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Revised quantitative insulin sensitivity check index: associations with the metabolic status of cows during early lactation

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ABSTRACT

The revised quantitative insulin sensitivity check index (RQUICKI) is the most commonly used indicator of insulin resistance in dairy cows. The aim of this study was to examine the characteristics of metabolic status in cows with different RQUICKI index values during early lactation. The experiment included 40 Holstein-Friesian cows in the first week of lactation. The cows were classified into four groups according to quartile (Q 1 to 4) values of RQUICKI indexes: Q1 = 0.35-0.41 (most insulin resistant), Q2 = 0.42-0.52, Q3 = 0.53-0.67, Q4 = 0.68-0.77 (most insulin sensitive). Metabolic parameters were significantly different in early lactation cows, classified according to the values of the RQUICKI index. The cows that were the most resistant to insulin (Q1) had higher levels of non-esterified fatty acid (NEFA), cortisol, somatotropic hormone (STH), beta-hydroxybutyrate (BHB), total bilirubin, aspartate aminotransferase (AST), malondialdehyde (MDA) and body condition score (BCS) in comparison to the cows that were the least resistant to insulin (Q4). The cows also had lower levels of insulin-like growth factor I (IGF-I), triiodothyronine (T3), thyroxine (T4), albumin, cholesterol, triglycerides, Ca and P as well as a tendency towards lower insulin and glucose concentrations. Metabolic parameters were strongly regressed by RQUICKI in the most insulin resistant cows (Q1) in relation to the cows in the other groups, Q2-4. The cows with a higher number of metabolic abnormalities in their metabolic profiles had lower RQUICKI values: 0.56 ± 0.045 (no abnormalities); 0.52 ± 0.041 (1 abnormality); 0.47 ± 0.042 (2 abnormalities) and 0.4 ± 0.043 (≥3 abnormalities). We concluded that the RQUICKI index could be applied in

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order to accurately identify metabolic status in cows during early lactation. However, the kinetics of insulin sensitivity should be further studied using more animals per group, as well as in other breeds of cows

Key words: cattle; insulin resistance; RQUICKI; metabolic profile; early lactation

Introduction

A negative energy balance in early lactation is characterized by "orchestrated and coordinated change in tissue metabolism" called homeorhesis. Homeorhesis involves a large number of endocrinological and metabolic adaptations. In early lactation, the concentration of somatotropic hormone and cortisol increases, and the concentration of insulin like growth factor I (IGF-I) and thyroid hormones decreases, which reflects the current nutrient availability in relation to milk production (GROSS and BRUCKMAIER, 2019; STEINHOFF et al., 2019). Adaptation in carbohydrate metabolism involves a decrease in glucose and insulin concentrations with the development of insulin resistance. Insulin resistance helps to direct glucose (energy) into the udders. Lipolysis (high non esterified fatty acids, NEFA) increase for the energy needs of other tissues, triggering the rest of the metabolic cascade (SUNDRUM, 2015; LAKIĆ et al., 2018). Excess NEFA leads to increased ketogenesis in hepatocytes (high beta hydroxy butyrate (BHB) concentration), which further leads to decreased production of albumin and cholesterol transport forms, and the accumulation of triglycerides in the liver. Lipid accumulation in the liver is characterized by an increase in total bilirubin, and the activity of transaminases in the blood. The development of oxidative stress with a high concentration of free fatty acids, leads to an increase in malondialdehyde (MDA) as a product of lipid peroxidation (ABUELO et al., 2015; HRISTOVSKA et al., 2018). In addition, blood calcium concentration decreases due to milk production and changes in the function of the parathyroid gland. A high body condition score (BCS) indicates high insulin sensitivity in dry period and, on the contrary, high insulin resistance in early lactation (DOŠENOVIĆ-MARINKOVIĆ et al., 2019).

Insulin is the main hormone that enables the restructuring of carbohydrate and fat metabolism in early lactation, and insulin resistance is one of the key parts of homeorhesis (CINCOVIĆ et al., 2018). Insulin resistance during early lactation is caused by reduced feed intake and negative energy balance (NEB). It is manifested as decreased insulin responsiveness (lower insulin production after stimulation) and/or decreased insulin sensitivity of peripheral tissues, resulting in a higher insulin : glucose ratio, and greater lipolysis and NEFA concentration in the bloodstream (DE KOSTER and OPSOMER, 2013). Measuring of insulin resistance can be carried out by direct and indirect tests, or by calculating a surrogate index. Insulin in dairy cows is the only hormone with a pronounced antilipolytic effect. Therefore, the RQUICKI (a surrogate index) is calculated based on the basal values of insulin, glucose and NEFA (HOLTENIUS and HOLTENIUS,

2007). The RQUICKI index is lower in cows with NEB and in feed restricted cows, when the NEFA concentration increases (GROSS et al., 2011; BJERRE-HARPØTH et al., 2012). The value of the RQUICKI index is highly determined by NEFA during early lactation (CINCOVIĆ et al., 2014). An increased concentration of NEFA is correlated with the following changes in the peripartum period: a higher degree of ketogenesis, reduced concentrations of cholesterol and triglycerides, fatty liver formation, oxidative stress, changes in cortisol and thyroid hormone concentrations, somatotropic hormone (STH) : IGF-I changes and a decrease in concentrations of Ca and iP (GONZALEZ et al., 2011; CINCOVIĆ et al., 2012). CINCOVIĆ et al. (2017) showed that the RQUICKI index determined many metabolic parameters in a linear relationship manner. DJOKOVIĆ et al. (2017) demonstrated that the RQUICKI-BHB index is an important control factor for correlation between the basal and dynamic values of glucose, NEFA, BHB and insulin during an intravenous glucose tolerance test in ketotic cows.

The aim of this study was to examine the characteristics of metabolic status in dairy cows with different RQUICKI index values during early lactation.

Materials and methods

Animals. The experiment was performed on 40 Holstein-Friesian cows at the beginning of the second and third lactations. No health disorders were recorded in these cows during the previous lactations, and their milk yield was more than 7000 L in the previous lactation. The cows were kept in a free stall system on deep litter. The transition period was carried out in a tied system in calving rooms. Rations were controlled and the cows were fed at 7h, 14h and 20h. The cows were provided with *ad libitum* access to fresh drinking water and a total mixed ration sufficient to meet their requirements: proteins (17.5-19.5% dry matter crude proteins, 30-33% degradable proteins, 35-40% non-degradable proteins), carbohydrates (acid detergent fiber, ADF, minimum 17-21%; neutral detergent fiber, NDF, minimum 28-31%; NDF from forages minimum 18-23%; nonstructural carbohydrates 35-42%; dry matter level from forages minimum 40-45%), net energy lactation (NEL, 7-7.4 MJ/kg dry matter of the ration) and 5-7% fat.

Sampling. Blood samples were taken in the first week after calving by puncture of the v. caudalis mediana, between 11:00 and 14:00 hours, in order to avoid a prandial effect on the metabolites. Samples were taken in heparin vacutainers and were placed in a fridge at 4 °C. The time from sampling to laboratory processing was about 3 hours.

Determination of metabolic parameters and body condition score. In order to evaluate metabolic status, concentrations of hormones, metabolic parameters and BCS were determined. The ELISA technique was used to determine the following hormones: insulin like growth factor I (IGF-I) (Cusabio, PRC), cortisol (Uscn-Life Science, PRC), somatotropic hormone (STH) (Endocrine technologies, USA), triiodothyronine

(T3) (Endocrine technologies, USA), thyroxin (T4) (Endocrine technologies, USA). A microtiter plate reader, Rayto (Rayto, Shenzhen, PRC), was used and reading was performed at the wave length 450 ± 2 nm. Further, the following metabolic profile parameters were determined: betahydroxybutirate (BHB), total proteins, urea, albumin, cholesterol, triglycerides, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), Ca, iP and malondialdehyde (MDA) using standard kits from Randox (Randox, Crumlin, UK) and Pointe scientific (Pointe scientific, Michigan, USA). The parameters of metabolic profiles in the blood samples were determined by the spectrophotometric method on an RT1904c device (Rayto, Shenzhen, PRC). Evaluation of BCS was performed at the moment of blood sampling according to Elanco Animal Health Bulletin Al 8478 (rev 9/96). Scores from 1-5 were given with a 0.25 increments.

Determination of RQUICKI index. The RQUICKI index was calculated according to the formula:

RQUICKI = 1 / [log (glucose mg/dL) + log (insulin μU/mL) + log (NEFA mmol/L)]

(HOLETENIUS and HOLTENIUS, 2007).

Statistical analysis of data and models. Upper, median and lower quartiles for the RQUICKI index were determined. Cows were divided into four quartiles (Q1-Q4; Q1 RQUICKI index below the lower quartile - most resistant to insulin; Q2 RQUICKI index between the lower and median quartiles; Q3 group RQUICKI index in a range from the median to the upper quartile. Q4 group of cows had values in the range of the upper quartile to the maximum values - most sensitive to insulin). The influence of the classification of cows on the concentrations of the selected metabolic parameters was examined. The ANOVA method and LSD test were used. Our special interest was to examine if there were differences in metabolic adaptation in the group of cows that showed the highest insulin resistance in comparison to the group that showed the least insulin resistance (Q1:Q4).

To establish if the value of metabolic parameters changed linearly with RQUICKI value, but with different intensity between groups Q1 and Q2-4, we first checked the graphical representation of the research hypothesis. Two straight lines were fitted for the piecewise regression analysis. We regressed the values of the metabolic parameters as a function of the value of the RQUICKI index in order to obtain intercepts and slopes: one for cows in Q1, and one for cows in the Q2-4 groups. Differences in slopes and intercept between the two groups were calculated using a *t*-test.

Finally, the cows were divided into four groups with 0, 1, 2 and ≥3 metabolic abnormalities, according to the cut-off values of the parameters: glucose <2.5 mmol/L, NEFA >0.6 mmol/L, BHB >1 mmol/L, AST >100 IU/L, triglycerides <0.11 mmol/L, total bilirubin >8 μmol/L, tCa <2.1 mmol/L, T3 <1 nmol/mL, T4 <30 nmol/L. We compared the RQUICKI values between the groups with different numbers of metabolic

abnormalities using the Student's *t*-test. The statistical software Statgraphics Centurion (Statpoint Technologies Inc. Warrenton, USA) and Excel (Microsoft, USA) were used for statistical analysis.

Results

The average values for insulin, glucose and NEFA were: 5.91 ± 1.73 μU/mL, 3.16 ± 0.84 mmol/L 0.51 ± 0.12 mmol/L, respectively. The values of RQUICKI quartiles were in the ranges 0.35-0.41 (Q1), 0.42-0.52 (Q2), 0.53-0.67 (Q3) and 0.68-0.77 (Q4) (Table 1).

The cows that were the most resistant to insulin (Q1), in comparison to the cows that were the least resistant (Q4) had significantly higher concentrations of NEFA, STH, BHB, total bilirubin, AST, MDA, BCS and lower levels of IGF-I, T3, T4, albumin, cholesterol, triglycerides, tCa and iP (Table 1).

Table 1. Hormone concentrations, metabolic profiles and BCS in the cows classified into quartiles of the RQUICKI index for insulin resistance

	Mean values of RQUICKI quartiles[1]				Pooled values of SEM	P[2]
	Q1	Q2	Q3	Q4		
NEFA mmol/L	0.65[a]	0.52	0.46	0.33[b]	0.02	<0.01
STH ng/mL	16.8[a]	16.2	15.9	15.4[b]	0.16	<0.05
IGF-I ng/mL	23.2[a]	24.6	28.1	32.7[b]	0.85	<0.01
Cortisol nmol/L	16.2[a]	15.1	14.5	12.9[b]	0.36	<0.05
T3 nmol/L	0.92[a]	1.11	1.17	1.29[b]	0.02	<0.05
T4 nmol/L	50.1[a]	59.2	68.3	80.6[b]	3.6	<0.05
BHB mmol/L	0.95[a]	0.86	0.74	0.63[b]	0.04	<0.01
T. bilirubin μmol/L	8.8[a]	7.6	6.4	5.9[b]	0.2	<0.01
AST IU/L	104.5[a]	87.3	80.2	70.5[b]	3.8	<0.05
Cholesterol mmol/L	2.02[a]	2.28	2.36	2.45[b]	0.06	<0.05
Triglycerides mmol/L	0.1[a]	0.12	0.12	0.13[b]	0.003	<0.01
Albumin g/L	33.8[a]	34.7	35.8	36.9[b]	0.42	<0.05
tCa mmol/L	2.05[a]	2.16	2.19	2.21[b]	0.03	<0.05
iP mmol/L	1.39[a]	1.49	1.55	1.67[b]	0.02	<0.01
MDA μmol/L	1.95[a]	1.74	1.78	1.67[b]	0.03	<0.05
Body condition score (BCS)	3.9[a]	3.8	3.7	3.3[b]	0.04	<0.01

[1] - Quartiles of RQUICKI index: Q1 = 0.35-0.41 (lower quartile, cow most resistant to insulin), Q2 = 0.42-0.52, Q3 = 0.53-0.67 and Q4 = 0.68-0.77 (upper quartile cow least resistant to insulin); [2] - Significance of ANOVA F test; [a,b] - Different superscripts within a row mean significant differences between the most insulin resistant cows in relation to the least insulin resistant cows to at of P<0.05.

The regression analysis confirmed the obtained metabolic changes in the function of the RQUICKI index. Graphical presentations showed three typical piecewise regressions of metabolic parameters in the function of the RQUICKI values. Three typical graphical presentations of the results are shown in Figs 1-3: the metabolic parameters dramatically decreased, increased, or no changes occurred if the RQUICKI was ≤0.41 (the most insulin resistant cows, Q1). The t-tests demonstrated that the Q1 slope differed significantly from Q2-4, so that the metabolic parameters were strongly regressed by RQUICKI, and the trends of the metabolic changes were more intensive in the most insulin resistant cows (Q1). Also, concentrations of T3, T4, AST, triglycerides, tCa, iP and BCS were regressed with RQUICKI only in the most insulin resistant cows. Differences in intercept values corresponded with differences in mean values between the metabolic parameters of the cows within different quartiles, which was confirmed by ANOVA and LSD tests. Regression parameters and intercept values are presented in the Table 2.

Table 2. Regression parameters and intercepts in piecewise regression analysis - hormone concentrations, metabolic profiles and BCS regressed with the RQUICKI index in the most insulin resistant cows (Q1) and the other cows (Q2-4).

	Regression				Intercept			
	B Q1[1]	B Q2-4	SEM	P	Q1	Q2-4	SEM	P
NEFA mmol/L	-0.54	-0.31	0.025	<0.01	1.01	0.87	0.023	<0.05
STH ng/mL	-14.68	-2.78	0.62	<0.01	22.31	15.77	0.65	<0.05
IGF-I ng/mL	-25.55	34.46	4.14	<0.05	33.97	15.31	1.22	<0.05
Cortisol nmol/L	-27.3	-8.78	1.25	<0.01	25.84	19.25	0.93	NS
T3 nmol/L	1.96	0.55*	0.16	<0.01	0.42	1.02	0.061	<0.05
T4 nmol/L	603.1	106.1*	32.71	<0.01	-162.52	11.21	3.82	<0.01
BHB mmol/L	-4.73	-0.86	0.19	<0.01	2.83	1.23	0.21	<0.01
T. bilirubin µmol/L	-16.03	-6.38	1.42	<0.01	14.93	10.88	0.48	<0.05
AST IU/L	-123.1	-49.6*	11.68	<0.01	159.31	114.5	3.1	<0.05
Cholesterol mmol/L	2.14	0.63	0.16	<0.01	0.81	1.74	0.11	<0.01
Triglycerides mmol/L	0.052	-0.003*	0.008	NS	0.08	0.12	0.004	<0.05
Albumin g/L	8.7	7.7	0.32	NS	28.21	29.3	0.29	NS
tCa mmol/L	0.85	0.19*	0.014	<0.01	1.56	2.54	0.14	<0.05
iP mmol/L	0.68	0.39*	0.031	<0.01	0.72	0.83	0.02	NS
MDA µmol/L	0.89	0.52	0.04	<0.05	0.88	0.99	0.019	NS
Body condition score (BCS)	-7.34	-1.81*	0.32	<0.01	4.62	6.71	0.28	<0.05

[1]- Quartiles of RQUICKI index: Q1 = 0.35-0.41 (lower quartile cows, most resistant to insulin), Q2 = 0.42-0.52, Q3 = 0.53-0.67 and Q4 = 0.68-0.77 (upper quartile cows, least resistant to insulin); *- B regression parameters not different from 0.

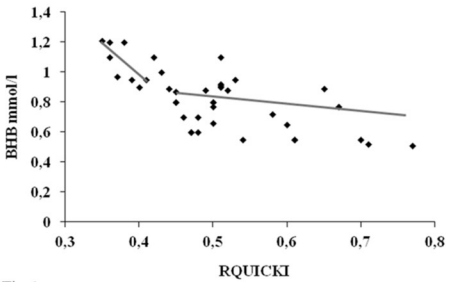

Fig.1

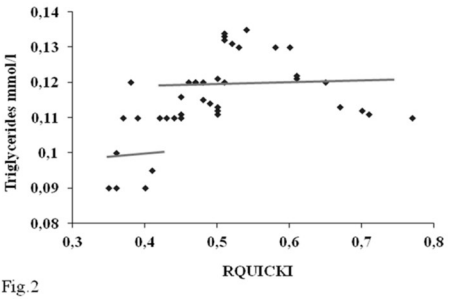

Fig.2

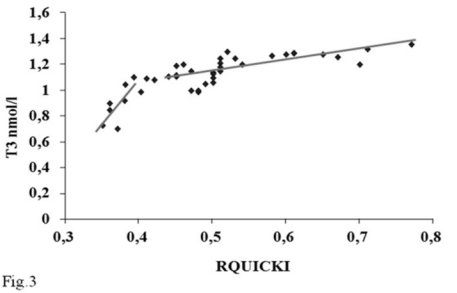

Fig.3

Figs 1-3. Graphical presentation of three typical piecewise regression lines of the metabolic parameters, such as BHB (Fig. 1), Triglycerides (Fig. 2) and T3 (Fig. 3) in the function of the RQUICKI when the cut-off point is RQUICKI ≤0.41 (lower quartile, the most insulin resistant cows)

The cows exhibiting a higher number of metabolic abnormalities had lower RQUICKI values: 0.56 ± 0.045 (no abnormalities); 0.52 ± 0.041 (1 abnormality); 0.47 ± 0.042 (2 abnormalities) and 0.4 ± 0.043 (≥3 abnormalities). The RQUICKI index was significantly lower in the cows with ≥3 abnormalities in metabolic parameters (Fig. 4).

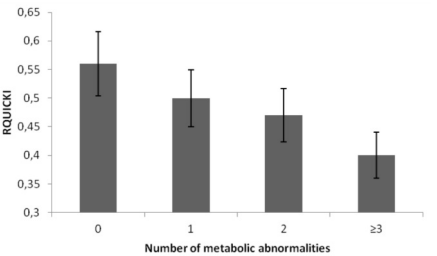

Fig. 4. The influence of the number of metabolic abnormalities in the metabolic profile of the cows on the values of the RQUICKI index

Discussion

The RQUICKI index is calculated in a range from 0.35-0.68 in dairy cows (HILTENIUS and HOLTENIUS, 2007; BALOGH et al., 2008; KERESTRES et al., 2009; GROSS et al., 2011). Most of the results obtained in this study were also within that range.

NEFA is associated with insulin resistance due to GLUT4 translocations, changes in post receptor signals and decreased density of GLUT4 (HAYIRLI, 2006). Lipid mobilization is characterized by high concentrations of adipokins, oxidative stress and proinflammatory cytokines which stimulate insulin resistance (LI et al., 2013). Also, the RQUICKI is highly determined by NEFA during early lactation (CINCOVIĆ et al., 2014). HRISTOVSKA et al. (2017) showed that NEFA and RQUICKI were in strong linear correlation, and in cows with a lower RQUICKI index, lower NEFA concentrations after application of niacin as an antilipolytic vitamin were established. Intravenous infusion of fat emulsion caused development of insulin resistance in Holstein-Frisian cows (PIRES et al., 2007).

The cows with the lowest RQUICKI index (the most insulin resistant) showed significantly reduced concentrations of IGF-I. IGF-I synthesis occurs in the liver under the control of STH. It is well known that STH concentration is higher during early lactation, while IGF-I concentration is reduced. One of the reasons which could explain this phenomenon is the low concentration of insulin, due to insulin resistance. Insulin resistance caused the reduced expression of the STH receptors (BUTLER et al., 2003; RHOADS et al., 2004). Therefore, the lack of insulin or insulin resistance may be directly related to a reduced concentration of IGF-I. GROSS et al. (2011) reported that NEB during early lactation caused a decrease in the RQUICKI index (insulin resistance) and IGF-I values. KERESTES et al. (2009) found a negative correlation between IGF-I and the RQUICKI. The T3 and T4 concentrations were notably reduced in Q1 (the most insulin resistant cows) in our study. BRENTA (2011) also showed a relationship between hypothyroidism and insulin resistance. Namely, thyroid hormones have a direct effect on genes that code GLUT receptors in peripheral tissues. It was found that low concentrations of T3 and T4 remained on that level during the high levels of NEFA and BHB.

The experiment performed by WEBER et al. (2013) showed significantly reduced RQUICKI indexes in the group of cows that had a higher degree of triglyceride accumulation in the liver. Data obtained in humans showed the development of fatty liver as a consequence of peripheral insulin resistance. In addition, the values of insulin resistance indicators and lipid profiles showed notable statistical differences in comparison with healthy patients (BONNET et al., 2011). Higher inflow of NEFA blocks the signal for insulin in hepatocytes and interrupted beta oxidation of fatty acids (NAGLE et al., 2009). Oxidative stress accompanies insulin resistance, so a higher MDA concentration, as a product of fatty acid peroxidation, was found in the most insulin resistant group

of patients. In human metabolic syndrome, a positive correlation between fatty acid peroxidation and insulin resistance level was observed (SHARMA et al., 2011).

The calcium concentration is significantly correlated with parameters of insulin resistance (positive correlation with the degree of insulin resistance) (SUN et al., 2005). The level of inorganic phosphorus was lower in ketotic cows showing a higher level of insulin resistance (CINCOVIĆ et al., 2017a).

The BCS of the cows was significantly correlated with the level of insulin resistance, so the cows that had higher BCS were the most insulin resistant. HOLTENIUS and HOLTENIUS (2007) found a negative correlation of the RQUICKI index with BCS. JAAKSON et al. (2013) showed the same relationship between these variables. It was found that the cows in the periparturient period did not show hepatic insulin resistance, but primarily fat tissue insulin resistance, especially when they were losing weight (ZACHUT et al., 2013).

Conclusion

The cows with a lower RQUICKI index and high BCS showed metabolic adaptations that indicated a katabolic load on the organism, the development of fatty liver, ion imbalances and oxidative stress. Metabolic parameters were strongly regressed by RQUICKI in the most insulin resistant cows in the first week of lactation. The cows exhibiting a higher number of metabolic abnormalities had lower RQUICKI index values. The RQUICKI index could be a potent indicator of metabolic status in cows during early lactation.

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SAŽETAK

Revidirani kvantitativni indeks provjeravanja osjetljivosti na inzulin (RQUICKI) najčešće se koristi kao pokazatelj otpornosti na inzulin u krava. Cilj ovoga istraživanja bio je ustvrditi karakteristike metaboličkog statusa u krava s različitom vrijednosti RQUICKI indeksa u ranoj laktaciji. Pokus je uključivao 40 krava Holstein-Friesian pasmine. Krave su razvrstane u četiri skupine prema kvartilima (Q 1 do 4) vrijednosti RQUICKI indeksa: Q1 = 0,35-0,41 (najrezistentnije na inzulin), Q2 = 0,42-0,52, Q3 = 0,53-0,67, Q4 = 0,68-0,77 (najosjetljivije na inzulin). Metabolički parametri bili su znakovito različiti u krava u ranoj laktaciji razvrstanima prema vrijednostima RQUICKI indeksa. Krave koje su bile najrezistentnije na inzulin (Q1) imale su i veće razine NEFA, kortizola, STH, BHB, ukupnog bilirubina, AST, MDA i bolju tjelesnu kondiciju u usporedbi s kravama koje su bile najmanje osjetljive na inzulin (Q4). Također, te su krave imale niže koncentracije IGF-I, T3, T4, albumina, kolesterola, triglicerida, Ca i P te sklonost smanjenju koncentracije inzulina i glukoze. U skupini krava koje su najrezistentnije na inzulin (Q1) regresijska analiza je pokazala jaču povezanost između metaboličkih parametara i RQUICKI nego što je to bio slučaj u ostalim skupinama krava (Q2, Q3 i Q4). Krave s većim brojem metaboličkih abnormalnosti profila imale su nižu vrijednost RQUICKI: 0,56 ± 0,045 (bez abnormalnosti); 0,52 ± 0,041 (jedna abnormalnost); 0.47 ± 0.042 (dvije abnormalnosti) i 0.4 ± 0.043 (≥3 abnormalnosti). Zaključujemo da bi se RQUICKI indeks mogao primijeniti za točnije identificiranje metaboličkog statusa krava tijekom rane laktacije. Međutim, kinetika osjetljivosti na inzulin trebala bi se dodatno istražiti na većem broju životinja kao i u krava različitih pasmina.

Ključne riječi: krave; inzulinska rezistencija; RQUICKI; metabolički profil; rana laktacija