ORIGINAL ARTICLE

Veterinary Research Forum. 2021; 12 (3) 325 - 331
doi: 10.30466/vrf.2020.104046.2495
Journal Homepage: vrf.iranjournals.ir

Veterinary Research Forum

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

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Article Info

Article history:

Received: 10 March 2019
Accepted: 24 February 2020
Available online: 15 September 2021

Keywords:

Cortisol
Horse
Insulin-proxies
Osteochondrosis dissecans

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 uric 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 (RISQI)] 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 footmark 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 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.

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.[1,2] The condition is regarded as part of the syndrome of developmental orthopedic disease (DOD), which includes physitis, angular limb deformities, and OCD.[3] 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.[4] Clinically the condition is manifested by detachment of cartilage from underneath bone.[5]

Historically, it was introduced into the veterinary literature by the phrase "intracapsular bony fragments of the distal tibia of the horse".[6] 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.[7] 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.[2,8]

The condition was reported to be heritable estimated to vary in a range of 0.00 to 0.52.[2,9,10] The link between OCD and growth rate had been established in species such as pigs and poultry.[11] Gilts receiving an *ad libitum* diet had higher odds of suffering from OCD than gilts treated by a restricted feeding.[12] 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

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of the horses.[8,13] Rapid growth rate caused by high energy intake, especially in the form of easily digestible carbohydrates, has been related to OCD.[14] It is thought that hormonal imbalance mediated by high plane of nutrition starts the cascade terminated into the development of OCD.[15] More recently, it has been reported that genetic effects significantly contribute to the development of OC via a polygenic and highly complex genetic basis.[16]

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.[14] 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.[4,17-20]

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 hr 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 ethics 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).[21,22]

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 6th 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 hr. 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. 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.[23]

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*.[24] 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 measure 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 to12 hr 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 (Immulite 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:

$$RISQI = 1/\sqrt{insulin} = insulin^{-0.5}$$

$$MIRG = [800 - 0.30 \times (insulin - 50)^2]/(glucose - 30)$$

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 inter-quartile 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, BF%, 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), BF%, BCS, waist circumference and weight in osteochondrosis dissecans (OCD) and control horses.

Parameters		Mean	Median	IQR	SD	SE	CI	*p*-value
Glucose (mg dL^{-1})	**OCD**	121.60	121.00	35.50	21.60	4.96	12.96-45.91†	S**
	Control	92.12	91.00	14.00	9.21	3.27		
Cholesterol (mg dL^{-1})	**OCD**	86.68	87.00	27.00	19.44	4.46	–14.60-15.72†	NS
	Control	86.12	85.00	26.50	15.84	5.60		
Albumin (g dL^{-1})	**OCD**	4.42	4.40	0.80	0.42	0.09	–0.17-0.39†	NS
	Control	4.31	4.25	0.45	0.27	0.09		
HDL (mg dL^{-1})	**OCD**	35.89	36.00	6.50	5.60	1.28	–4.50-4.54†	NS
	Control	35.87	35.50	9.25	4.79	1.69		
LDL (mg dL^{-1})	**OCD**	16.94	17.00	3.50	3.73	0.85	–6.68-0.32†	NS
	Control	20.12	20.00	8.25	4.73	1.67		
Uric acid (mg dL^{-1})	**OCD**	0.67	0.60	0.15	0.14	0.03	–0.17-0.09‡α	NS
	Control	0.73	0.80	0.28	0.15	0.05		
Triglyceride (mg dL^{-1})	**OCD**	20.35	19.00	7.50	5.84	1.41	–25.27-–9.61‡α	S**
	Control	37.50	37.50	20.25	14.48	5.11		
Insulin (µI mL^{-1})	**OCD**	4.90	1.50	6.95	5.89	1.43	–1.44-5.44α	NS
	Control	2.59	1.60	0.60	2.95	1.04		
Cortisol (µg dL^{-1})	**OCD**	5.20	5.60	3.65	2.59	0.63	–3.21-3.920†	NS
	Control	4.58	3.35	1.88	4.13	1.46		
T3 (ngdL^{-1})	**OCD**	157.5	125.00	119.00	94.60	22.96	–56.08-88.46 α	NS
	Control	134.90	151.50	103.75	53.70	18.22		
T4 (µg dL^{-1})	**OCD**	4.31	4.60	2.40	1.28	0.29	–1.20-2.01†	NS
	Control	3.91	3.90	1.45	1.86	0.65		
RISQI[1]	**OCD**	0.67	0.81	0.58	0.29	0.07	–0.30-0.16 α	NS
	Control	0.76	0.79	0.16	0.20	0.07		
MIRG[2]	**OCD**	7.30	6.76	4.18	2.70	4.18	–5.76-–1.70†	S**
	Control	11.13	11.38	3.86	2.10	3.86		
Fat (%)	**OCD**	33.00	31.53	1.43	2.96	0.79	–12.96-2.24α	S*
	Control	38.36	37.13	7.21	9.03	3.19		
BCS	**OCD**	5.79	6.00	1.00	0.71	0.16	–1.58-0.43α	S***
	Control	6.80	7.00	0.00	0.44	0.20		
Weight (kg)	**OCD**	439.90	445.00	92.25	50.17	12.10	–10.58-180.40†	NS
	Control	335.00	355.00	92.25	14.84	10.50		
Waist (cm)	**OCD**	182.00	182.00	11.00	8.73	2.000	–26.82-10.07†	NS
	Control	190.40	210.50	69.25	37.60	13.30		

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)^2] × (glucose – 30)$^{-1}$, unit: ($mU_{insulin}^2 \times [10Log\ mg_{glucose}]^{-1}$).

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.

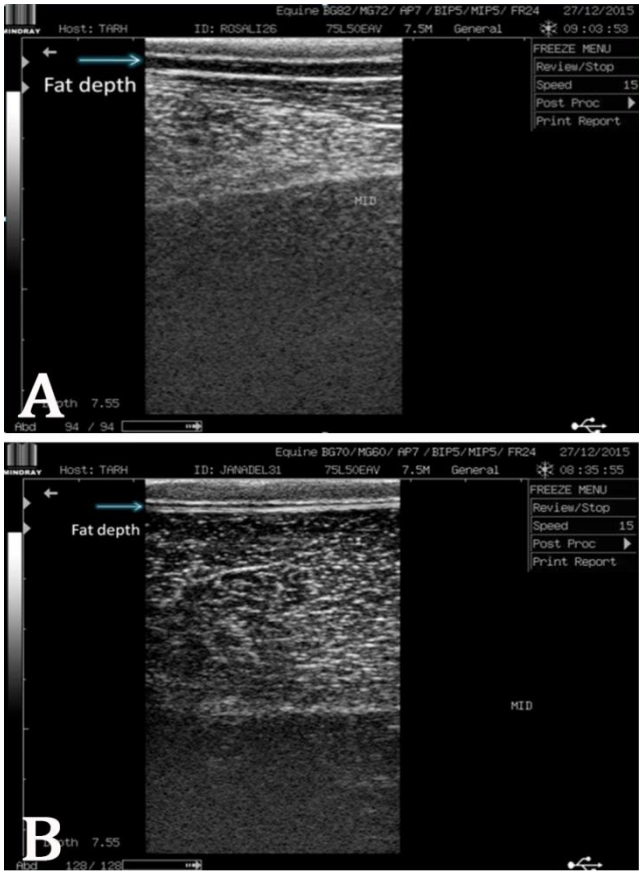

Fig. 1. Subcutaneous fat depths in **A)** control and **B)** OCD groups.

Discussion

The OCD is often caused by normal stress on abnormally developing bone.[26] 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.[27] 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[28], however, the results may be potentially flawed.[29] More recently, proxies were developed due to the technical and financial problems with specific quantitative methods to measure insulin sensitivity/resistance.[27,30] 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.[25]

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.[31] 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) anddifferent 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

Table 2. Data representing T4 in osteochondrosis dissecans (OCD) and control horses as mean ± SD, subdivided by age (≤ 5 and > 5 years old), when the effect of age as a covariate was significant ($p = 0.005$).

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

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.[25] 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.[1,32] 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.[33]

Frank *et al.*, reported numerically but not significantly higher plasma TGs in obese horses with IR than non-obese horses.[34] 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.[35] 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, hyper-triglyceridemia in IR is concomitant with cortisol derangement in several species.[36,37] 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.[38,39] 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,[40] 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.[41] However, lack of a thyroid-stimulating hormone (TSH) assay in horses precludes further interpretation just based on T3 and T4.[42]

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 footmark 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.

Acknowledgments

This research was financially supported by the administration of the Dean for Research of Ferdowsi University of Mashhad, Mashhad, Iran (Project code 3/3374, 06-Jan-2015).

Conflict of interest

We declare that there is no conflict of interest.

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