ORIGINAL ARTICLE

Veterinary Research Forum. 2024; 15 (10): 523 - 528
doi: 10.30466/vrf.2024.2023763.4188
Journal Homepage: vrf.iranjournals.ir

Veterinary Research Forum

Features of glucose-insulin homeostasis at different stages of gestation in cows

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Article Info

Article history:

Received: 25 February 2024
Accepted: 29 June 2024
Available online: 15 October 2024

Keywords:

Calves
Cattle
Gestation
Glucose
Insulin

Abstract

An increase in morbidity during times of relatively high functional load on the body such as during pregnancy, confirms the role of metabolic overload in the occurrence of metabolic failures. It is better to take preventive measures such as adjusting metabolic regulation mechanisms in light of the ideal dietary composition. However, this direction is constrained by the lack of information about neurohumoral regulation. The goal of the present study was to learn more about the dynamics of changes in insulin and glucose levels in pregnant cow's blood. Research on the levels of glucose and insulin in lactating cows demonstrated that ruminants had distinct characteristics in the metabolism of carbohydrates, most notably a lessened reliance of blood glucose on insulin levels. A rise in blood glucose and insulin levels was observed as the gestational stage increased during the third trimester of pregnancy. The intensity of this insulin tolerance was contingent upon the level of productivity and glucose levels during the preceding stages of gestation.

Introduction

The primary determinant of an animal productivity and overall health is its metabolism along with its immune system. Metabolic disorders are a constant component of most diseases. A rise in metabolic diseases has occurred recently as a result of active selection correcting the genetic potential for productivity and the ensuing functional load on the body.[1] An increase in morbidity during times of relatively high functional load on the body such as during pregnancy confirms the role of metabolic overload in the occurrence of metabolic failures.[2,3]

The tactics of combating this group of pathologies is the oral or parenteral administration of an increased amount of biologically active substances into the body in order to prevent their occurrence or to compensate for their existing excess or deficiency.[4,5] However, this approach is associated with the risk of one imbalance of biologically active substances and the emergence of a new pathology.[6] The risk of such a clinical scenario is the highest during periods of high functional stress on the body especially during pregnancy. In this case, preventive measures are more rational including the correction of regulatory metabolic mechanisms against the background of the optimal composition of the diet. However, this direction is limited by the lack of information about neurohumoral regulation although its study is an ongoing research task for many generations of scientists. Especially with regard to carbohydrate metabolism, the role of counter-insular hormones, the functional opposition of hormones and many of their functions, especially insulin, have not been sufficiently studied.[7] Insulin synthesized by the beta cells of the pancreas affects most cells of the body. In particular, it controls the flow of glucose into them.[8] Although this hormone was discovered more than 100 years ago, many of its functions are still being researched. There is an obvious lack of knowledge particularly in the area of species-specific hormonology. Many authors point out the features of the islet apparatus of the pancreas in ruminants focusing on the mechanisms of insulin synthesis and secretion.[9,10] The dynamics of insulin during pregnancy and its role in fetal growth and development are studied.[11-13]

However, many questions in veterinary hormonology have not yet been investigated. There is no information on the role of insulin in the development of perinatal pathologies in animals, although this problem is one of the most pressing in human medicine.[14,15] The goal of the present study was to learn more about the dynamics of changes in insulin and glucose levels in pregnant cow's blood.

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Materials and Methods

The research was conducted from November 18, 2022, to April 20, 2023, on a dairy farm located in the Voronezh region. The subjects of the study were pregnant red-motley cows aged 3 - 5 years and the calves delivered. Adult animals were kept freely in group sections with individual laying boxes for resting and their diet was developed taking into account their physiological state and productivity level.[16] When the gestation period reached 7 months, the supply of juicy and milk-promoting feed was reduced and after 5 - 7 days a one-time drying off was carried out with the implementation of mastitis prevention measures. As soon as signs of labor appeared, the cows were moved to individual cubicles. After the mother licked them, the newborns were kept in calf drying boxes for 60 min and received the first portion of colostrum. The newborns were then placed in individual boxes set up in a special pavilion. The studies were carried out in accordance with the principles of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes, the rules of Good Laboratory and Clinical Practice (GLP and GCP) as well as the requirements of Directive 2010/63/EU of the European Parliament and of the Council of the European Union dated 22 September 2010 for the Protection of Animals Used for Scientific Purposes. The study design was approved by the Bioethics Committee of the St. Petersburg State University of Veterinary Medicine (permission No. 1; February 12, 2023). The cows were under constant observation during the second and third trimesters of pregnancy and during calving. In addition, a comprehensive examination of all cows a gestation period of 4.5 - 5 months was carried out and 315 clinically healthy animals were selected. They underwent another examination at 7.5 - 8 months of gestation. The results of the examination and observation showed that 87 animals developed certain pathologies or had abnormal calving, therefore, they were excluded from the experiment. The remaining 228 cows were clinically healthy during the observation period and gave birth to visually healthy newborn calves due to natural calving. These animals became the subject of a retrospective analysis.

When assessing the health status of cows, methods of clinical and instrumental examination and laboratory blood tests were used. Pregnancy monitoring and fetal condition were performed using a portable ultrasound scanner (Draminski, Sząbruk, Poland). The clinical and instrumental examination of the cows were carried out between 7:00 and 8:00 AM and blood samples were taken after a 30-minute rest period. All studies were performed 11 - 12 hr after the previous feeding (7:00 - 8:00 PM), 1.5 hr after milking lactating animals and 1 hour before the next feeding. The above gives reason to believe that the blood sample was taken on an empty stomach.

The choice of laboratory research methods, carried out in specialized laboratories, was focused on assessing the state of health and identifying possible pathologies. However, taking into account the goal of the work, the emphasis of the blood analysis was placed on the study of the content of glucose (a set of reagents for veterinary medicine, DS. Med LLC, Russian Federation) and insulin (a set of reagents for enzyme-linked immunosorbent assay, DRG Instruments GmbH, Marburg, Germany). Based on the results of a study of glucose levels in the blood serum of cows with a gestation period of 4.5 - 5 months, groups were created whose level of this metabolite was more or less than 2.00 mmol L^{-1} (n = 97 and n = 131 accordingly). The calves they obtained were observed during the first 72 hr of life and, in order to determine the level of the parameters examined, a blood sample was taken from them at 5, 2, 12, 24 and 72 hr of age.

Taking into account the difference in glucose content in arterial and venous blood, blood samples were collected only from the jugular vein in ELAMED vacuum tubes with a coagulation activator (Joint Stock Company "Yelatom Instrument Plant", Ryazan, Russian Federation). After 40 - 45 min, the blood was centrifuged (415 g for 15 min) and the serum was collected in two test tubes one of which was used to determine glucose levels within 60 min. The blood serum in the second test tube was stored at a temperature of – 20.00 ˚C and the insulin level was determined there for 1 - 1.5 months.

Statistical analyses. The research results were subjected to mathematical processing with the calculation of the Caro coefficient (CC), the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and the quantitative insulin sensitivity check index (QUICKI) indices using the following formulas:[17,18]

$$CC = GL/Ins$$

$$HOMA\text{-}IR = Gl*Ins/22.5$$

$$QUICKI = 1/(\log Gl + \log Ins)$$

where, *GL* is glucose content in blood serum (mmol L^{-1}), *Ins* is insulin level in blood serum (μU L^{-1}).

In addition, the results were statistically processed using the Statistica 10.0 program (version 13.3.721; StatSoft, Moscow, Russia). The arithmetic means and its error (M ± m), the significance of the difference (p) using Student's test and the Pearson correlation coefficient (r) were calculated. The significant level was set at < 0.05.

Results

Ninety seven out of 228 cows (42.54%) had glucose levels above 2.00 mmol L^{-1}, however, 131 (57.45%) animals had glucose levels below this (Table 1). In the normoglycemic group, a relatively high average daily milk yield was observed in 56.70% of the animals and in

glucose-deficient animals it was 45.80%. In addition, in the former, the value was 10.80% lower and the insulin level was 2.90% lower than in animals with hypoglycemia and low milk yield was found at 43.30 and 54.20%, respectively. In ruminants, the main processes of fiber metabolism take place in the proventriculus, however, their walls do not pass glucose and are subject to fermentation by the microflora living there. This creates volatile acids that are absorbed into the blood and in the liver, glucose is formed from propionates. Some carbohydrates, particularly starch, are metabolized in the intestine rather than in the proventriculus. The glucose formed enters the blood and then the liver.[19-21] In addition to the important role of glucose in energy metabolism, it plays an important role in the synthesis of milk components in lactating cows and productivity is often found to depend on the content of this carbohydrate.[22,23] However, despite the larger number of highly productive cows in the normoglycemia group, the correlation dependence of milk production on glucose levels ($r = -0.044$, $p > 0.5$) and insulin ($r = -0.015$, $p > 0.5$) turned out to be inversely weak. While the connection between glucose and insulin was directly evident on the Chaddock scale ($r = 0.629$, $p < 0.05$), this confirmed the well-known role of insulin (an insulin-like hormone) in regulating carbohydrate metabolism.

With glucose level, the HOMA-IR index and the CC had a close direct association, however, the QUICKI index had an inversely high association with a correlation coefficient of 0.962, 0.731, and – 0.969 ($p < 0.05$). Insulin had a direct strong association with the HOMA-IR index ($r = 0.804$, $p < 0.05$) and an inversely strong association with QUICKI ($r = -0.800$, $p < 0.05$), however, there was no association with CC.

As the stage of pregnancy progresses, blood sugar and insulin levels are increased. In the initial normo- and hypoglycemia groups, glucose was increased by 1.90 and 4.80%, respectively, and insulin was increased by 55.00 and 18.70%, respectively, in highly productive animals and in less productive animals, the value of the first metabolite was increased by 10.20 and 3.60%, respectively, and hormone by 13.70, and 15.10%, respectively.

Thus, cows in the third trimester of pregnancy experience transient hyperglycemia, the severity of which depends on productivity and glucose levels in the previous periods of pregnancy. Therefore, during active lactation (4 - 5 months), it is associated with high glucose consumption for milk synthesis and active use of glycogen.[24] However, to ensure the contractility of the uterine muscles during calving and the synthesis of colostrum and milk at the beginning of a new lactation, energy substrate reserves, especially glycogen, are required. Therefore, during the dry period, glycogenesis processes are activated- the main regulator of which is insulin (an increase in its level and less pronounced hyperglycemia). These changes in carbohydrate metabolism are more pronounced in animals with relatively high milk production and are less dependent on initial glucose levels in mid-lactation. Thus, transient hyperglycemia is a physiologically determined compensatory process aimed at creating reserves of energy substrates necessary for fetal development, calving and milk synthesis at the beginning of lactation. However, the adequacy of energy reserves is largely determined by blood insulin levels and not glucose levels. This opinion is also confirmed by the fact that the correlation between glucose levels in the 4.5th and 8th month of pregnancy was directly high ($r = 0.989$, $p < 0.05$), while the relationship between insulin levels was weak ($r = 0.252$, $p > 0.05$), indicating a role in the formation of hormone levels in the third trimester of a multifactorial situation with energy reserves.

At the same time, the benefit of the manifestation of the functional activity of insulin depends on the state of the intracellular mechanisms of glycogenolysis which is

Table 1. Indicators of cow productivity and blood composition.

Parameters	Glucose content			
	> 2.01 mmol L^{-1}		≤ 2.00 mmol L^{-1}	
Total animals	55	42	60	71
Pregnancy 5 months (2nd phase of lactation)				
Average daily milk yield for the previous decade (kg)	21.00 ± 1.17 *	16.20 ± 1.13 †	22.30 ± 1.38 *	15.00 ± 2.23 †
Glucose (mmol L^{-1})	2.63 ± 0.11	2.95 ± 0.21	2.09 ± 0.05	1.93 ± 0.14
Insulin (μU L^{-1})	8.00 ± 0.30	10.20 ± 0.25	8.00 ± 0.26	8.60 ± 0.22
HOMA-IR	0.94 ± 0.08	1.34 ± 0.06	0.74 ± 0.11	0.65 ± 0.08
Caro coefficient	0.33 ± 0.01	0.29 ± 0.02	0.26 ± 0.02	0.22 ± 0.17
QUICKI	0.75 ± 0.00	0.67 ± 0.00	0.81 ± 0.01	0.82 ± 0.01
Pregnancy 8 months (dry period)				
Productivity *per* lactation (kg)	7,153.00 ± 18.52	5,850.80 ± 50.0	7,210.50 ± 15.80	4,751.00 ± 21.50
Glucose (mmol L^{-1})	2.68 ± 0.20 ‡	3.25 ± 0.17	2.19 ± 0.13	2.00 ± 0.11
Insulin (μU L^{-1})	12.40 ± 0.51	11.60 ± 0.35	9.50 ± 0.25	9.90 ± 0.32
HOMA-IR	1.47 ± 0.09	1.67 ± 0.11	0.92 ± 0.09	0.88 ± 0.11
Caro coefficient	0.22 ± 0.06	0.28 ± 0.08	0.23 ± 0.05	0.20 ± 0.05
QUICKI	0.65 ± 0.00	0.63 ± 0.01	0.51 ± 0.00	0.77 ± 0.01

HOMA-IR: Homeostasis model assessment of insulin resistance, * > 18.50, † < 18.50, and ‡ glycogen deficiency.

assessed indirectly using index parameters.[25] The interdependence of insulin glucose with HOMA-IR, CC and direct was very high, with a correlation coefficient of 0.979 and 0.889, 0.883 and 0.357 (moderate), however, in QUICKI these monosaccharides and hormones had an inversely weak relationship (r = – 158 and – 0.157). This did not affect the mechanisms of the functional connection between glucose and insulin.

The absolute values of the HOMA-IR index were 56.40 and 24.30% higher in the third trimester compared to the second trimester in high-yielding cows with initial absence or presence of glucose deficiency, respectively. However, other indices determined were lower: CC by 33.30 or 11.50%; QUICKI by 29.80, and 37.30%, respectively. In animals with relatively low productivity, changes in index parameters were similar in direction but less pronounced. The strongest difference was found in cows with initially high productivity, regardless of the presence or absence of hypoglycemia indicating a higher tension in their carbohydrate metabolic mechanisms including glycogenolysis due to the more active use of glycogen during lactation.

Discussion

One of the most important physiological significance of the hormone is the regulation of glucose consumption by cells which is important not only for their function but also for the regulation of carbohydrate levels in the blood.[26-28] Changes in cell sensitivity to insulin (insulin tolerance or insulin resistance) are due to cell dysfunction underlying which is a universal mechanism for triggering many pathologies.[29-31] After confirming the existence of interdependence between glucose and insulin levels in the blood of cows their ratio was determined and used to determine the sensitivity of cells to assess insulin. However, as mentioned above, a moderate relationship between glucose and insulin was found while in a clinically healthy human being there is a pronounced functional interdependence.[29] Therefore, the calculated index parameters in cows differ from those considered as reference in human medicine.[30,32]

In clinical practice, insulin resistance is evidenced by a tendency to increase the HOMA-IR index, but to decrease CC and QUICKI.[18,30,33] A decrease in the sensitivity of cells to glucose in animals with increasing gestational stage becomes apparent. The expediency of physiological insulin resistance is explained not only by the need for sufficient glucose transport to the fetus,[34] but also by the active participation of insulin with carbohydrates in lipid and protein metabolism the correction of which occurs as the stage of pregnancy increases.[35-39] Glucose crosses the placental barrier and is required for fetal development. Therefore, their concentration is increased with pregnancy.[40-42] At the same time, insulin levels also is increased which should activate the cells glucose consumption and reduce its concentration. However, in this case there would be a risk of glucose deficiency in the fetus. However, activation of insulin synthesis in the last trimester of pregnancy is necessary to correct other metabolic mechanisms of pregnancy. However, it could be assumed that the activity of glycogenesis was decreased, therefore, the formation of energy reserves in the form of glycogen should have probably been occurred in earlier stages of pregnancy. This was not insulin resistance, but rather temporary insulin resistance in pregnant cows (physiological insulin tolerance).

Studies on glucose and insulin levels in lactating cows have shown that ruminants have peculiarities in carbohydrate metabolism, in particular a less pronounced dependence of blood sugar on insulin levels. As the stage of pregnancy is increased, an increase in the level of glucose and insulin in the blood was noted with the formation of temporary insulin tolerance in the third trimester of pregnancy, the severity of which depends on the level of productivity and glucose in the previous stages of pregnancy.

Acknowledgments

The authors are grateful for the supports of the All-Russian Research Veterinary Institute of Pathology, Pharmacology and Therapy, Voronezh, Russia, and Saint Petersburg State University of Veterinary Medicine, Saint Petersburg, Russia.

Conflict of interest

There is no conflict of interest.

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