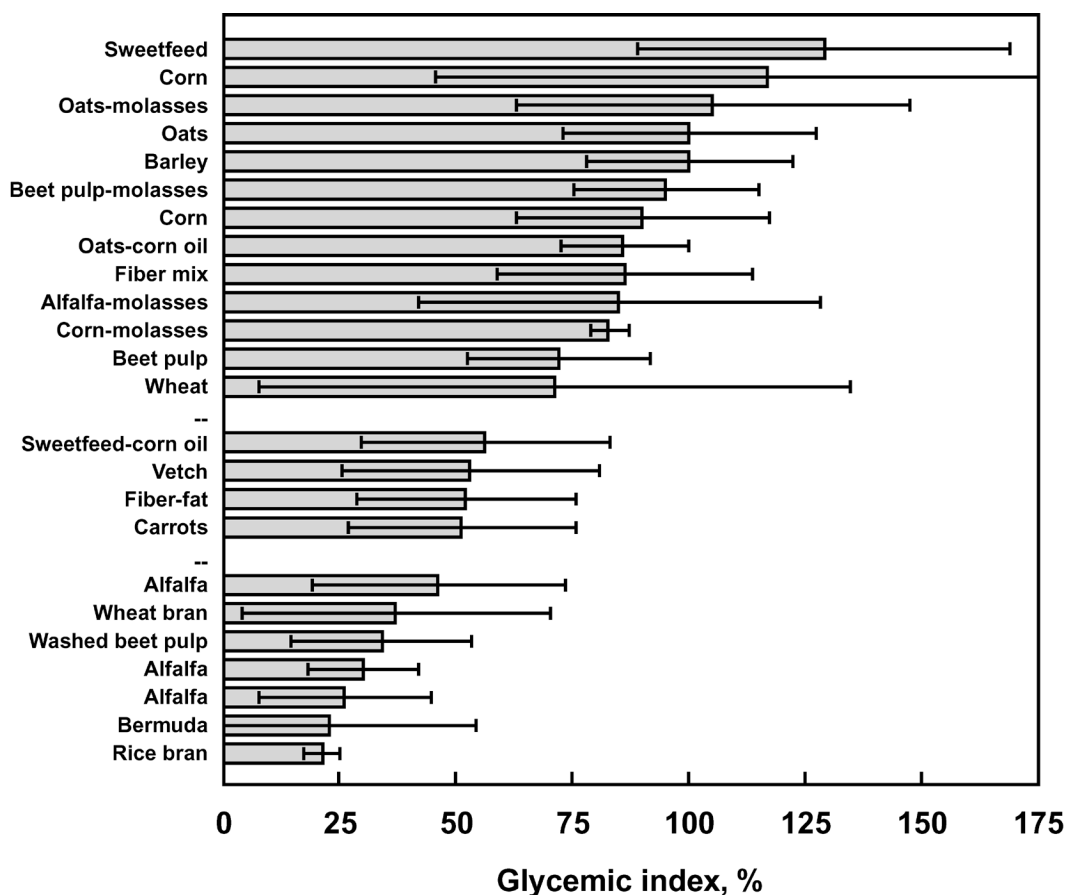


Figure 2. Means and standard deviations of glycemic indexes of horse feeds have been collated from six studies (Stull and Rodiek, 1988; Pagan et al., 1999; Groff et al., 2001; Williams et al., 2001; Rodiek, 2003; Jose-Cunilleras et al., 2004). Proponents of the glycemic index apply simple linear arithmetic to calculate weighted average for meals or diets, and the sum of glucose loads for a meal or daily intake. Others observe that the means are imprecise and that the glucose-insulin regulatory system that determines the glycemic response of the animal is certainly non-linear, such that linear calculations are inappropriate and sure to be imprecise (modified from Kronfeld et al., 2004).

ear. Thus, the simple arithmetic of adding glycemic indexes and loads, and finding weighted averages, must yield inexact results.

Glycemic Dietetics and Disease

Despite the limitations of the glycemic index, it offers some guide for the design of diets intended to promote performance and to avoid the nutritional risks of disease. Much of the relevant information has come about incidentally to the study of fat-fortified diets, most of which are presumed to have low or moderate glycemic indices (approximately 55% or less; Figure 2) compared with similar “sweet” feeds (approximately 110 to 125%; Figure 2). For example, the Virginia Tech starch-and-sugar feed is a typical textured “sweet” feed, and the fat-and-fiber feeds have grain and molasses exchanged for corn oil, soybean meal, and various fiber sources. This isocaloric, isonitrogenous exchange decreases the glycemic effect by 40 to 60%, and the insulinemic effect by approximately 85% (Williams et al., 2001). It also eliminates the insulin insensitivity associated with chronic adapta-

tion to “sweet” feed in weanlings and in older horses that are not obese (Hoffman et al., 2003; Treiber et al., 2004a).

This chronic insulin insensitivity follows repeated large glycemic and insulinemic responses to twice-daily meals of grain and molasses (Staniar et al., 2002). These initial responses resonate along the somatotrophic axis, so that plasma IGF-1 is much higher in horses adapted to sweet feed than in those supplemented with fat and fiber feed (Staniar et al., 2002; Treiber et al., 2004c). Insulin-like growth factor-1 strongly influences all stages of chondrocyte proliferation, differentiation, and maturation in the conversion of cartilage to bone.

Oral glucose tolerance curves were higher in young horses affected with osteochondritis dissecans than in healthy controls (Ralston, 1996). An association was claimed for a higher incidence of surgically treated osteochondritis dissecans and a higher glycemic index in the feed on six farms (Pagan et al., 2001). The data for the top farm were outliers, and their deletion eliminated the statistical significance of the linear regression; however, a logarithmic transformation restored the significant association (Kronfeld and Harris, 2003). Thus, there is

evidence for an association and a causative mechanism that supports that claim that it is prudent to avoid a high-glycemic diet for young horses at risk of osteochondritis dissecans. In contrast, no evidence is available currently to support a claim that a low-glycemic diet will prevent this disease.

Insulin resistance has been implicated in laminitis by nonspecific indicators, but not yet by specific quantitative methods (Kronfeld et al., 2005). Some 32 nutritional modalities were recommended for the prevention and treatment of equine metabolic syndrome (Johnson et al., 2004), apparently by analogy with human insulin resistance because none of these modalities was supported by equine data or the strong evidence required for such claims by the FDA (1997).

Insulin hypersensitivity has been demonstrated by the euglycemic clamp in equine polysaccharide storage myopathy (Annandale et al., 2004). Greater glucose availability inside muscle cells may contribute to exaggerated glycogen synthesis. Serum creatine kinase activity 4 h after treadmill exercise was greatly decreased in horses adapted for 6 wk to a diet in which 40% of DE was provided by a concentrate containing 4% DE as starch and 13% DE as corn oil and rice bran (Ribeiro et al., 2004). The authors cited studies of fat adaptation and suggested that adaptation to the low-starch, high-fat feed, combined with physical training, may have promoted fatty acid metabolism and spared glucose metabolism in muscle.

Glycemic Dietetics and Exercise

Speed depends partly, perhaps mainly, on the power of muscle contraction that is directly related to the rate of ATP generation, which in turn is determined by the substrate or fuel utilization (Houston, 2001). The slowest method is fatty acid oxidation, which is sustainable for many hours. More powerful for many minutes or a few hours is glucose oxidation. Much more powerful but only for several seconds is glycolysis; and the most powerful for a few seconds is ATP formation from creatine phosphate. Mixtures of substrates and metabolic pathways are used between the extremes of light and hard intensities.

Much of human exercise physiology has aimed to maximize oxidation of glucose from muscle glycogen and blood-borne glucose, with the goal of replacing glycolysis, and thereby decreasing fatigue and fatty acid oxidation and increasing power (Houston, 2001). This objective is achieved by carbohydrate loading from the provision of a high-glycemic diet. Similarly in horses, the provision of high-starch meals before and after submaximal work has been recommended to promote glucose oxidation and glycogen repletion.

A large meal of corn (25% of the daily DE intake) fed 2 h before exercise led to a high-glycemic response followed by a rapid decrease in plasma glucose concentration during the first half of 60 min of submaximal exercise in both fit and unfit horses (Rodiek et al., 1991).

These results suggested that the high-glycemic meal 2 h before submaximal exercise promoted glucose utilization.

This conclusion was confirmed and amplified by a study of glucose kinetics using stable isotopes (Jose-Cunilleras et al., 2002). The study compared the effects of fasting for 18 h or eating a meal (25% of daily DE intake) of corn or alfalfa 2 to 3 h before submaximal exercise for 60 min on a treadmill. Compared with fasting, the corn meal increased muscle utilization of blood-borne glucose during exercise, but it failed to have a sparing effect on muscle glycogen. Compared with alfalfa, the corn meal increased carbohydrate oxidation and decreased lipid oxidation during exercise. The authors concluded that feeding a high-glycemic meal 2 h before moderate exercise might be "indicated" (possibly beneficial).

Muscle glycogen repletion after exercise is much slower in the horse than other species. In an attempt to accelerate glycogen repletion, a 500-kg horse was offered a 2.2-kg, high-glycemic meal every 8 h (Lacombe et al., 2004). Muscle glycogen content was depleted to 22% of basal values by heavy and prolonged exercise. Repletion reached 42% in 12 h and 100% in 72 h. This regimen was suggested to benefit horses undertaking events on successive days, with a caution about gastrointestinal disorders and the need for careful feeding management.

In summary, the use of high-glycemic meals to promote exercise performance involves the use of a high-glycemic meal 2 to 3 h before an event and every 8 h thereafter for 72 h (Jose-Cunilleras et al., 2002; Lacombe et al., 2004). This regimen might suit a horse that works hard twice a week or every 3 or 4 d, such as a race horse or a fox hunter. It promotes glucose oxidation during submaximal exercise and glycogen synthesis for 72 h after exercise. It also increases health risks, such as acute digestive disorders associated with rapid fermentation and chronic metabolic disorders associated with insulin resistance (Kronfeld and Harris, 2003).

An alternative approach to a high-glycemic meal has been developed in our laboratory: the use of a fat-fortified, moderately glycemic, low-insulinemic feed (Williams et al., 2001). This approach has found less favor in human exercise physiology, but a moderate glycemic meal with a high-fiber content consumed 45 min before prolonged moderate exercise was taken to confer metabolic advantages for performance in human athletes (Kirwin et al., 1998).

In horses, chronic adaptation to fat-fortified feeds, which have moderate or low glycemic effects (Figure 2), confers benefits to athletic performance that may be due to insulin sensitivity in addition to other aspects of fat adaptation. According to a bioenergetic model, a complete feed that has 10% corn oil exchanged for 5% oats and 5% hay on an energy basis leads to less production of feces, acid, and heat (i.e., improvement in energetic efficiency) (Kronfeld, 1996). The acidogenic effect of repeated sprints was further decreased by adapting horses to a feed that exchanged corn oil for protein as well as starch (Graham-Thiers et al., 2001).

Faster times were recorded for fat-adapted horses in two studies on the track, one over 600 m (Oldham et al., 1990), the other for 1,600 m with the gain mainly in the first 200 m (Harkins et al., 1992), when glycolysis is needed for maximal power to accelerate. In addition, greater maximal accumulated oxygen deficits, longer run times to fatigue at 115% $\text{VO}_{2\text{max}}$, and higher peak plasma lactate concentrations were observed in fat-adapted horses (Eaton et al., 1995).

The increase in plasma lactate concentration during exercise reflects the rate of glycolysis. Studies have shown that this increase in plasma lactate is moderated during slow or moderate work in horses adapted to a feed in which vegetable oil was exchanged for starch and sugar (Greiwe et al., 1989; Sloet van Oldruitenborgh-Oosterbaan et al., 2002), a difference that can be explained by increased fatty acid oxidation sparing glucose utilization (Pagan et al., 2002). In contrast, the increase in plasma lactate is accentuated during hard work in horses adapted to feeds in which fats or oils have replaced starch (Oldham et al., 1990; Ferrante et al., 1993). This difference in plasma lactate responses to moderate- vs. high-intensity work was taken to indicate enhanced metabolic regulation in horses adapted to high-fat, moderately glycemic feeds (Kronfeld et al., 1995).

The proposal of superior metabolic regulation was confirmed and amplified by a study of lactate threshold (Kronfeld et al., 2000). The lactate threshold was increased (i.e., the breakpoint was delayed until a higher speed) in Arabian horses after 12 wk of physical conditioning and adaptation to a fat-and-fiber feed compared with a starch-and-sugar feed. In an incremental exercise test, plasma lactate was unchanged until approximately 5 m/s but, once started, it increased more rapidly and reached a higher peak in horses adapted to the 14% fat feed. These results reinforced previous studies that had suggested improved regulation of the rate of glycolysis relative to the intensity of exercise in horses adapted to feeds in which fats or oils replaced grains and molasses. These fat-and-fiber feeds also eliminate the loss of insulin sensitivity in horses adapted to starch-and-sugar feeds (Hoffman et al., 2003; Treiber et al., 2004a). We now propose that they also may sustain or enhance other signaling functions of insulin receptors on glycolysis and lipid utilization (Saltiel and Kahn, 2001).

During exercise, the insulin receptor signaling system interacts with other hormonal systems in complex ways that will be summarized here only briefly (Houston, 2001). Plasma insulin concentration falls at the start of exercise, and this allows counter-regulatory hormones to accelerate lipolysis in adipose tissue with the release of NEFA that are bound to albumin. Plasma NEFA are taken up by the liver and converted mainly to very-low-density lipoprotein, commonly measured as plasma triglyceride (triacylglycerol) in the horse. Fatty acids derived from NEFA and very-low-density lipoprotein are taken up by muscle cells, and their oxidation seems to be facilitated in the trained horse, probably under the influence of insulin receptor signaling. The movement

of GLUT4 transporters to the muscle cell surface during contraction is prompted by signals arising from Ca^{2+} translocation (Richter et al., 2004), thereby subordinating signals from the tyrosine kinase insulin receptor that predominate in noncontracting muscle. At higher work intensities, the release of catecholamines augments glycogenolysis and glycolysis (Stainsby and Brooks, 1990; Kronfeld et al., 2000), thereby increasing the rate of ATP production and the power of muscle contraction.

Somewhere in this complex chemical communications network are explanations for aspects of exercise that have been found only in the horse. One is the enhanced (or at least unimpaired) regulation of glucose utilization and fatty acid oxidation during exercise in fat-adapted horses. Others are the relatively slow rates of muscle glycogen depletion during exercise and subsequent re-synthesis to achieve preexercise values.

To avoid starch overload and rapid fermentative disorders (Kronfeld and Harris, 2003), our approach to the acceleration of muscle glycogen resynthesis was to test a glucose polymer of approximately 5 to 8 glucose units (Polycose; Abbott Laboratories, North Chicago, IL). Its glycemic and insulinemic effects are like those of glucose in humans, and its main advantage is elimination of the tendency for osmotic diarrhea (Wahlqvist et al., 1978). Similar desirable effects and safety benefits may be expected in horses, together perhaps with the avoidance of rapid fermentation in the cecum, but they remain to be confirmed. A combined endurance and sprinting protocol depleted muscle glycogen to 79% of basal value in 12 Arabians (Hess et al., 2004). Then, horses were given five hourly doses of 1 g/kg (a total of 5 g/kg or 2.5 kg for a 500-kg horse) of glucose equivalents by gastric gavage. Repletion reached 89% of the basal value in 12 h (Hess et al., 2004). Stools were evaluated, and all remained well formed.

Relationships of metabolic objectives or proxies for actual exercise performance are seldom established unambiguously in regard to efficacy and safety. Equine examples are preferred substrates for work of various durations and intensities, which apparently changes from the typical mammalian pattern in fat-adapted horses, and the value of muscle glycogen resynthesis, which is strongly resisted by the horse itself. Experiments concerning glycemic dietetics, including fat adaptation and insulin sensitivity, have yielded provocative results but no final resolution.

Implications

Studies of insulin resistance in horses are guiding improvement in health maintenance (the avoidance of risk factors for certain diseases) and performance. The use of specific quantitative methods and statistically validated simple surrogates is replacing nonspecific and ambiguous indications of insulin resistance. Because claims of avoidance vs. prevention require different kinds of supporting evidence, dietetics is discriminating between the use of specified diets for the prevention and

therapy of disease (e.g., laminitis) and the avoidance of excessive intakes of nutrients, such as starch and fructan, regarded as risk factors of disease. Use of the glycemic index should take into account its lack of precision and its nonlinearity. Despite these limitations, glycemic dietetics has yielded results of potential value in the management of certain diseases associated with rapid carbohydrate digestion and in enhancing metabolic proxies of exercise performance.

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