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Effects of Subclinical and Clinical Ketosis on The Incidence of Mastitis, Metritis, Culling Rate and Some Hematological Parameters in Dairy Cows

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ABSTRACT

The study was conducted on 197 milk dairy cattle randomly selected from 950 breeding dairy cattle. These animals were monitored immediately after delivery and blood count and serum BHBA analyzes were performed weekly for the first 8 weeks. According to the results of the BHBA obtained, all animals in the study were divided into three groups as follows; a) Control Group "C"; serum BHBA levels below 1.2 mmol/l during the study b) Subclinical Ketosis Group "SK"; serum BHBA levels between 1.2 and 2.9 mmol/l c) Clinical Ketosis Group "CK"; serum BHBA levels were above 2.9 mmol/l. All performance parameters such as milk yield and reproductive efficacy obtained from the herd management program (Dairy Plan, Gea / Germany). TLS, LS, NS, MS levels were found to be higher in the SK and CK compared to the C. Especially, a strong positive interaction between TLS and blood BHBA level was determined (P <0,000). In addition, the incidence of mastitis, metritis and coexistence of these two infections was significantly higher in the SK and CK than in the C (p <0,013). Furthermore, the rate of culling was significantly higher in the SK and CK than C and it was also observed that this ratio increased in parallel with the severity of the ketosis (p <0.008). These findings show that hematologic parameters change significantly in animals that have undergone clinical or subclinical ketosis and that susceptibility to significant infectious diseases during the periparturient period such as mastitis and metritis increases and as a result, the rate of culling increases.
Keywords: Ketozis, Mastitis, Metritis, Culling Rate, Dairy Cows

Süt İneklerinde Görülen Subklinik ve Kinik Ketozisin Bazı Hematolojik Parametreler, Mastitis, Metritis İnsidensleri ile Sürü Dışı Kalma Oranına Etkileri

ÖZ

Bu çalışma 950 adet süt sığırı içerisinden rastgele seçilen 197 adet süt sığırı üzerinde yürütülmüştür. Hayvanlar doğum yaptıkları günden itibaren takibe alınmış olup ilk 8 hafta boyunca kan sayımı ve serum BHBA analizleri haftalık olarak yapılmıştır. Elde edilen BHBA sonuçlarına göre çalışmadaki tüm hayvanlar aşağıdaki şekilde üç gruba ayrılmıştır; a) Kontrol Grubu "K"; çalışma boyunca serum BHBA seviyesi 1.2 mmol/l'nin altında seyredenler b) Subklinik Ketozis Grubu "SK"; serum BHBA seviyesi 1.2 ile 2.9 mmol/l arasında seyredenler c) Klinik Ketozis Grubu "KK"; serum BHBA seviyesi 2.9 mmol/l'nin üzerinde seyredenler. Çalışmada kullanılan tüm parametreler sürü yönetim programından (Dairy Plan, Gea, Westfalia/Almanya) alınmıştır. Çalışmada kullanılan tüm hayvanlar aynı rasyonla beslenmiş olup hiçbir hayvana özel bir koşul uygulanmamıştır. Yapılan analizler sonrasında TLS, LS ve NS'nın en yüksek olduğu grup KK, en düşük olduğu grup K olarak tespit edilmiştir. Özellikle TLS ve BHBA seviyeleri arasında güçlü bir ilişki tespit edilmiştir (p<0,000). Bununla birlikte hem mastitis hem metritis hem de bu iki enfeksiyonun birlikte seyretme insidensi subklinik ve klinik ketozis gruplarında kontrol grubuna göre çok yüksek bulunmuştur. Bununla birlikte subklinik ve klinik ketozis geçiren hayvanlarda sürü dışı bırakma oranı kontrol grubuna göre çok daha yüksek bulunmuş aynı zamanda ketozisin şiddetinin artması ile bu oranının da doğru orantılı bir şekilde yükseldiği görülmüştür. Bu bulgular göstermektedir ki gerek klinik gerekse subklinik ketozis geçiren hayvanlarda hematolojik parametreler ciddi oranda değişmekte, mastitis ve metritis gibi periparturient dönemin önemli enfeksiyöz hastalıklarına yatkınlık artmakta ve tüm bunların bir sonucu olarak sürü dışı kalma oranı yükselmektedir.
Anahtar Kelimeler: Ketozis, Mastitis, Metritis, Sürü Dışı Bırakma Oranı, Süt Sığırı

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INTRODUCTION

Ketosis is a metabolic disease characterized by the excessive increase of acetoneacetic acid (AcAc), betahydroxybutyric acid (BHBA) and acetone (Ac) concentrations which are ketone bodies in tissues and fluids. This disease is extremely important for dairy cattle production. The reason is that it is common, it develops insidiously and causes major economic losses (Ketoglu and Başoğlu, 2004).

Ketosis develops when the liver metabolism can not respond adequately to the gluconeogenesis need which has increased due to the influence of the negative energy balance that occurs when the energy expenditure in the organism is higher than the dietary energy intake. The oxaloacetate pool, one of the most important factors determining the capacity of gluconeogenesis in the liver, is depleted, fatty acids can not be completely oxidized and are converted into ketone bodies and released into the blood. Thus, the ketone level rises in all fluids such as blood, milk, saliva and so on (Baird et al., 1968).

Milk production is the primary cause for the ketosis that leads to the exacerbation of the negative energy balance in dairy cows (Grummer, 1993). The rapid rise in milk production after birth triggers and exacerbates the energy deficit associated with feed consumption which is too low to meet metabolic needs yet. In response to this, the fat stores rapidly break down and are released into the blood in the form of Non-Esterified Fatty Acid (NEFA) and delivered to the liver. The liver is unable to fully oxidize fatty acids due to the exhausted oxaloacetate reserve, uses some of it for gluconeogenesis and glucose production, stores some of it in its own cells and returns some of it back into the blood by converting it into ketone bodies. As this vicious cycle continues, fat accumulation and ketone production in the liver continues to increase, resulting in major metabolic diseases which have negative impact on both the yield and the health of the animal (Overton and Waldron, 2004).

The elevation NEFA level in blood is the most important indicator of the negative energy balance, which is the prognostic factor for ketosis. The plasma concentration of NEFA doubles between 17 days before birth and 2 days before birth and doubles again on the day of delivery to reach peak levels. There are many reasons that trigger the onset of NEFA concentration in blood. The most common of these is the initiation of fat mobilization from the adipose tissue to meet the energy needs of fetal and maternal tissues growing towards the end of the dry period (Sandra et al., 1992, Grummer, 1993). Therefore, the basis for conditions that lead the animal to ketosis is laid before parturition and the animal gives birth predisposed to metabolic diseases.

The most important indicator of ketosis is the rise of the BHBA (Betahydroxybutyrate Acid) level, which is one of the ketone bodies in blood. However, there is no clear number of what this level is. Some researchers (Nielen et al., 1994; Enjalbert et al., 2001) described subclinical ketosis as a blood BHBA level of 1.00 to 1.4 mmol / L, whereas Andersson (1988) describes subclinical ketosis only when the hyperketonemia tabulation is above 1.2 mmol/l. Oetzel (2004), who is one of the most important names with current studies in this issue, defines clinical ketosis when the ketone level in blood is in excess of 3 mmol/l and subclinical ketosis when the ketone level in blood is over 1,2 mmol/l.

The subclinical course of ketosis is more dangerous than the clinical course. The diagnosis of clinical ketosis can be made quickly and precisely. The subclinical course is clandestine and insidious, often without any symptoms, coincides with other diseases that cause the animal to lose its economic value and is often unrecognizable even during this period. (Oetzel, 2004). Therefore, while ketosis on its own is an important metabolic disorder for dairy cattle it becomes much more dangerous when it forms a complex tableau with other diseases. Correa et al. (1993) clearly demonstrate a link between clinical ketosis formation in dairy cows and diseases such as metritis, abomasum displacement and mastitis. Furthermore, some researchers (Dohoo and Martin, 1984; Whitaker et al., 1993) report that subclinical ketosis is associated with decreased milk yield, increased risk of diseases such as clinical ketosis, metritis, cystic ovaries, reduced reproductive performance and other disorders. As a result of these diseases and disorders that come together, the animals lose their economic value and are ostracized from the herd. The aim of this study is to reveal the relationship between clinical and subclinical ketosis and mastitis, metritis and culling rate from the herd in dairy cattle.

MATERIAL and METHOD

Study Population

This study has been carried out using records belonging to animals raised in Niğtaş Agricultural Enterprises operating in Niğde. The veterinarians in the enterprise record the health, milk and reproductive trait parameters of the animals and the laboratory results on a daily follow up program (Dairy Plan, Gea / Westfalia, Germany). Thus, it is possible to access individual past information of all animals in the herd when necessary. All animals on the farm are grouped according to milk yield levels and are housed in separate paddocks. The dry period is divided into 2, the animals are housed in the first section (early dry period) for 41 days and the second section (last period) until delivery. In addition, all postnatal animals are housed in the "early lactation" group during the first 30 days of lactation, regardless of milk production. Details of the rations for all these periods are explained in detail in Table 1. The ration was prepared as TR (Full Ration) for the animals and served *ad libitum*. Thus surplus feed in all groups were collected daily, weighed and recorded. This way feed consumption was determined and taken under control on a group basis. All feed raw materials used in the rations and TR samples taken weekly were transported in a cold chain to Afyon Kocatepe University Veterinary Faculty, Department of Animal Nutrition and Nutritional Diseases Laboratory and analyzed for crude oil, crude protein, crude ash, dry matter according to Weende Analysis Methods (AOAC, Williams, 1984), for ADF (Acid Detergent Fiber and NDF (Neutral Detergent Fiber) according to Georing Van Soest (1970). The nutrient levels of feedstuffs were calculated according to the obtained results and these analysis results were used in ration formation.

Study Design and Data Collection

All the animals on the farm are checked over by the responsible veterinarian on duty at least once per day, treatment is started immediately when disease is diagnosed. A small laboratory on the farm is used to finalize diagnosis. This laboratory is equipped with small scale equipment such as a centrifuge, hemogram, device for monitoring blood gases and Elisa reader. When detailed analysis is needed, such samples are dispatched to private laboratories in the region and to the Laboratory of Afyon Kocatepe University Veterinary Faculty, Department of Animal Nutrition and Nutritional Diseases. The records of the animals that have undergone metabolic or infectious disease during the delivery period are evaluated in a separate perspective by the farm management, animals that have been unable to conceive in spite of all the ovary synchronization and artificial insemination during the first 200 days of lactation and whose milk yield is below 10 l/day are excluded from the herd. Thus, the culling criteria used in our study establishes the same perspective.

All animals used in the study were randomly selected from among animals that had only been diagnosed with ketosis, mastitis or metritis and had not had any other illnesses, had a single live birth (delivered a single calf) in a healthy manner without aborting or difficulty and had been dispatched to the 'high yield group' for producing at least 40 l of milk per day after early lactation and were housed in this section for at least 200 days. Accordingly, 197 dairy cows were used as animal material. These animals were monitored by us from the day they delivered and their blood serum and serum BHBA analyzes were performed weekly for the first 8 weeks. Hemogram analysis was carried out with the Mindray BT2800 brand and model device in the enterprise and relevant kits available while the BHBA analyzes were also performed using the relevant kits (Randox, UK) with the Biotek brand spectrophotometric reading device available at the enterprise. All the animals in the study were divided into three groups in line with the report of Oetzel (2004) in accordance to the obtained BHBA results;

a) Control Group; those with serum BHBA levels below 1.2 mmol / l during the study

b) Subclinical Ketosis Group; serum BHBA levels ranging from 1.2 to 2.9 mmol / l

c) Clinical Ketosis Group; serum BHBA levels over 2.9 mmol / l.

Statistical Analyses

The model assumptions of normality and homogeneity of variance were examined by Shapiro-Wilk and Levene test, respectively. The statistical analysis was performed with MedCalc (MedCalc Software bvba, Oostend, Belgium, v.18). Log transformation was performed for some data group. For hematology values (continuous variable), One Way ANOVA was used for group comparison followed by Tukey-Kramer for post-hoc. Also, Pearson's chi-square test selected to determine the relationship between two variables for categorical variables (culling rates and incidences of diseases). The level of significance was determined as $p<0.05$ and values are expressed as $\bar{X} \pm SEM$ on tables.

RESULTS

According to the hemogram results examined in the study the number of Total Leukocytes (TLS), Number of Lymphocytes (LS), Number of Neutrophils (NS) and Monocyte counts were found to be higher in the animals with clinical and subclinical ketosis compared to the control group and especially TLS increased in accordance with BHBA (Table 2.). This data shows that monitoring blood hemogram parameters during the natal period can help identify metabolic functions as well as detect infectious diseases and can be used as a method to help measure blood BHBA levels in ketosis diagnosis. It is clear that both metritis and mastitis incidence significantly increased in animals exposed to subclinical and clinical ketosis compared to the animals in the control group (Table 3). However, no significant difference was detected between these two disease courses. However, the rate of culling increased significantly in animals with subclinical and clinical ketosis. As a result, the productive life expectancy of animals that have undergone ketosis during the natal period is shortened. According to the result obtained by comparing the rate of culling among the groups, this ratio was found to be much higher in the animals that had undergone subclinical and clinical ketosis than in the control group and it was observed that this ratio increased in proportion to the severity of ketosis.

Table 1. Ingredients and Chemical Composition of The Diet

Ingredients	*(% DM)*
Corn Silage	30,05
Alfalfa Hay	10,89
Corn (Fine Ground)	15,78
Barley (Cracked)	6,76
Potato	2,25
Molasses	0,75
Soybean Meal (48% CP)	6,76
Sunflower Meal (36% CP)	3,01
Corn Gluten Meal	2,63
Wheat Bran	2,25
Whole Cotton Seed	6,38
Brewers Grains (22% DM)	3,08
Sugar Beet Pulp (21% DM)	2,25
DDGS (Corn)	4,51
Premix	1,87
Sodium Bicarbonate	0,56
Magnesium Oxide	0,22
Chemical Analysis (% DM)	
Crude Protein	16,35
Lysine (%CP)	6,35
Methionine (%CP)	2,05
NeL (mEq/100 g of DM)	1,68
Fat	4,83
Starch	26,15
NFC	35,72
NDF	32,15
ADF	16,52
Ca	1,02
P	0,44
Mg	0,32
K	1,16
Cl	0,57
Na	0,52
S	0,21

Premix contained; 21,55% Calcium; 6,35% Mg; 2,57% K; 2,95% S; 1,75% Mn; 1,50 Zn; 12000 mg/kg Fe; 2700 mg/kg Cu; 250 mg/kg I; 250 mg/kg Co; 105 mg/kg Se; 275000 IU/kg Vit.A; 120000 IU/kg Vit.D and 750 IU/kg Vit.E

DISCUSSION

Although there are very limited epidemiological studies regarding ketosis there are many studies about hyperketonemia or hyperkeratosis (Duffield, 2000). The underlying reason for this is that clinical symptoms that distinguish subclinical and clinical ketosis from each other are not fully known (Andersson, 1988). The time frame that should be focused to determine hyperketonemia is the first two months after delivery. This period is the primary risk period (Baird, 1982)). Dohoo and Martin (1984a) divided this period into two and compared the first month with the second month, and reported that the peak prevalence for hyperketonemia was the 3rd and 4th weeks after delivery. There are other studies reporting this finding (Andersson and Emanuelson, 1985, Kauppinen, 1983, Simensen et al., 1990). However, there are also studies reporting hyperketonemia peaking during the first two weeks which may be considered as the early period (Duffield et al., 1997b; Duffield et al., 1998). The reason for this early peak may be that genetic advances and mishaps in the feeding management may cause severe negative energy balance in animals approaching delivery (Duffield, 2000). A number of studies (Kauppinen, 1983; Andersson, 1988; Nielen et al., 1994, Duffeild et al., 1997a) report the incidence of hyperketonemia in dairy cows within the first two months after delivery as ranging from 8.9% to 34%. Dohoo and Martin (1984a) reported that this incidence varied between 12.1% and 100%, depending on the severity of the negative energy balance and the time interval at which it was effective. In this study, the incidence of subclinical ketosis was 36.54% and the incidence of clinical ketosis was found to be 12.69%. Of course, it is natural to get different results in the studies mentioned. The range of measurements made during studies is extremely variable. For example in the study carried out by Duffield, 2000 the time interval between milk ketone tests was 30 days in 8 enterprises and 90 days in 24 enterprises. In this study, measurements were made for 8 weeks after delivery. As Duffield (2000) reported, it is very difficult to obtain a realistic hyperketonemia or subclinical ketosis prevalence, since measurement times and durations vary among studies.

Although there are many studies indicating the relationship between ketosis and many diseases, the number of diseases that indicate the association between ketosis and the periparturient period is very low (Duffield, 2000). In this study, there was a significant positive correlation between clinical and subclinical ketosis and metritis. Many studies (Suthar et al., 2013; Dohoo and Martin, 1984b; Huzzey et al., 2007; Duffield et al., 2009) conclude that there is a positive link between hyperketonemia and metritis in a manner consistent with this finding. According to Huzzey et al. (2007) the main reason for this link is the reduction in feed consumption starting at 1 or 2 weeks of delivery. In this case, the circulation of NEFA level (Duffield et al., 2009; Ospina et al., 2010; Chapinal et al., 2011) and BHBA level (LeBlanc et al., 2005; , Santos and LeBlanc, 2011), which is an important risk factor for metritis increases in the blood. Several studies report that the decrease in the levels of glucose utilization from tissues, the increase in NEFA and BHBA levels either suppress or negatively affect the immunological system in many ways (Hammon et al., 2006; Scalia et al., 2006; 2012). Furthermore, Hammon et al. (2006) reported a significant association between puerperal metrithiasis due to inadequate neutrophil function in immunosuppression induced by these or similar causes. Neutrophil function needs to work in a robust way in order to be able to protect the uterus with the local immune system which is open to external infection when the bond between mother and calf is severed and expelled after delivery. Otherwise, the uterus will become more susceptible and vulnerable to infection. Immunosuppression in the form of hyperketonemia paves the way for this.

Table 2. Effects of Ketosis on Blood Parameters

GRUPLAR	TLS	LS	NS	MS	BHBA
C	8,99±0,07^C	4,09±0,05^A	3,16±0,05^A	0,365±0,001^B	0,498±0,027^A
SK	11,01±0,21^B	3,66±0,01^B	4,66±0,02^B	0,504±0,013^A	1,971±0,045^B
CK	12,13±0,19^A	3,66±0,02^B	5,13±0,11^C	0,523±0,023^A	3,484±0,059^C
p	***<0,001***	***<0,001***	***<0,001***	***<0,001***	***<0,001***

C (Control), SK (Subclinical Ketosis), CK (Clinical Ketosis)

Table 3. Effects of Ketosis on The Incidence of Disorders

GROUPS	H	ME	MA	ME+MA
C	86 (%86,0)	10 (%10,0)	3 (%3,0)	1 (%1)
SK	47 (%65,3)	18 (%25,0)	3 (%4,2)	4 (%5,6)
CK	15 (%60,0)	6 (%24,0)	1 (%4,0)	3 (%12,0)

Pearson Ki-Kare testi p=0,013
C (Control), SK (Subclinical Ketosis), CK (Clinical Ketosis)
H (Healthy), ME (Metritis), MA (Mastitis), ME+MA (Both of Metritis and Mastitis)

Table 4. Effects of Ketosis on Culling Rate

GROUPS	NO	YES
C	88 (%88,0)	12 (%12,0)
SK	53 (%73,6)	19 (%26,4)
CK	16 (%64,0)	9 (%36,0)

Pearson Ki-Kare testi p=0,008
C (Control), SK (Subclinical Ketosis), CK (Clinical Ketosis)

Likewise a strong association between positive subclinical and clinical ketosis and mastitis was observed in this study. The other tissue that is affected in the same way as the uterus in the case of immunosuppression is udder tissue. Both local and systemic immunity need to be strong in order to protect udder tissue from infection. However, Duffield et al. (2009) and Suthar et al. (2013) did not establish a link between subclinical ketosis and mastitis. The researchers attributed the cause of this to the fact that no animal had clinical mastitis form within 15 days after delivery. In other words, since the animals were not infected or metabolically followed by the researchers, information about the days of lactation were not available. On the other hand, there are two important studies manifesting this association. According to the results of a study conducted by Grohn et al. (1989), the susceptibility of Ayrshire breed cows infected with mastitis to get ketosis is increasing. Kremer et al. (1993) reported that animals with BHBA levels above 1.4 mmol / L were more severely affected with experimental mastitis in comparison with normal animals. The main reason behind the association between mastitis and ketosis is the repressive effect of ketone bodies on white blood cells (White et al., 1968). According to Duffield (2000) negative energy balance and related subclinical ketosis have negative effects on some important immune functions. Furthermore, according to Duffield et al., (1999) the application of monensin as a

controlled release to postpartum dairy cattle reduces the risk of multiple diseases in animals. According to Duffield (2000) the positive effect of monensin on energy metabolism also helps to regulate immune functions. However, researchers have reported that more work should be done in this area to try to clarify the matter. In addition to these, there are studies that report that mastitis is not directly related to negative energy balance and associated immunosuppression and that negative environmental conditions are more effective in the formation of mastitis (Ruegg, 2003; Kahn and Line, 2010) and that immunosuppression caused by ketosis only increases the severity of the disease Drackley, 1999, Suriyasathaporn et al., 2000, LeBlanc 2010).

In this study, a strong positive correlation between the rate of culling and subclinical and clinical ketosis has been determined. The main criteria for culling in the enterprise where the study was carried out are the same as they are in many modern farms all over the world where dairy cattle breeding is carried out is chronic, persistent or recurrent diseases, old age or the end of its productive life of the animal, low milk yield, and most importantly the inability to conceive. For reasons other than natural causes such as old age, the exclusion of any animals from the herd has a significant negative impact on the economic dynamics of the enterprise. In this study, subclinical or clinical ketosis increased the rate of mastitis and metritis, two important and persistent diseases, due to the reasons described above, which led to severe fertility problems. As a result, the rate of culling was significantly increased. To examine the causes of adverse effects of hyperketonemia on reproductive efficiency; Butler et al. (1989) reported that the first ovulation after calving is delayed if the degree of negative energy balance increases in dairy cattle during the early lactation period. According to the researchers, this delay reduces the pregnancy rate in the first insemination because the impregnation success is related to the number of cycles of the ovulation cycle that takes place until the insemination (Stevenson and Call, 1983; Whirmore et al., 1974). Hyperketonemia is an indication of energy metabolism that has been impaired due to severe negative energy balance, therefore it is unavoidable that defects in energy metabolism will affect reproductive efficiency adversely (Duffield, 2000). However, it has been determined that the first postnatal insemination or postnatal insemination interval increases in herds with increased incidence of hyperketonemia (Andersson and Emanuelson, 1985). Furthermore, there is also a strong association between subclinical ketosis and ovarian cysts (Dohoo and Martin, 1984a). In hyperketonemia, milk fat is elevated, which is also observed in the case of negative energy balance (Duffield 2000). From this, Miettinen and Setala (1993) reported that the interval between birth and conception is high in dairy cows with high milk yield and milk fat. In addition, Whitaker (1993) determined that the onset of postpartum cyclic activity in cattle without energy metabolism problems within the first 14 days postpartum was shorter. All these studies show that severe negative energy balance and hyperketonemia formed in this way affects fertility efficiency in a negative way in one way or another. Increased fertility problems due to hyperketonemia determined in this study and the consequent increase in the rate of culling are compliant with the results of the studies mentioned above.

CONCLUSION

The findings obtained in this study indicate that the immune system is affected negatively in animals with clinical ketosis as well as animal with subclinical ketosis which progresses much more insidiously than the former one and that the incidence of mastitis and metritis, the most significant and most damaging diseases of the periparturient period and as a result the productive retention times of these animals in the herd is seriously shortened. Therefore, this developing tableau leads to more profound economic challenges in countries like Turkey where the number of breeding dairy cattle is not sufficient and which are obliged to import live animals continuously from abroad. Taking all this into consideration, it will be beneficial for both the farm and the country economy to support the breeding dairy cattle metabolically before and after birth, to ensure that they deliver with a robust and strong liver performance and that they are protect from the negative effects of negative energy balance after delivery.

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