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Insulin dysregulation in horses with induced obesity[1]

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ABSTRACT.- Ribeiro R.M., Ribeiro D.S.F., Paz C.F.R., Gobesso A.A.O. & Faleiros R.R. 2020. **Insulin dysregulation in horses with induced obesity**. *Pesquisa Veterinária Brasileira 40(1):39-45*. Graduate Program in Animal Science, Escola de Veterinária, Universidade Federal de Minas Gerais, Campus Pampulha, Av. Antônio Carlos 6627, Cx. Postal 567, Belo Horizonte, MG 31270-901, Brazil. E-mail: faleirosufmg@gmail.com

Insulin deregulation (ID) is a central player in the pathophysiology of equine metabolic syndrome (EMS), which is associated with generalized and/or regional obesity. The objective of this experiment was to characterize the alterations in the hormonal profile in horses exposed to a hypercaloric diet. A total of nine Mangalarga Marchador adult horses with initial body condition score (BCS) of 2.9±1/9 (mean±SD) were submitted to a high calorie grain-rich diet for 5 months. The data was collected before the start of the experiment and every 15 days until the end of the experiment and glucose and insulin concentrations were measured in the plasma. Proxies G:I, RISQI, HOMA-IR and MIRG were calculated. The low-dose oral glucose tolerance test (OGTT) was performed and the total area under the glucose (GTA) and insulin (ITA) curves at three different timepoints (before inducing obesity, after 90 days and after 150 days) was used. Analysis of variance of the results was performed considering the time effects and the means were compared with repeated measures by the Tukey's test (P≤0.05). The ID was observed during the first 90 days of the experiment and was characterized as a decompensated ID, showing an increase of basal glucose and insulin plasma levels, changes in all proxies and a significant increase in GTA (P<0.001) and ITA (P<0.05). However, a clear compensation of the ID was evident after 150 days of experiment, which was supported by data from the insulin secretory response of β cells of the pancreas that showed an increase in insulin plasma levels, after fasting or exposure to gastric glucose, with a concomitant decrease in fasting glucose and fructosamine levels, and a decrease of GTA and marked increase of ITA (P<0.0001) in the dynamic test. These findings confirm the occurrence of hyperinsulinemia associated with insulin deregulation in Mangalarga Marchador horses exposed to hypercaloric diets.

INDEX TERMS: Insulin dysregulation, horses, obesity induction induced metabolic syndrome, insulin resistance, overweight, Mangalarga Marchador horses.

RESUMO.- [**Desregulação da insulina em equinos com obesidade induzida.**] A desregulação insulínica (DI) é o ponto central dos mecanismos fisiopatológicos da síndrome metabólica equina (SME), que é associada à obesidade generalizada e/ou regional. O objetivo deste experimento foi caracterizar as alterações no perfil hormonal em equinos submetidos à dieta hipercalórica. Foram utilizados nove equinos Mangalarga Marchador adultos com escore corporal (EC) médio (±DP) inicial de 2,9±1 (escala de 1-9) submetidos à dieta hipercalórica atingindo um EC de 8,3±1 após cinco meses. Os dados foram coletados antes do início do experimento e com o intervalo de 15 dias até o final do experimento, os valores plasmáticos foram obtidos para mensuração das concentrações de glicose e insulina. Foram calculados os proxies G:I, RISQI, HOMA-IR e o MIRG. Foi realizado o teste de baixa dose de glicose oral (TBDGO) utilizando a área total sob a curva de glicose (ATG) e insulina (ATI) em três momentos, antes da

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indução a obesidade, após 90 e 150 dias. Os resultados foram submetidos à análise de variância considerando-se os efeitos de tempo e as médias comparadas com medidas repetidas pelo teste de Tukey, com o valor P≤0,05. A DI foi observada nos primeiros 90 dias de experimento, se caracterizando como um quadro de DI descompensada, apresentando um aumento dos níveis plasmáticos basais de glicose e insulina, pelas alterações em todos os proxies e com um aumento significativo da ATG (P<0,001) e ATI (P<0,05). Contudo, ficou evidente uma compensação do quadro de DI após 150 dias de experimento, sendo demonstrado pelos dados da resposta secretória insulínica das células β do pâncreas, que se manifestaram pelo aumento dos níveis plasmáticos de insulina pós-jejum ou exposição à glicose gástrica com concomitante redução nos níveis de glicose e frutosamina pós-jejum e pela redução da ATG e pela marcada elevação de ATI (P<0,0001) no teste dinâmico. Tais achados comprovam a ocorrência de hiperinsulinemia associada à desregulação insulínica em equinos Mangalarga Marchador expostos a dietas à dieta hipercalórica.

TERMOS DE INDEXAÇÃO: Desregulação insulínica, equinos, obesidade, síndrome metabólica induzida, indução da obesidade, cavalos, resistência à insulina, sobrepeso, insulina, Mangalarga Marchador.

INTRODUCTION

Equine obesity has become a challenge for equine veterinarians and can be observed in up to 40% of equine populations (Wyse et al. 2008, Thatcher et al. 2012). Obesity induction occurs due to the supply of diets rich in grains and forages (grass and hay) with high levels of non-structural carbohydrates and is a consequence of excess feed supply, which exceeds the metabolic requirements for the horses' physical activity (Schott et al. 2001, Johnson 2002).

Among the main alterations related to obesity in horses are exercise intolerance, thermoregulatory inefficiency, abnormal reproductive performance and increased probability of developing mesenteric lipomas (Henneke et al. 1983, Cymbaluk & Christison 1990, Garlinghouse & Burrill 1999, Garcia-Seco et al. 2005). In addition to these alterations, the obese equines remain in a persistent chronic inflammatory state, which can occur due to maximum storage of lipids by the adipocytes of overweight animals, leading to changes in energy efficiency, inflammatory processes and cellular stress (Goossens 2008).

Several studies show that regional fat accumulation closely correlates with insulin dysregulation (ID), hyperinsulinemia, dyslipidemia, elevated leptin levels, elevated non-esterified fatty acids, gene expression of proinflammatory cytokines, increased protein concentration in the peripheral blood and increased risk of developing laminitis (Johnson 2002, Sutherland et al. 2004, Vick et al. 2007, 2008, Carter et al. 2009).

ID is a central mechanism in the pathophysiology of equine metabolic syndrome (EMS) and most of the affected horses and ponies will show generalized or regional obesity. However, not all horses with EMS are obese and not all obese animals develop ID (Treiber et al. 2006).

There are two theories to explain the correlation between obesity and ID. The first theory is based on the decrease in insulin signaling caused by the action of adipokines and cytokines produced by the adipose tissue and the second is based on the intracellular accumulation of lipids in insulin sensitive tissues. This situation can occur after the supply of a diet rich in glucose, which is converted to fat through lipogenesis. The increased circulating fat concentration will be stored in the intracellular region of non-adipose tissues, such as the skeletal muscle, liver and pancreas, which occurs when the storage capacity of the adipose tissue is exceeded, leading to accumulation of lipids within these cells and causing changes in normal functions, such as impairment of insulin receptor signaling (Summers 2006).

With the hypothesis that the induction of obesity in horses can promote metabolic changes and lead to the development of insulin resistance (IR), the objective of this study was to examine the physiological alterations that can trigger the development of ID caused by obesity in horses to better understand the pathophysiology and provide an early diagnosis of IR.

MATERIALS AND METHODS

This study was approved by the Ethics Committee on Animal Experimentation (CETEA) of the "Universidade Federal de Minas Gerais" (UFMG), protocol number 49/2014. In total, nine Mangalarga Marchador healthy horses were used (5 non-pregnant females and 4 castrated males) with mean age (±SD) of 48±5 months and initial weight of 316±62.68kg. To standardize the supply of the diet, the horses were housed in properly identified individual stalls, with the floor covered with sawdust and access to water ad libitum. The experiment was carried out at Pedro Leopoldo Model Farm of the UFMG.

Obesity was induced by supplying digestible energy (DE) in quantities 100% higher than the maintenance requirement value established by the reference literature (NRC 2007). The maintenance DE (DEm) was calculated based on the mathematical formula DE=1.4 + (0.03 x kg live weight [l.w.]), as demonstrated by the NRC (2007) over a period of 150 days.

To avoid gastrointestinal disorders, it was previously established that the animals would receive the DEm once as concentrate and once as forage. For this, the following digestible energy values for the provided food were used: commercial concentrate (Guabi Equitage Laminados) (DE = 3.650Mcal/kg) and grass hay *Cynodon dactylon* (L.) Pers.Var. "Coast cross" (DE = 2.0Mcal/kg). Thus, the amounts of hay and feed were calculated by considering the DEm of each animal divided by the digestible energy concentration of each type of feed: Amount of concentrate (kg): DE = (1.4 + (0.03 x kg of l.w.))/3.650; Amount of coast cross (kg): DE = (1.4 + (0.03 x kg of l.w.))/2.

This calculation was repeated every fifteen days, after measuring the weight of the animals, to maintain the 100% increase regarding the DE requirement established by the NRC (2007) during the 150 days of the experimental period. The diet was provided in individual feeders, in 3 (three) daily meals, distributed in equal parts ad supplied at 6 a.m., 12 a.m. and 6 p.m. (Table 1).

Before inducing obesity and fortnightly until the end of the experiment, the weight of the animals (W) was determined, the animals were examined for claudication and the hoof sensitivity was performed before inducing obesity and every 30 days until the end of the experiment.

To analyze basal insulin and glucose, venous blood samples were collected through venipuncture of the left external jugular vein using a vacuum collection system (vacutainer), placed in vials without anticoagulants and with sodium heparin, respectively, and immediately centrifuged and stored at -18ºC. Samples were

collected between 7 and 9 a.m., with the first sample collected before inducing obesity (which was called basal) and samples collected throughout the experimental period (which were called based on the time - 15, 30, 45, 60, 75, 90, 105, 120, 135 and 150). Samples were collected after a fasting period of 12 hours to determine basal glucose values for all samples collected every 15 days and basal insulin levels were analyzed in samples collected every 30 days until completing the 150 days of the experiment.

The assays were performed using a spectrophotometric identification system in an automated biochemical analyzer (Cobas Mirage-Roche Diagnostic System®) using specific commercial kits (Labtest®). The GOD-Trinder methodology was used to determine plasma glucose levels (ref. 133) (Lindåse et al. 2016). Serum insulin was determined by a radioimmunoassay (RIA) technique (Milipore's Porcine Insulin RIA), performed in a commercial laboratory. Tinworth et al. (2011) observed that Porcine Insulin RIA is the most accurate assay for measuring equine insulin concentrations.

To determine if the animals used in this experiment presented insulin dysregulation, the values of the proxies were calculated and the low-dose oral glucose tolerance test (OGTT) was performed.

The proxies used in this experiment were based on the glucose and insulin basal values and included the ratio of glucose to insulin (G:I), insulin sensitivity (RISQI), insulin secretory response by pancreatic β cells (MIRG) and the homeostasis evaluation model (HOMA-IR), following the methodology by Treiber et al. (2005), with the respective formulas described below:

$$G:I = \text{glucose/insulin}$$
$$RISQI = 1/\sqrt{\text{insulin}} = \text{insulin} - 0.5$$
$$MIRG = (800 - 0.3\ [\text{insulin} - 50]\ 2)/(\text{glucose} - 30)]$$
$$HOMA\text{-}IR = \text{glucose (mg/dL)} \times 0.0555 \times \text{insulin (µU/mL)}/22.5$$

As normality parameters, a G:I>10, compensatory IR for values between 4.5 and 10 and severe IR for values <4.5 were considered (Treiber et al. 2005, 2006). Regarding RISQI, it was considered normal for values >0.32, IR for values between 0.22 and 0.32, and severe IR for values <0.22. For MIRG, it was considered normal if <5.6 and, for HOMA-IR, IR was considered for values >2.71 (Geloneze & Tambascia 2006).

The low-dose oral glucose tolerance test (OGTT) was performed before supplying the experimental diet (basal), and 90 and 150 days after such diet supple. After a 12-hour fasting period, glucose (0.25g/kg) was administered through a nasogastric tube. Blood samples were collected at the following timepoints: basal and 30, 60, 90, 120, 150 and 180min after administrating dextrose. Blood samples were used to measure glucose and insulin plasma levels.

To interpret the results, it was considered that healthy animals show a glucose peak of 90 to 120mg/dL between the samples collected at 60 and 90min, and insulin should be below 20µIU/mL after the samples collected at 60 and 90min (Ralston 2002). The total area (TA) under the curve was also calculated, defined as the areas under the glucose and insulin curves, until the x axis. These were obtained by calculating the integral of the curve and expressed in mg/dL/min, derived from the glucose (GTA) and insulin (ITA) values obtained in the OGTT (Correa et al. 2007).

The Sigma (Sigma Stat, Systat) software was used for the statistical analysis; the data with a normal distribution was analyzed by analysis of variance in randomized blocks with measures repeated by the time, followed by the Tukey's test to compare the means. For all tests, a significance level of P≤0.05 was considered.

Table 1. Bromatological composition of the concentrate (Guabi Equitage Laminados®) and hay (*Cynodon dactylon* (L.) Pers.Var. "Coast cross") and their respective ingredients used during the experimental period

Ingredients	Concentrate	Hay
Energy		
DE (Mcal/kg)	3.50	2.0
Nutrients (%)		
DM	87	89.4
MM	10	5.48
CP	12	17
NDF	10	56.8
Corn flour	27	1.5
EE	9	1.43
Ca	1,6	0.48
P	0.5	0.35
Energetic ingredients (%)		
Corn	19	-
Oats	12	-
Oil	5	-

DM = Dry matter, MM = mineral matter, CP = crude protein, NDF = neutral detergent fiber, EE = ethereal extract, Ca = calcium, P = phosphorus; data provided by suppliers.

RESULTS

During the experimental period, the horses consumed a daily mean of 0.94% (±0.02) of concentrate and 1.72% (±0.04) of coast cross in relation to their live weight. There were no cramps, evidence of claudication or signs of hoof sensitivity.

At the end of the experimental period, the animals showed a mean weight gain corresponding to 27.45% of the original, with significant values (P<0.001) (Table 2).

There were significant alterations in plasma glucose concentrations only in samples collected after 45 days of the experiment (P<0.0001). Regarding basal plasma insulin concentrations, there was an increase of up to 156.67% in the first 30 days of the experiment (P>0.05) and the concentration remained higher than the basal level until the end of the experiment (Table 3).

Among the proxies, G:I and RISQI showed a similar trend, with a significant reduction in relation to the basal values already in the first samples collected after supplying the hypercaloric

Table 2. Mean and standard deviation of weight of Mangalarga Marchador horses subjected to obesity induction

Time (days)	Weight (Kg)	
	Mean	SD
Basal	316	62.68
15	348.44**	69.6
30	348.55**	71.18
45	356.22**	66.2
60	356.22**	66.2
75	375.55**	66.4
90	386**	65.15
105	390.22**	61.88
120	394.55**	63.56
135	400.77**	58.77
150	402.77**	58.31

Tukey's test, significant P value ≤0.05: * P<0.05, ** P<0.001, *** P<0.0001

diet (P<0.0001), which was maintained until the end of the experiment. However, the MIRG showed significant increases after 75 and 105 days of experiment (P<0.05), it was not significant for samples collected after 135 days of experiment (P=0.18) and was again significant for samples collected after 150 days of experiment (P<0.0001). The HOMA-IR showed significant increases for sample collected at 45 (P<0.05), 75 (P<0.001), 105 (P<0.001), 135 (P<0.001) and 150 (P<0.05), with a decreased value at the last collection (Table 4).

Insulin results obtained for the dynamic OGTT test are shown in Figure 1. The curve shows the period prior to the supply of the diet and an insulin peak from 60 to 90 minutes after glucose supply, with the respective values of 16.67 and 19.36mg/dL, decreasing to 10.45mg/dL in samples collected after 180 minutes. The analysis performed at 90 days showed the two highest values for samples collected at 60 (31.12mg/dL) and 90 (33.52mg/dL) minutes and the subsequent values remained elevated until the end of the test. At the end of the experiment, there was an increase in insulin concentration levels already after 30 minutes (46.45mg/dL), with a peak at 60 minutes (50.17mg/dL), and the values remained elevated until the collection performed at 120min (42.05mg/dL) (Fig.1).

Glucose results obtained for the dynamic OGTT test are shown in Figure 2. Before the diet supply, the two highest values are observed after 60 (135.5mg/dL) and 90 (131.5mg/dL) minutes, with a decrease to 123.0mg/dL for samples collected after 120 minutes. At 90 days, a high basal value of 105.94mg/dL was observed in relation to the others, with a peak after 90 minutes (172.62mg/dL) and a decrease after 150 minutes (128.86mg/dL). At the end of the experiment, the basal value was 65.82mg/dL, with the peak after 60 minutes (149.12mg/dL) and starting to decrease after 120 minutes, reaching its lowest value after 180 minutes (69.05mg/dL).

The results of the areas under the insulin and glucose curve are shown in Table 5. For insulin, there was a significant increase already after 90 days (P<0.05), which was maintained until the 150 days of experiment (P<0.001). Regarding glucose, there was an increase after 90 days (P<0.001) and a value that was considered a trend after 150 days of experiment (0.06).

Table 3. Mean and standard deviation of glucose and insulin plasma values in Mangalarga Marchador horses subjected to obesity induction and their respective reference values

Time (days)	Glucose (mg/dL)		Insulin (µU/mL)	
	Mean	SD	Mean	SD
Basal	102.37	18.92	5.87	3.4
15	88.01	14.74	-	-
30	130.24	22.44	15.02*	2.84
45	147.54***	34.07	14.42	7.49
60	102.04	21.34	-	-
75	120.07	25.01	20.03**	6.28
90	100.2	18.85	-	-
105	109.23	20.4	18.69**	7.44
120	126.36	16.83	-	-
135	115.43	11.43	18.61**	5.52
150	73.65	13.91	16.74*	11.64
Reference values	70 - 135[a]	8.5	<20[b]	-

Tukey's test, significant P value ≤0.05: * P<0.05, ** P<0.001, *** P<0.0001; [a] Kaneko et al. (1997), [b] Hassel et al. (2009).

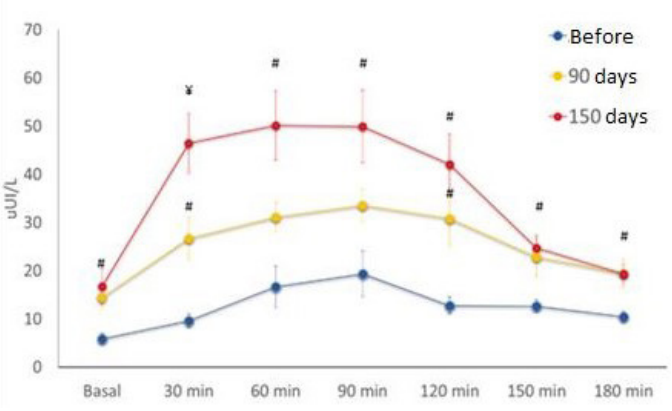

Fig.1. Means and standard errors of insulin plasma concentrations after gastric glucose administration (0.25g/kg) in Mangalarga Marchador horses before and 90 and 150 days after obesity induction. Significant values in relation to the results of the previous time point (#), significant values in relation to the results of the previous time point and 90 days (¥).

Table 4. Mean and standard deviations of the proxies plasma values of Mangalarga Marchador horses subjected to obesity induction

Time (days)	G:I (mg/dL/µU/mL)		RISQI ($\mu U/mL^{-0,5}$)		MIRG ($\mu U_{ins}^{2}/[10.L.mg_{gli}]$)		HOMA-IR	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Basal	22.87	11.5	0.46	0.13	3.07	1.4	1.5	0.92
30	8.93***	2.32	0.26***	0.03	4.44	0.92	4.85*	1.29
45	12.1***	4.69	0.29***	0.07	3.53	1.2	5.51*	3.66
75	6.29***	1.4	0.23***	0.03	6.04*	1.59	6.02**	2.36
105	6.37***	1.68	0.24***	0.05	6.28**	1.21	5.28*	2.95
135	7.27***	2.26	0.24***	0.03	5.28	1.27	5.79*	1.83
150	6***	2.69	0.28***	0.07	10.07***	3.85	3.24	2.76

Tukey's test, significant P value ≤0.05: * P<0.05, ** P<0.001, *** P<0.0001; G:I = ratio between glucose and insulin, RISQI = insulin sensitivity, MIRG = secretory insulin response, HOMA-IR = homeostatic evaluation model.

Table 5. Mean and standard deviation of the areas under the curve regarding insulin and glucose plasma concentrations after gastric glucose administration (0.25g/kg) in Mangalarga Marchador horses before and 90 and 150 days after obesity induction

	Before		90 (days)		150 (days)	
	Mean (µUI or mg/dL/min)	SD	Mean (µUI or mg/dL/min)	SD	Mean (µUI or mg/dL/min)	SD
Insulin	27545.9	10509.93	56327.64*	24164.73	78569.93**	29015.53
Glucose	25990.22	32361.21	32042.15**	38933.51	22787.52	30514.51

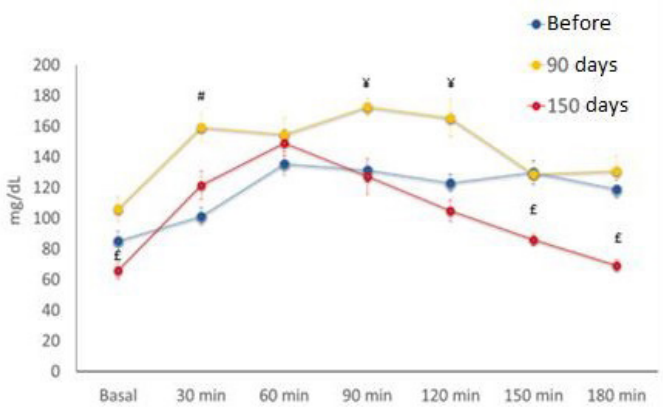

Fig.2. Means and standard errors of glucose plasma concentrations after gastric glucose administration (0.25g/kg) in Mangalarga Marchador horses before (control) and 90 and 150 days after obesity induction. Significant values in relation to the results of the previous time point (#), significant values in relation to the results of the previous time point and 90 days (¥), significant values in relation to the values of the time points 150 and 90 days (£).

DISCUSSION

The mean basal glycemia of the animals used in this experiment showed an increase of up to 27.22% in the first 30 days of the experimental period, with a significant peak after 45 days, demonstrating a metabolic impairment in these animals and a possible insulin resistance that was still decompensated up to this point. However, after this period, the values returned to basal values. Such subtle changes in basal glucose values has been observed in other studies with obese equines and can be due to the compensatory production of insulin to counteract insulin resistance in the tissues (Waller et al. 2011, Morgan et al. 2015).

On the other hand, basal insulin plasma values showed a significant increase in the first 30 days of the experiment, but in a more consistent and lasting manner after 75 days. This finding is in agreement with the glycemia results. In the first 75 days, increases in blood insulin concentrations are more discrete and insufficient to prevent glycemia from rising above the normal range, accounting for a decompensated insulin resistance condition. However, from this time point onwards, insulinemia reached its peak and kept its values above 16µU/mL, which were able to maintain glycemia within the reference range (Waller et al. 2011).

This increase in insulin plasma values can be interpreted dysregulated insulin responses to oral glucose developed by these animals during the weight gain period, a finding confirmed by the low-dose oral glucose tolerance tests (OGTT). This was evidenced by the total area under the insulin curve, which showed a significant increase when comparing the OGTT data on days 90 and 150 with the control and could be interpreted as a sign of a decompensated insulin resistance condition in the first 90 days of the experiment. Analysis of the total area under the glucose curve showed a significant increase in glucose only on day 90. This finding shows that the animals evolved to a compensated IR condition after a three-month period, since the increased production of insulin was able to maintain the glucose values close to the control.

The values obtained with the PROXIES confirm the idea of the compensated insulin resistance condition at the end of the experimental period. The ratio of glucose to insulin (G:I) and the RISQI showed significant results from day 30 of the experiment, with P values lower than 0.0001 in both cases, revealing that the animals developed a metabolic alteration that is in agreement with an insulin resistance condition, with G:I results showing a compensatory insulin resistance condition.

The MIRG proxy accounts for the insulin secretory response of the pancreatic β cells in response to glucose, demonstrating the ability of the pancreas to respond to tissue insulin resistance and its results were significant from day 75 ($P<0.05$) and 105 ($P<0.001$), with an improvement at day 135 and a considerable worsening at day 150 ($P<0.0001$) of the experiment, thus showing that the animals presented a secretory response after 75 days of experiment.

The MIRG trend was confirmed by the HOMA-IR values, which were significant between samples collected at day 30 and day 135 ($P<0.05$) of the experiment, with the most significant value at day 75 ($P<0.001$), indicating that the animals presented IR in the initial period and evolved to a compensatory IR at the end of the experiment.

The present study is in agreement with the data obtained in Standardbred horses, which were submitted to a hypercaloric diet for 6 weeks, presenting a decrease in insulin sensitivity that was compensated by an increase in plasma insulin production (Stewart-Hunt et al. 2010). This decrease in insulin sensitivity is consistent with other studies in equines where an adaptation to a diet rich in non-structural carbohydrates has been observed, which may alter insulin signaling and change the metabolism of glucose and fatty acids (Jenkins et al. 1987, Hoffman et al. 2003, Samaha et al. 2003, Treiber et al. 2005, Pratt et al. 2006).

This is the first study that shows the development of insulin resistance in Mangalarga Marchador horses and is in agreement with international studies, confirming that fat accumulation is associated with insulin resistance, hyperinsulinemia and dyslipidemia (Johnson 2002, Sutherland et al. 2004, Vick et al. 2007, 2008, Carter et al. 2009). This association of fat accumulation with insulin deregulation can be

explained by the decreased expression of insulin receptors in insulin-dependent cells. Decreases expression of the receptors can be explained by two hypotheses: the first is that the adipokines and cytokines produced by the adipose tissue act on insulin-dependent cells and the second is based on the accumulation of lipids in insulin-sensitive tissues that are sensitive to insulin as Summers (2006) observed. In addition to this, the insulin receptor has a negative feedback in response to circulating insulin and higher plasma insulin concentration lead to a lower availability of receptors in the cell membranes (Shanik et al. 2008).

Another pathway that could interfere with GLUT-4 translocation would be the one caused by the toxic effects of plasma hyperglycemia. Glucose is influenced by glutamine to be converted into glucosamine-6-phosphat and this excess glucosamine can impair GLUT-4 translocation (Sposito et al. 2007). The impaired insulin action ultimately leads to a glucose intolerance condition, with a relative increase in glucose concentrations. However, hyperglycemia values are mild in horses with IR and this can be explained in horses as an increase in insulin production seems to compensate for its reduced action, leading to a compensated insulin resistance condition (Cosentino & Luscher 1998).

CONCLUSIONS

Exposure to the hypercaloric diet promoted weight gain and had an important impact on the metabolism of the horses studied, with an increase in blood glucose and insulin concentrations.

Insulin deregulation was already evident in the first 75 days due to an increase in plasma glucose and insulin levels, with a considerable increase in glucose levels during this period, which can be considered a decompensated insulin resistance condition. In the first 75 days, it was possible to observe the effects of this resistance on glucose metabolism, through increases in basal glucose and fructosamine concentrations. However, from that point onwards, there was a compensation of the insulin secretory response by pancreatic β-cells, which was confirmed by the increase in fasting insulin plasma levels, with a concomitant decrease in glucose levels.

These findings confirm the occurrence of hyperinsulinemia associated with insulin deregulation in Mangalarga Marchador horses exposed to a hypercaloric diet and that insulin dysfunction does not occur uniformly, and thus further studies are necessary to better understand the dynamics of this phenomenon.

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