Osteochondrosis dissecans (OCD) in horses: hormonal and biochemical study (19 cases)

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Abstract

To investigate the hormonal and biochemical profiles of horses with osteochondrosis dissecans (OCD), serum insulin, cortisol, triiodothyronine, thyroxine, fasting blood glucose (FBG), cholesterol, triglyceride (TG), high- and low-density lipoproteins, albumin and urea acid were measured in horses definitely diagnosed with OCD (n=19) as well as clinically normal horses (n=18). Proxies representing insulin sensitivity [reciprocal of square root of insulin concentration (RISQ)] and beta cell responsiveness [modified insulin to glucose ratio (MIRG)] were calculated. Body fat percent (BF%) was estimated according to fat depth over the rump using ultrasonography. Body condition score (BCS), weight, and waist circumference were also determined. Glucose was significantly higher and MIRG, BCS, BF% and TG were significantly lower in OCD- horses compared to control group. Based on BCS scores, horses in control group were overweight. The results of the present study, higher FBG and lower MIRG, might implicate the existence of a footprint of insulin/glucose derangement. The body mass index and muscle mass were not measured in this study; nonetheless, a lower BF% might implicate a higher body mass index and muscle mass in OCD affected horses, which were comparably underweight compared to control group. While insulin resistance does also occur in human individuals and horses with lower BF%, horses with higher muscle mass may show greater potential for exercise, which in turn, exerts greater physical pressure on cartilages. An underlying hormonal predisposition could make these horses more prone to OCD, originally triggered by mechanical pressures.

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Introduction

Osteochondrosis dissecans (OCD) is a major problem in the equine industry, which has been regarded as an important cause of lameness in sport horses. The condition is regarded as part of the syndrome of developmental orthopedic disease (DOD), which includes physitis, angular limb deformities, and OCD. It occurs worldwide in many breeds, the incidence appears to be steadily increasing. It is usually seen in young, rapidly growing horses and more commonly affects males than females. The condition manifests by failing of an area of growth cartilage to undergo matrix calcification or vascular invasion, followed by failure to be converted to bone. Clinically the condition is manifested by detachment of cartilage from underneath bone.

Historically, it was introduced into the veterinary literature by the phrase “intracapsular bony fragments of the distal tibia of the horse”. This definition was substantiated by other studies that reported cases of OCD, which endorsed by radiographically detectable disturbances of endochondral ossification during the first three months of life. Several etiological factors have been proposed for the description of the condition. It appears to be multifactorial in origin, involving heredity, growth rate, breed, age, body size, nutrition, mineral imbalances, endocrinological dysfunction and biomechanical trauma.

The condition was reported to be heritable estimated to vary in a range of 0.00 to 0.52. The link between OCD and growth rate had been established in species such as pigs and poultry. Gilts receiving an ad libitum diet had higher odds of suffering from OCD than gilts treated by a restricted feeding. The link in horses, however, is remained to be elucidated. While thoroughbred and standardbred horses are at greater risks of developing the condition, the risk is decreasing significantly with the age of the horse.
of the horses. Rapid growth rate caused by high energy intake, especially in the form of easily digestible carbohydrates, has been related to OCD. It is thought that hormonal imbalance mediated by high plane of nutrition starts the cascade terminated into the development of OCD. Moreover, it has been reported that genetic effects significantly contribute to the development of OC via a polygenic and highly complex genetic basis.

It has been suggested that postprandial hyperglycemia and/or hyperinsulinemia may be correlated with the development of OCD lesions in young Standardbred horses, in which age differences in responses were also observed. Based on the literature, increased insulin and its derivatives as well as parathormone levels, cause the incremental processes of multiplication of chondrocytes, which fail to differentiate to osteoblasts. The bone matrix is altered as well. Collectively the process of changing chondrocytes to bone tissue will be declined and altered, which lead the process to osteochondrosis. Moreover, increased insulin causes decline in thyroid hormones production, which itself impairs the level of vascularization in active areas of bone synthesis. Increased intake of readily digestible carbohydrates causes hyperglycemia and consequently hyperinsulinemia, which causes a vicious cycle leading to osteochondrosis.

We assumed that part of the genetic influence on the development of OCD may be mediated by hormonal imbalances. Therefore, the aim of the present study was to investigate the hormonal and biochemical profiles of horses affected by OCD in comparison with normal horses.

Materials and Methods

Experimental location. This case control study was conducted at Ferdowsi University of Mashhad Veterinary Teaching Hospital from June 2015 until June 2016. During this period, nineteen horses with a definitive diagnosis of OCD were selected. They had been fasted for 10 to 12 h before admission to the hospital by the client. Eighteen clinically normal horses were referred to the hospital in the same period for pre-purchase examination, served as controls. The general procedure was approved by the committee of the Faculty of Veterinary Medicine, Ferdowsi University of Mashhad. Body condition score (BCS) of horses were subjectively appraised by two experienced observers on each occasion using Kohnke’s modification of the system originally described by Henneke et al., ranging from BCS 1 (very poor) to BCS 9 (extremely fat).

Experimental procedure. All methods were in compliance with the guide for the care and use of agricultural animals in agricultural research and teaching in Ferdowsi University of Mashhad, which has been critically evaluated and approved on 6 Jan 2015. All horses received a mixture of barley grain (4.00-7.00 kg daily), alfalfa hay, wheat straw and a variety of mineral/vitamin supplements. Foals shared their mother’s feed when kept together in the same stall. The owners had been told to fast the horses before admission to the hospital for 10-12 h. Most horses were carried from the north of Iran after a 500-600 km road travel (12 hr ride) to the hospital by horse carriage trucks. A general protocol was carried out on all horses including a complete clinical examination and lameness evaluation including palpating the limbs, gait was observed while walking and trotting. Tests of joint flexion involved passive flexion of individual joints for 60 sec followed immediately by observing the gait while trotting. Tests of joint flexion involved passive flexion of individual joints for 60 sec followed immediately by observing the gait while trotting. Nerve block and intrasynovial anesthesia by lidocaine HCl (Aburaihan, Tehran, Iran) were also used to localize the affected area/joint during a clinical examination. Diagnosis of OCD was confirmed by lateral, craniocaudal and oblique radiographs of affected joints and ultrasonography, which were completed within arthroscopy for the correction of the lesion.

After hair coat clipping and cleansing by alcohol on the right rump 5.00 cm lateral from the midline at the center of the pelvic bone as well as application of coupling gel on the shaved area of the skin, body fat percentage (BF%) was determined by measuring the fat depth over the rump according to the equation BF% = 5.07 × (fat depth, (cm) + 6.22) developed by Westervelt et al using an ultrasound machine with a 7.50 MHz linear transducer (DP6600; Mindray, Szechuan, China). Ultrasonograms were recorded by a DVD recorder, then, fat depth was measured in three points and the means were used for further calculation and analysis using Image J software (National Health Institute, Bethesda, USA). Horses without a definitive diagnosis and/or not fasted were excluded. A control was defined as a horse which did not have a history of any orthopedic disease prior to admission and was not diagnosed with an orthopedic problem during soundness tests. Horses’ characteristics (age, gender, physical condition, and breed) are presented in Table 1.

Blood sampling. Sampling was performed after 10 to 12 h fasting, venous blood samples were obtained from the jugular vein and collected into vacutainer tubes, immediately transferred to laboratory, centrifuged at 3,000 g for 10 min, while serum was removed within 30 min and stored at −20.00°C until analysis.

Biochemical analysis. Serum glucose, triglyceride (TG), albumin, cholesterol and uric acid concentrations were determined by chemical auto analyzer (Selectra XL; Vital Scientific, Spankeren, The Netherlands) using Pars Azmoon kit (Tehran, Iran). Plasma high density lipoprotein (HDL), and low density lipoprotein (LDL) concentrations were determined using the same auto analyzer and Bionik kit (Tehran, Iran). Insulin, cortisol, triiodothyronine (T3) and thyroxine (T4), were determined using chemiluminescence method (Immulate 2000; Siemens, Munich, Germany).
Inter-assay and intra-assay coefficients of variations (%) of biochemical criteria were as follow, respectively: Glucose (0.84, 1.28), TG (1.04, 1.82), albumin (1.44, 1.12), cholesterol (1.22, 0.61), uric acid (1.13, 1.180), HDL (1.10, 0.70), T3 (4.60, 4.40), T4 (4.70, 2.40), cortisol (8.40, 7.50) and insulin (7.30, 5.50).

**Insulin sensitivity.** Insulin sensitivity and β-cell responsiveness of pancreas including reciprocal of square root of insulin concentration (RISQI) and modified insulin to glucose ratio (MIRG) were determined using proxies as follow:

\[ RISQI = 1/\sqrt{\text{insulin}} = \text{insulin}^{-0.5} \]
\[ MIRG = [800 - 0.30 \times (\text{insulin} - 50)]/(\text{glucose} - 30) \]

Then, the results were matched to nomograms described by Treiber et al, to find out the relevant quintile.25

Statistical Analysis. Data were expressed as mean ± standard deviation, standard error or median and interquartile range. Normal distribution of data was tested by determining the Kolmogorov-Smirnov and Shapiro-Wilk, W and associated p-values as well as by examining the normal probability plots. Values were log transformed when necessary to obtain a normal distribution. Data with a normal distribution were analyzed using t-test. Mann-Whitney U test was used to analyze non-normal data, which was presented as median and interquartile range. Glucose, cholesterol, albumin, HDL, LDL, cortisol, T4, MIRG, waist circumference and weight had normal distribution, and analyzed parametrically. Uric acid and triglyceride data were log transformed and analyzed parametrically. Insulin, T3, RISQI, BP%, and BCS were not normally distributed, even after log transformation and analyzed non-parametrically.

### Table 1. Data representing criteria of hormonal and biochemical plasma levels, insulin responsiveness proxies (RISQI and MIRG), BP%, BCS, waist circumference and weight in osteoarthritis dissectans (OCD) and control horses.

| Parameters         | OCD         | Control    | IQR | SD  | SE  | CI      | p-value |
|--------------------|-------------|------------|-----|-----|-----|---------|---------|
| Glucose (mg dL⁻¹)  | 121.60      | 121.00     | 35.50 | 21.60 | 4.96 | 12.96-45.91† | S**     |
| Cholesterol (mg dL⁻¹) | 86.68      | 87.00      | 27.00 | 19.44 | 4.46 | 14.60-15.72† | NS      |
| Albumin (g dL⁻¹)   | 4.42        | 4.40       | 0.80  | 0.42  | 0.09 | 0.17-0.39†  | NS      |
| HDL (mg dL⁻¹)      | 35.89       | 36.00      | 6.50  | 5.60  | 1.28 | 4.50-4.54†  | NS      |
| LDL (mg dL⁻¹)      | 16.94       | 17.00      | 3.50  | 3.73  | 0.85 | 6.68-0.32†  | NS      |
| Uric acid (mg dL⁻¹) | 0.67        | 0.60       | 0.15  | 0.14  | 0.03 | 0.17-0.09†  | NS      |
| Triglyceride (mg dL⁻¹) | 20.35      | 19.00      | 7.50  | 5.84  | 1.41 | 25.27-9.61† | NS      |
| Insulin (µl mL⁻¹)  | 4.90        | 1.50       | 0.00  | 0.00  | 0.00 | 2.59-1.04   | NS      |
| Cortisol (µg dL⁻¹) | 5.20        | 5.60       | 0.60  | 2.95  | 0.43 | 4.31-0.32†  | NS      |
| T3 (ngdL⁻¹)        | 157.5       | 125.00     | 0.00  | 94.60 | 22.96 | 56.08-88.46* | NS      |
| T4 (µg dL⁻¹)       | 134.90      | 151.50     | 103.75 | 53.70 | 18.22 | 12.96-2.24* | NS      |
| RISQI†             | 3.91        | 3.90       | 1.45  | 1.86  | 0.65 | 0.30-0.16α  | NS      |
| MIRG²               | 7.30        | 6.76       | 4.18  | 2.70  | 4.18 | 5.76-1.70†  | S**     |
| Fat (%)            | 33.00       | 31.53      | 1.43  | 2.96  | 0.79 | 12.96-2.24* | NS      |
| BCS                | 38.36       | 37.13      | 7.21  | 9.03  | 3.19 | 159.43-84.39 | S**     |
| Weight (kg)        | 439.90      | 454.00     | 92.25 | 50.17 | 12.10 | 10.58-180.40† | NS      |
| Waist (cm)         | 180.00      | 182.00     | 11.00 | 8.73  | 2.00 | 26.82-10.07† | NS      |

IQR: Interquartile range; SD: Standard deviation; SE: Standard error; CI: Confidence interval.

1 calculated as insulin⁻0.5 (mIU L⁻¹); 2 Calculated as: [800-0.30(Insulin - 50)] × (glucose - 30); unit: (mIU insulin⁻0.5 × [10Log mgglucose⁻1]).

NS: Non-Significant; S: Significant; *p < 0.05; **p < 0.01; ***p < 0.10; † Normally distributed; †† Normalized after Log transformation; α Confidence intervals determined non-parametrically as the 2.50th percentile to the 97.50th percentile.
Statistical comparisons were performed using SPSS Software (version 21.0; IBM Corp., Armonk, USA). A difference level of 0.05 was considered as significant. A level of 0.1 was considered significant for BCS scores.

Results

In the healthy and OCD horses, BCS varied from 6-7 and 4-7, respectively. Subcutaneous fat depths, 5 cm lateral to the midline over the right rump were measured (Fig. 1) to estimate body fat percent (BF%), (Table 2). Horses with OCD had significantly higher fasting blood glucose (FBG) level ($p < 0.01$). In contrast, Serum TG, MIRG, BF% and BCS were significantly higher in control horses ($p < 0.01$ for all comparisons). Horses affected by OCD showed significantly lower BF% and BCS ($p < 0.01$).

Levels of Cholesterol, albumin, HDL, LDL, Uric acid, insulin, cortisol, T3, T4, RISQI, as well as weight and waist circumference were not significantly different between the two groups ($p < 0.01$). Data of the abovementioned criteria are illustrated in Table 2.

Discussion

The OCD is often caused by normal stress on abnormally developing bone. Several factors have been incriminated as potentially influencing OCD risks in young horses, including diet, genetics, growth rate, trauma, hormone imbalance, and excessive exercise. We performed a prospective case control study on locally referred cases in order to trace the probability of the existence of hormonal and/or biochemical abnormalities in horses with OCD admitted to our teaching hospital. Our data suggested that there were no significant differences in insulin, T3, T4, cortisol, HDL, LDL, cholesterol, uric acid, albumin, and RISQI in OCD horses compared to the control group. However, significant differences were observed between the two groups in terms of BF%, FBG, TG and MIRG.

It has been reported that OCD may be associated with changes in insulin sensitivity. There are difficulties in relying on the interpretation of glucose and insulin levels alone in young horses with radiographic evidence of OCD, therefore, some authors have also used basal glucose/insulin ratio instead, to report their data. Two useful surrogates or proxies are proposed based on plasma samples for determination of basal glucose and insulin concentrations to evaluate the glucose-insulin system. They are supposed to serve as predictors of some diseases because they describe the chronic undistorted state of the patient. The RISQI and the MIRG were developed to predict insulin sensitivity and acute insulin response to glucose (AIRg), respectively, which were thought to be associated with some diseases, including OCD.

In the present study, levels of RISQI which estimates insulin resistance (SI), was not significantly different between the control group and OCD-affected horses. In contrast to the study by Robles et al. which had observed a greater OCD foals born to obese mares, levels of MIRG as a proxy for AIRg were significantly lower in OCD-affected horses than the control. Part of this discrepancy between the results may be due to different population of horses, different feeding strategy (availability of pasture vs. hand fed alfalfa hay and barley grain) and different age range (6-12 months vs. 1-12 years in OCD-horses). This may implicate that a different profile of risk factors could play roles in the pathogenesis of OCD in referred horses to our hospital. A lower MIRG along a higher FBG in OCD affected horses.

| T4 mean (µg dL⁻¹) | OCD (n) | Control (n) | 95% confidence interval | p-value |
|-------------------|---------|-------------|------------------------|---------|
| Under 5 year      | 4.41 ± 1.11 (15) | 5.47 ± 1.68 (10) | −2.19 - 0.06 | 0.064 |
| Over 5 year       | 3.98 ± 1.99 (4)  | 3.29 ± 1.08 (9)  | −2.30 - 3.60    | 0.55   |

Fig. 1. Subcutaneous fat depths in A) control and B) OCD groups.
horses in the present study might implicate a comparably lower acute insulin response to glucose. Therefore, any comparison should be done cautiously.

Moreover, based on the quintiles suggested by Treiber et al., RISQI and MIRG, were within the 5th quintile range, except for MIRG of one case in OCD-affected horses. This might implicate similar glucose to insulin system, reflecting a resembling feeding system of both OCD- and control groups.

Both BCS and BF% were significantly lower in OCD horses than the control group. Based on body condition scoring, horses in the control group with a BCS of seven (median) were considered overweight. The waist circumference had provided useful information in man; however, it was not significantly different here. In contrast to other species, the visceral adipose tissue depots of the adult light breed horses do not have greater expression of genes encoding inflammatory cytokines when compared to subcutaneous adipose tissue depots. The results suggests that in contrast to humans, waist circumference as a proxy for visceral adipose tissue do not provide additional information regarding insulin resistance in horses.

Frank et al., reported numerically but not significantly higher plasma TGs in obese horses with IR than non-obese horses. In contrast, the data in the present study showed a significantly lower triglyceridemia in OCD affected horses, which presumably could be expectable regarding significantly lower BF% in OCD horses. Levels of HDL, LDL and cholesterol, which were metabolically correlated with TG, were not significantly different ($p < 0.05$).

Cortisol has an important role in increasing serum TG levels. In the present study, a similar cortisol levels in OCD affected horses compared to the control group might implicate that higher TG levels were largely due to higher BF%. It has been reported, however, hypertriglyceridemia in IR is concomitant with cortisol derangement in several species. According to our results, it was unlikely that measurement of cortisol provides additional information regarding either insulin resistance or OCD pathophysiology.

Level of uric acid was measured in order to reveal any history of laminitis, which itself might have a confounding effect of the overall results. It has been reported that increase in uric acid concentrations were associated with a history of laminitis in ponies. Data showed no evidence of increased uric acid levels or significant differences.

On an overall view, thyroid hormones were not significantly different between OCD- and control groups (Table 2). Although levothyroxine sodium is a component of a therapeutic regimen in the treatment of equine metabolic syndrome, roles of thyroid hormones was not elucidated in IR in horses. In the past, hypothyroidism was incriminated as an attribute to obesity, which itself is a component of equine metabolic syndrome. However, lack of a thyroid-stimulating hormone (TSH) assay in horses precludes further interpretation just based on T3 and T4.

Because of multifaceted nature of the development of OCD in horses, describing the phenomenon, based on one or two etiological factors is very difficult. The results of the present study, higher FBG and lower MIRG might implicate the existence of a footprint of insulin/glucose derangement. The authors are not aware of the magnitude of its effect based on the data of the present study. The Body mass index and muscle mass were not measured in this study, nonetheless, a lower BF% might implicate a higher body muscle mass in OCD affected horses. While insulin resistance does occur in human individuals and horses with lower BF%, horses with higher muscle mass may show greater potential for exercise, which in turn, exerts greater physical pressure on cartilages. An underlying hormonal predisposition could make these horses more prone to OCD, originally triggered by mechanical pressures. Based on the present results incriminating other hormones than insulin, e.g. cortisol or thyroid hormones (especially, in the absence of a TSH assay in horses) needs further convincing evidence. A prospective longitudinal study with the inclusion of body muscle mass and body mass index warrants spotting further light on the dynamics of relevant etiological factors that are incriminated in the pathogenesis of OCD with larger sample size.

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Conflict of interest

We declare that there is no conflict of interest.

References

1. Burns TA, Geor RJ, Mudge MC, et al. Proinflammatory cytokine and chemokine gene expression profiles in subcutaneous and visceral adipose tissue depots of insulin-resistant and insulin-sensitive light breed horses. J Vet Intern Med 2010;24(4): 932-939.

2. Russell J, Matika O, Russell T, et al. Heritability and prevalence of selected osteochondrosis lesions in yearling Thoroughbred horses. Equine Vet J 2017;49(3): 282-287.

3. Pagan JD, Nash D. Managing growth to produce a sound, athletic horse. In: Pagan JD (Ed). Advances in equine nutrition. 4th ed. Leicestershire, UK: Context products Ltd. 2009; 247-258.
4. Ytrehus B, Carlson CS, Ekman S. Etiology and pathogenesis of osteochondrosis. Vet Pathol 2007; 44(4): 429-448.
5. Şirin Ö, Alkan Z. Developmental orthopaedic diseases in foals. Kafkas Univ Vet Fak Derg 2010; 16(5): 887-892.
6. Birkeland R, Haakenstad LH. Intracapsular bony fragments of the distal tibia of the horse. J Am Vet Med Assoc 1968; 152(10): 1526-1529.
7. Jeffcott LB. Osteochondrosis-An international problem for horse industry. J Equine Vet Sci 1996; 16(1): 32-37.
8. Mohammed HO. Factors associated with the risk of developing osteochondrosis in horses: a case-control study. Prev Vet Med 1990; 10(1-2): 63-71.
9. van Weeren R. Fifty years of osteochondrosis. Equine Vet J 2018; 50(5): 554-555.
10. Grøndahl AM, Dolvik NL. Heritability estimations of osteochondrosis in the tibiotarsal joint and of bony fragments in the palmar/plantar portion of the metacarpo-and metatarsophalangeal joints of horses. J Am Vet Med Assoc 1993; 203(1): 101-104.
11. van Weeren PR, Barneveld A. Introduction: Study design to evaluate the influence of exercise on the development of the musculoskeletal system of foals up to age 11 months. Equine Vet J 1999; 31(S31): 4-8.
12. de Koning DB, van Grevenhof EM, Laurensen BFA, et al. The influence of dietary restriction before and after 10 weeks of age on osteochondrosis in growing gilts. J Anim Sci 2013; 91(11): 5167-5176.
13. McIlwraith CW. Incidence of developmental joint problems. In proceedings: AQHA Developmental orthopedic disease symposium. Amarillo, USA: 1986; 15-20.
14. Ralston SL. Hyperglycemia/hyperinsulinemia after feeding a meal of grain to young horses with osteochondrosis dissecans lesions. Pferdeheilkunde 1996; 12(3): 320-322.
15. Donabhéidh M, Fleurance G, Perona G, et al. Effect of fast vs. moderate growth rate related to nutrient intake on developmental orthopedic disease in the horse. Anim Res 2006; 55: 471-486.
16. Naccache F, Metzger J, Distl O. Genetic risk factors for osteochondrosis in various horse breeds. Equine Vet J 2018; 50(5): 556-563.
17. van Weeren PR. Equine osteochondrosis: a challenging enigma. Pferdeheilkunde. 2005; 21(4): 285-292.
18. Jeffcott LB. Osteochondrosis in the horse--searching for the key to pathogenesis. Equine Vet J. 1991; 23(5): 331-338.
19. McIlwraith CW. Update on bone disease: The impact of skeletal disease on athletic performance. In: Pagan JD (Ed.). Advances in Equine Nutrition. 4th ed. Nottingham, UK: Nottingham University Press. 2009; 101-121.
20. Semevolos SA, Nixon AJ. Osteochondrosis: Etiologic factors. Compendium: Equine edition. 2007; 2(3): 158-164.
21. Kohnke J. Feeding and nutrition: The making of a champion. 1st ed. Sydney, Australia: Birubi Pacific; 1992;163-166.
22. Henneke DR, Potter GD, Kreider JL, et al. Relationship between condition score, physical measurements and body fat percentage in mares. Equine Vet J. 1983;15(4): 371-372.
23. Lindesell CE, Hilbert BJ, McGill CA. A retrospective clinical study of osteochondrosis dissecans in 21 horses. Aust Vet J. 1983; 60(10): 291-293.
24. Westervelt RG, Stouffer JR, Hintz HF, et al. Estimating fatness in horses and ponies. J Anim Sci. 1976; 43(4): 781-785.
25. Treiber KH, Kronfeld DS, Hess TM, et al. Use of proxies and reference quintiles obtained from minimal model analysis for determination of insulin sensitivity and pancreatic beta-cell responsiveness in horses. Am J Vet Res 2005; 116(12): 2114-2121.
26. Duthie RB, Houghton GR. Constitutional aspects of the osteochondroses. Clin Orthop Relat Res 1981; 158: 19-27.
27. Kronfeld DS, Treiber KH, Geor RJ. Comparison of nonspecific indications and quantitative methods for the assessment of insulin resistance in horses and ponies. J Am Vet Med Assoc 2005; 226(5): 712-719.
28. Vugiu P, Saenger P, Dimartino-Nardi F. Fasting glucose insulin ratio: a useful measure of insulin resistance in girls with premature adrenarche. J Clin Endocrinol Metab 2001(86): 4618-4621.
29. Quon MJ. Limitations of the fasting glucose to insulin ratio as an index of insulin sensitivity. J Clin Endocrinol Metab 2001; 86(10): 4615-4617.
30. Ferrannini E, Mari A. How to measure insulin sensitivity. J Hypertens 1998; 16(7): 895-906.
31. Robles M, Nouveau E, Gautier C, et al. Maternal obesity increases insulin resistance, low-grade inflammation and osteochondrosis lesions in foals and yearlings until 18 months of age. PLoS One 2018; 13(1): e0190309. doi:10.1371/journal.pone.0190309.
32. Yang YK, Chen M, Clements RH, et al. Human mesenteric adipose tissue plays unique role versus subcutaneous and omental fat in obesity related diabetes. Cell Physiol Biochem 2008; 22(5-6): 531-538.
33. Grundy SM. Metabolic syndrome pandemic. Arterioscler Thromb Vasc Biol 2008; 28(4): 629-636.
34. Frank N, Elliott SB, Brandt LE, et al. Physical characteristics, blood hormone concentrations, and plasma lipid concentrations in obese horses with insulin resistance. J Am Vet Med Assoc 2006; 228(9): 1383-1390.
35. Freestone JF, Wolfeheimer KJ, Ford RB, et al. Triglyceride, insulin, and cortisol responses of ponies to fasting and dexamethasone administration. J Vet Intern Med 1991;5(1): 15-22.
36. Dunn FL. Hyperlipidemia and diabetes. Med Clin North Am 1982; 66(6): 1347-1360.
37. Eigenmann JE, Peterson ME. Diabetes mellitus associated with other endocrine disorders. Vet Clin North Am Small Anim Pract 1984; 14(4): 837–858.

38. Treiber K, Hess TM, Kronfeld DS, et al. Insulin resistance and compensation in laminitis-predisposed ponies characterized by the minimal model. Pferdeheilkunde 2007; 23(3):237-240.

39. Treiber KH, Kronfeld DS, Hess TM, et al. Evaluation of genetic and metabolic predispositions and nutritional risk factors for pasture-associated laminitis in ponies. J Am Vet Med Assoc. 2006; 228(10):1538-1545.

40. Frank N, Geor RJ, Bailey SR, et al. Equine metabolic syndrome. J Vet Intern Med 2010; 24(3): 467-475.

41. Frank N, Sojka JE, Patterson BW, et al. Effect of hypothyroidism on kinetics of metabolism of very-low-density lipoprotein in mares. Am J Vet Res 2003; 64(8): 1052-1058.

42. Breuhaus BA. Serum thyroid hormone and thyrotropin concentrations in adult horses as they age. J Equine Vet Sci 2018; 68:21-25.