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RESEARCH ARTICLE

Evaluation of hepatokines, proinflammatory cytokines, oxidative stress and energy related metabolism analytes and hematological parameters in dairy cows with placental retention

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Plasental retansiyonlu süt ineklerinde hepatokinlerin, proinflamatorik sitokinlerin, oksidatif stres ve enerji ile ilgili metabolizma analitlerinin ve hematolojik parametrelerin değerlendirilmesi

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Öz

Amaç: Bu çalışmada, plasenta retansiyonlu (PR) ineklerde serum ANGPTL4, FGF21, IL-1β, IL-6, SOD, MDA düzeylerinin ve enerji ile ilgili metabolizma analitleri ve hematolojik parametrelerin araştırılması amaçlandı.

Gereç ve Yöntem: Çalışmada 10 PR'li ineğin ve 10 sağlıklı kontrol ineğin (CC) koksigeal venlerinden kan örnekleri alındı. Tüm örnekler serum glikoz, esterleşmemiş yağ asitleri (NEFA), trigliserid, HDL, toplam protein, albümin, aspartat aminotransaminaz (AST) süper oksit dismutaz (SOD) ve malondialdehit (MDA) bakımından analiz edildi. Kan serumu hepatokinleri (anjiyopoietin benzeri protein 4 (ANGPTL4) ve fibroblast büyüme faktörü 21 (FGF21)) ve proinflamatuar sitokin yanıtına (IL-1 beta ve IL-6) ilişkin parametrelerin düzeyleri değerlendirildi.

Bulgular: PR'li ineklerin karaciğer fonksiyonu ile ilgili olarak serum AST ($p < 0.05$) düzeyinde yükselme saptandı. Negatif enerji dengesine adaptasyon sürecinde serum NEFA düzeyinde yükselme ve serum HDL düzeyinde azalma ortaya çıktı ($p < 0.05$). Antioksidan sistemin durumunu yansıtan serum SOD ($p < 0.001$) ve MDA ($p < 0.05$) düzeylerinde önemli yükselme belirlendi. Serum IL-6 ($p < 0.05$), SOD ve MDA düzeylerindeki önemli artış ineklerde metabolik, inflamatorik ve oksidatif stresin etkin olarak ortaya çıktığının; serum ANGPTL4 ve FGF21 ($p < 0.001$) değerlerinin yüksek bulunmasının ise karaciğerin adaptasyonla başedebildiğinin göstergesi olarak yorumlandı. PR'li ineklerde monosit sayısı anlamlı olarak daha düşüktü ($p <0.05$).

Öneri: PR'li ineklerde serum ANGPTL4 ve FGF21 düzeylerindeki önemli artışların enerji dengesi, etkili sitokin yanıtlar ve oksidatif stres ile ilişkili olduğu sonucuna varıldı.

Anahtar kelimeler: Hepatokinler, Oksidatif stress, plasental retansiyon, sitokinler, sütçü inekler

Abstract

Aim: To investigate the serum levels of angiopoietin-like protein 4 (ANGPTL4), fibroblast growth factor 21 (FGF21), interleukin 1 beta (IL-1β), IL-6, superoxide dismutase (SOD), malondialdehyde (MDA), and energy-related metabolism analytes and hematological parameters in cows with placental retention (PR).

Materials and Methods: In the presented study, blood samples were taken from the coccygeal veins of 10 cows with PR and 10 healthy control cows. All of the samples were analyzed to determine the serum glucose, unesterified fatty acid (NEFA), triglyceride, high-density lipoprotein (HDL), total protein, albumin, aspartate aminotransaminase (AST), SOD, and MDA levels. Blood serum hepatokines, ANGPTL4, FGF21 levels, proinflammatory cytokine response parameters, IL-1 beta, and IL-6 levels were evaluated.

Results: As a result, the increase in serum AST ($p < 0.05$) indicated altered liver function. During negative energy balance, the serum NEFA levels ($p < 0.05$) increased, and serum HDL levels ($p < 0.05$) decreased as indicators of an increased risk of metabolic pathology. Increases in the serum ANGPTL4, FGF21, CRP, and SOD ($p < 0.001$) and IL-6, MDA, creatine kinase levels ($p < 0.05$) were evaluated as indicators of the development of effective metabolic, inflammatory, and oxidative stress. The monocyte count was significantly lower ($p < 0.05$) in the cows with PR.

Conclusion: It was concluded that significant increases in the serum ANGPTL4 and FGF2 levels were associated with energy balance, effective cytokine responses, and oxidative stress in dairy cows with PR.

Keywords: Hepatokines, oxidative stress, placental retention, cytokines, dairy cows,

Introduction

Placental retention (PR) is one of the most common postpartum reproductive disorders (Dervishi et al 2016) that causes substantial economic losses in dairy farms due to prolonged calving intervals and decreased milk yield. Changes in immune cell function and metabolic stress in cows with PR adversely affect the immuno-metabolic status of cows (Loor et al 2013, Kimura et al 2014, Mordak and Stewart 2015). The majority of cattle expels the fetal membranes within 8 hours after delivery. However, this physiological process may sometimes take up to 24 hours to accomplish. If fetal membranes are not expelled within 24 h after delivery, this is considered PR (Han et al 2005).

While the incidence of various diseases increases in cows with low body condition score (BCS) values, immune response deficiency occurs in cows with high BCS values (Roche et al 2006). In cows with a postpartum BCS below 3.25 or above 3.75, the level of oxidative stress and the incidence of disorders such as PR increase (Çolakoğlu and Kuplülü 2016, Zhao et al 2019, Çolakoğlu et al 2020).

In the postpartum period in cows, the body's energy needs are met by the mobilization of body lipid reserves. In this period, it is essential to evaluate the liver functions and serum non-esterified fatty acid (NEFA) levels, which show the general health status, energy metabolism, and immune defense mechanism in dairy cows (Semacan and Sevinç 2005, Podpecan et al 2020). In addition, it is recommended to monitor the postnatal functional activities of peripheral neutrophils and lymphocytes in terms of the risk of PR in dairy cattle (Kimura et al 2002, Moretti et al 2016).

Grummer (1993) indicated that there are significant associations between hepatocyte degenerations and analyte levels associated with liver enzymes and lipid metabolism in postpartum cows. Gluconeogenesis and lipodystrophy occurring in the liver and adipose tissue are critical metabolic pathways for negative energy metabolism in postpartum cows. The lipid oxidation capacity of the liver and adipose tissues in these cows is important in meeting energy demands and regulating metabolic pathways (Xu et al 2015).

Angiopoietin-like protein 4 (ANGPTL4) and fibroblast growth factor 21 (FGF21) are important hepatokines that are synthesized from the liver and adipose tissue for the stimulation of lipolysis, inhibition of lipogenesis in the liver, and oxidation of hepatic lipids and fatty acids (Chen et al 2018). In addition, FGF21 has important regulatory functions, such as the regulation of gluconeogenesis, glucose metabolism, and stimulation of proinflammatory cytokines. Caixeta et al (2017) reported that serum FGF21 and NEFA levels increased simultaneously in the postpartum period when lipid mobilization occurs in the liver. Therefore, it could be favorable to monitor the serum FGF21 concentrations in the evaluation of metabolic stress status, since it has an important role in the regulation of energy metabolism in dairy cows (Xu et al 2015, Chen et al 2018, Krumm et al 2019).

The lipid mobilization in cows with negative energy balance leads to the activation of phagocytic cells and proinflammatory cytokines (Valko et al 2007). In the postpartum period, with the increase in serum NEFA and beta-hydroxybutyric acid (BHBA) levels, an increase occurs in the levels of proinflammatory cytokines, such as interleukin 1 beta IL-1β and IL-6, which are known to play an active role in lipid metabolism and immune system function. It was stated that IL-6 also plays a role in the development of metabolic inflammation occurring in PR and in the formation of the immunological response. In addition, IL-6 has important roles in lipoprotein metabolism, fatty acid oxidation, and urea cycling, as well as oxidative stress and activation of the proteosome (Loor et al 2007, Wankhade et al 2017).

The increase in the oxidative stress complex in postpartum cows is a part of the metabolic adaptation process (Bernabucci et al 2005, Turk et al 2013, Abuelo et al 2015). Metabolic stress causes significant increases in the by-products of cellular respiration in mitochondria and free radical levels in the blood, which is an indicator of oxidative stress (Mordak and Stewart 2015). One of the parameters used to determine oxidative stress is superoxide dismutase (SOD), which functions in the natural elimination of O2–, and the other is malondialdehyde (MDA), which occurs as a by-product of lipid peroxidation (Agalakova and Gusev 2011).

This study aimed to evaluate the effects of PR on postpartum negative energy balance in dairy cows. To this end, the serum levels and hematological parameters of serum ANGPTL4, FGF21, IL-1β, IL-6, SOD, MDA, and energy-related metabolism analytes were evaluated.

Material and Methods

Twenty (20) multiparous dairy cows included were, aged 3–5 years, delivered a singleton, on the same farm, and were determined to have BCSs of 3.25–3.75 following birth, without dystocia, and with similar milk yield. The prepartum and postpartum cows were fed a total mix ratio twice daily ad libitum. The barns were naturally ventilated and had artificial lighting. Cows were considered to have developed PR if the fetal membranes had not been expelled and a part of the placenta protruded from the vulva within 24 h after parturition (Manhani et al 2021).

The body condition scoring method explained by Ferguson et al (1994) was used, and the BCS values of these cows were scored between 1 and 5.

The first group consisted of 10 cows with PR, while the second group consisted of 10 healthy cows. A total of 7 mL of blood samples were taken from the coccygeal vein of each of the 20 cows. Next, 5 mL were placed into tubes without anticoagulant, and 2 mL were placed into tubes with ethylenediaminetetraacetic acid (EDTA). The hematological parameters of the blood samples with EDTA were measured within 1–2 h after collection using a blood count device (Mindray BC 5000 vet, Shenzhen, China). Blood serums of the blood samples without anticoagulants were removed within 2–3 h after collection, and the serum samples were stored at –80 °C in plastic godets.

Glucose, triglyceride, total protein, albumin, and high-density lipoprotein (HDL) levels were measured using an automatic biochemistry analyzer (Mindray BS300, Shenzhen, China) in the serum samples.

Blood serum ANGPTL4, FGF21, and NEFA, IL-1β, IL-6 levels were measured using respective ELISA test kits (Sun Red Biotechnology Company, Cat No: 201-04-291, Cat No: 201-04-3155, Cat No: 201-04-0186, Cat No:201-04-0157 and Cat No:201-04-0008 respectively).

Albumin, glucose, urea, uric acid, creatinine, total protein, aspartate aminotransaminase (AST), and total bilirubin levels were investigated in the serum samples using an automated biochemistry analyzer (Mindray BS120, Shenzhen, China). Serum SOD levels were measured using the Cayman 706002 commercial test kit. Serum MDA levels were measured using a commercial ELISA test kit (Sun Red Biotechnology Company, Cat No: 2.01-04-0255).

For statistical assessment, prior to testing statistical significance, all of the data were tested for parametric test assumptions, namely normality with the Shapiro-Wilk test, and homogeneity with the Levene test. The differences among the two groups were analyzed using the Student t–test when the parametric assumptions were met and the Mann-Whitney U test otherwise. All statistical analyses were examined with a 5% margin of error. Data were analyzed using SPSS Statistics for Windows 14.01 (SPSS Inc., Chicago, IL, USA).

Results

The results of the study are presented in Tables 1–3. The cows with PR were slightly sluggish, restless, and their appetites were reduced. Body temperature, respiration, and pulse rates were within normal limits. The healthy cows in the control group expelled their placentas after delivery, and had good appetites. Their body temperatures, respiration, and pulse rates were within normal limits.

Table 1. Blood serum glucose, albumin, total protein, CK, AST, triglyceride, HDL, and AST levels

Groups (Biochemical Parameters)	Glucose (g/dl)	Albumin (mg/dl)	Total Protein (g/dl)	Triglyceride (mg/dl)	HDL (mg/dl)	AST (U/L)	CK (U/L)
Control cows	64,30±10,82	3,65±1,14	5,63±0,71	7,91±2,09	58,31±12,57	91,10±24,42	173,90±43,75
Cows with PR	62,40±10,74	3,88±0,61	5,79±0,42	8,89±2,69	46,79±6,11*	138,30±40,84*	368,70±185,13**

The results are presented as arithmetic mean ± standard deviation.
*The AST and HDL measurements ($p < 0.05$) of the cows with PR and control cows were significantly different (AST p = 0,006, HDL p = 0,018).
** The CK levels of the cows with PR and the control cows were significantly different ($p < 0.001$).

Table 2. Blood serum NEFA, ANGPTL4, FGF21, SOD, MDA, CRP, IL-1β and IL-6 levels

Groups (Biochemicak Parameters)	NEFA (µmol/mL)	ANGPTL4 (ng/mL)	FGF (ng/L)	CRP (mg/L)	IL-1β (ng/mL)	IL-6 (ng/mL)	SOD (U/g protein)	MDA (nmol/g protein)
Control cows	0,50± 0,09	7,67± 0,89	1059,39±87,84	0,25±0,04	117,88± 16,99	11,19 ± 2,71	17,77 ± 3,31	2,68 ± 0,29
Cows with PR	0,68± 0,14*	11,25± 1,82**	1295,53±143,14**	0,33±0,04**	131,58±17,22	16,67±3,95*	25,86±1,80**	3,20±0,39*

The results are presented as arithmetic mean ± standard deviation.
* The NEFA, IL-6 and MDA levels of the cows with PR and the control cows were significantly different ($p<0.05$) (NEFA p=0,002, IL-6 p=0,002, MDA p = 0.003,).
** The CRP, ANGPTL4, FGF21, and SOD levels of the cows with PR and the control cows were significantly different ($p < 0.001$).

Table 3. Blood WBC, lymphocyte, monocyte and neutrophil counts

Groups (Hematological Parameters)	WBC (10^9/L)	Lymphocyte (10^9/L)	Monocyte (10^9/L)	Neutrophil (10^9/L)
Control cows	8,82± 2,41	4,60± 1,59	1,05± 0,74	2,54± 0,86
Cows with PR	9.56± 3,19	4,77± 1,77	0.51± 0.23*	2,61± 0,79

The results are presented as arithmetic mean ± standard deviation.
* The monocyte levels of the cows with PR and the control cows were significantly different ($p < 0.05$) (Monocyte p= 0,023).

The serum creatine kinase (CK) and AST levels were significantly higher in the cows with PR than in the control group. The mean serum HDL value in the cows with PR was significantly lower than that in the control group.

As can be seen from the results, the NEFA, IL-6, SOD, MDA, CRP, ANGPTL4, and FGF21 levels of the cows in which PR developed were statistically significantly increased when compared to those in the control group (Table 2).

In addition to these findings, the monocyte values of the cows with PR were significantly lower than those in the control group (Table 3).

Discussion

The results provide essential data about placental tissue destruction and the increase in lipid metabolism activity and tissue interaction in the liver and revealed important data about the negative energy balance of PR in dairy cows and the degree and importance of oxidative stress. It also explained the degree of inflammatory and immunological reactions that develop with tissue destruction in cows with PR.

There was a significant positive correlation between the changes in the oxidative stress parameters, immune response, and proinflammatory cytokine concentrations in the dairy cows with PR (Sordillo 2013).

In the postpartum period, as a result of the activation of adaptation mechanisms related to the energy requirement of metabolism, the parameters related to oxidative stress, such as blood cell count, hepatokines, and proinflammatory cytokines, change (Gitto et al 2002). Chen et al (2018) reported that there was an increase in serum ANGPTL4 and FGF21 levels in response to changes in lipid metabolism in cows with PR. Consistent with these data in this study, the serum ANGPTL4 and FGF21 levels in the cows with PR were significantly ($p < 0.001$) higher than those obtained from the cows in the control group. Many researchers (Badman et al 2009, Fisher et al 2014, Park et al 2016) have reported that when lipid metabolism is activated due to energy requirement, the increase in serum FGF21 values is a protective mechanism to limit the destructive effect of fat accumulation in the liver. The release of ANGPLT4 is stimulated by fatty acids and inhibited by lipoprotein lipase, which has an important role in preventing the degeneration that may develop due to excessive fat accumulation in cells by inhibiting the clearance of triglycerides (Georgiadi et al 2010). Wang et al (2018) stated that serum ANGPLT4 and FGF21 levels in pregnant dairy cows increased in the days close to calving and decreased 15 days after calving. They also reported that there was a positive correlation between the serum ANGPLT4 and FGF21 levels. The serum NEFA levels in the cows proved that ANGPLT4 and FGF21 are important in the adaptation mechanisms to body energy requirements. Many researchers (Mazur and Rayssiquier 1988, Grummer et al 1993, Özyurtlu et al 2008, Civelek et al 2011, Kessler et al 2014) have stated that it is useful to monitor serum triglyceride levels to assess the re-esterification or oxidation of HDL and NEFA. It has been reported that at the beginning of lactation in dairy cows, there are significant relationships between milk yield and serum albumin and liver enzymes, which are liver/intestinal lipoproteins. In addition, the importance of monitoring serum HDL and triglyceride levels was emphasized in the evaluation of activation of lipid metabolism after birth (Zhao et al 2019). In the current study, it was evaluated that the significant increase in serum NEFA, AST, and HDL values in the cows with PR was due to the increased activity in the lipid metabolism of cows with PR, and it was a sign that the liver was mildly to moderately affected in these cows.

It has been reported that the increase in metabolic activity in cows with PR suppresses antioxidant defense and as a result, oxidative stress occurs (Eşirir et al 2006, Konvicna et al 2015). In addition to the leukocytosis, lymphopenia, and monocytosis detected in buffaloes with PR, an increase in serum malondialdehyde value and a decrease in the SOD value were evaluated as markers of oxidative stress development (Ahmet et al 2009). It was reported that IL-8 triggers the accumulation of neutrophils and mononuclear cells in the uterus in dairy cows with PR (Kimura et al 2002). Yazlık et al (2019) stated that the serum SOD and blood leukocyte values are parameters that should be evaluated in patients with PR. In the current study, a significant decrease ($p < 0.001$) in the serum SOD levels in the cows with PR and a significant increase in the serum MDA levels ($p < 0.05$) showed that a significant oxidative stress situation occurred.

Moretti et al (2016) found that the number of monocytes de-

tected at 48–72 h after birth in cows with PR was lower than the values in the control group. In the study herein, the monocyte levels were significantly increased in the cows with PR when compared to the control cows ($p < 0.05$). It is believed that this indicated the inflammation associated with PR seen in cows with PR.

Many researchers have stated that IL-6 has a function in metabolic, inflammatory, and oxidative stress pathways in the body (Esposito et al 2014, Dervishi et al 2016). Trevisi et al (2012, 2015) found an increase in the serum IL-1β, IL-6, and oxidative stress levels in cows prenatally. In addition, a positive correlation was reported between systemic inflammation, and the metabolic stress and serum concentrations of IL-1 Beta, IL-6, and FGF21 (Trevisi et al 2012, Trevisi 2015, Lee et al 2018). The significant increase ($p < 0.05$) in the serum IL-6 level in cows with PR in the current study was similar to the data in the studies mentioned above.

Brodzki et al (2015) and Al-Watar et al (2021) stated that they found the serum CK concentration to be high in cows with PR and the increases in the serum CK and CRP levels were an indicator of the development of cellular destruction and inflammation. Similarly, in the study herein, the blood serum CK and CRP levels in the cows with PR were found to be higher than the values obtained from the cows in the control group.

Conclusion

It was concluded that postpartum negative energy balance was negatively affected in dairy cows with PR. Significant increases in the serum ANGPTL4 and FGF2 values of the cows indicated that severe inhibition of lipolysis and lipogenesis in the liver and oxidation of hepatic lipids and fatty acids occurred. In addition, the significant increase in the CK, AST, and HDL levels showed that the response to liver lipid metabolism occurred in the cows with PR. Regarding the severity of inflammation, a significant increase in the serum CRP, and monocytes count and IL-6 was interpreted as an indicator of significant metabolic inflammation and immunological response in the cows with PR. It was concluded that immunological and hepatokine response, and activation of liver fat metabolism have very important roles in dairy cows with PR.

Conflict of Interest

The authors did not report any conflict of interest or financial support.

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During this study, any pharmaceutical company which has a direct connection with the research subject, a company that provides and / or manufactures medical instruments, equipment and materials or any commercial company may have a negative impact on the decision to be made during the evaluation process of the study or no moral support.

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Ethical Approval

This study was granted ethical approval by the Ankara University Animal Experiments Local Ethics Committee (Decision No: 2020-18-158).

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