EFFECTS OF DAYLIGHT AND SEASONAL FACTORS ON SERUM AND MILK IGF-1 LEVELS IN HOLSTEIN DAIRY COWS AT DIFFERENT LACTATION PERIODS

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ABSTRACT

The research was carried out on 34 Holstein dairy cows in their first lactation period, which were determined to be healthy by general examination in a commercial dairy farm with 800 heads of Holstein and Simmental but predominantly Holstein dairy cows. These animals were fed the same ration and housed in the same environment during the experiment. These 34 Holstein pregnant heifers that will give calve for the first time were followed up and their development was monitored, blood samples were taken from the v. jugularis before the morning feeding on the 15th, 35th and 45th days following the calving, blood plasma and milk IGF-1 levels were determined by Enzyme Linked Immunoassay method and morning-evening change and seasonal changes were determined.

According to the data obtained, the lowest plasma IGF-1 levels were determined in the samples on the 45th day in all periods; In addition, it was found that plasma IGF-1 values

increased periodically in three different seasonal transition periods. It was observed that plasma IGF-1 levels showed the highest value (94.46 ng/ml) on the postnatal 35th day, and the lowest value (79.37 ng/ml) was obtained on the 45th day, with a difference at P<0.001 significance level. Plasma IGF-1 levels in morning samples were higher (P<0.01) compared to evening samples.

Milk IGF-1 values in milk samples sampled on the 15th and 45th days reached the highest value in March (P<0.01); there was a decrease (51.61 ng/ml; 47.13 ng/ml) on the 45th day compared to the 15th day. Periodic increases (P<0.01) were observed in milk IGF-1 levels, like plasma ratios.

Keywords: Blood and milk, IGF-1, dairy cow, lactation, seasonal variations

Introduction

Insulin Like Growth Factor-I (IGF-1) is part of the IGF system and has a 70 amino acid polypeptide chain bounded with disulphide bridges, like to insulin. The IGF system consists of IGF-1, II and IGF binding receptors (IGFBR1-6) and perform their biological effects systematically [17,55]. In live organisms 99% of IGF-1 has been founded as bound to IGFBs, less than 1 % of IGF-1 circulates freely unbound to IGFBPs [8,28,35].

The role of the IGF system in dairy cows is explained by more information from rats, and the species-specific mechanisms are not yet well understood. The role of somatropin in the local release of IGF-1 in the mammary glands and the interactions between IGF-1 and II, the cellular and molecular mechanisms of the regulatory effects of the IGFBPs on IGF bioactivity have been among the topics of research in recent years in ruminants [9,18].

IGF-1 is not a species-specific hormone, and can be synthesized by all tissues, mainly the liver in many animal organisms, it is responsible for many physiological processes such as somatic cell growth, development, tissue regeneration, reproductive system, embryonic development, and lactation [15].

In pregnancy process and postpartum periods IGF-1 plays a critical action on foetal growth, mammary gland development including cell proliferation and control cell survival contributes to the number of milk-secreting cells in mammary gland and postpartum uterus involution through both endocrine and paracrine/autocrine mechanisms. IGF-1 is thus known as a mitogenic hormone but also has an anti-apoptotic effect [7,9]. The mammary gland is controlled by several hormones and tissue factors. The main factor that stimulates milk synthesis in the breast glands from the stage of postnatal galactopoiesis is growth hormone, as shown by Bauman et al. (1985) with parenteral administration of GH.

The somatotropic axis between the receptors of GH, IGF-1, and IGFBPs is the main mechanism that controls milk synthesis in the mammary glands, and the high milk yield potential in Holstein milk cows can be attributed to the genetically different hormonal regulation of these species [21].

In the periparturient period and at the time of insemination, the plasma IGF-1 concentration has been described as a useful indicator for reproductive performance in dairy cattle [58]. At the first week after calving if a cow had plasma IGF-1 of <40 ng/mL, she was less likely to conceive after first service [2,5]. Then, a low concentration of plasma IGF-1 in the postpartum period was also related to the length of the interval from calving to resumption of cyclicity [10].

The concentration of IGF-1 in cow milk depends on the stage of lactation, milk composition, and other environmental factors such as ambient temperature, humidity, season, photoperiod in a day and varies widely from approximately 1 ng/ml to 150 ng/ml [33]. Thus, the highest concentrations of IGF-1 occur immediately after postpartum in colostrum and then gradually decrease until it falls to the level of 1 to 5 ng/ml [6,46]. Studies have established that IGF-1 has been found in the milk of many animal species as a complex molecule or bound to milk proteins named as whey or casein [37]. Milk IGF-1 is likely absorbed intact in a bioactive form by the intestines. It was detected that some dietary factor especially protease inhibitors, such as soybean trypsin inhibitor and egg white protease inhibitor prevented IGF-1 degradation in the gastrointestinal tract, but the whey supernatant fraction represented more effective inhibition [30]. These results suggested that the whey fraction might contain specific inhibitors that protect IGF-1 from the proteolytic degradation in the gastrointestinal conditions. Therefore, the whey supernatant fraction in goat milk could be a potential resource for the development of the effective oral IGF-1-based products [62].

Several studies have been conducted to investigate the relationship between blood levels of IGF-1 and environmental factors. Spicer et al. (1994) determined that IGF-1 levels increased due to increased sunlight in dispersed heifers. Dahl et al. (1997) found that the galactopoietic effect of IGF was more pronounced in goats and reptiles during prolonged days, while in lactating cows the rate of transmitted IGF-1 to the mammary gland increased due to high plasma IGF-1 concentration during prolonged days. Moyes et al. (2003) found that when animals have a negative energy balance in the postnatal period, plasma IGF-1 levels decrease immediately.

It was shown that during pregnancy maternal milk intake has positive effects on either maternal or foetal serum IGF-1 concentrations [38,57] and is positively associated with increased neonatal body weight gain and birthweight in healthy [4]. In children, milk consumption also increases serum IGF-1 concentrations and body size [23,63].

In the other hand IGF-1 in milk and dairy products may be one of the etiopathogenetic factors in the development of cancer [29,39,59]. It has been established that high IGF-1 levels in milk contribute to the growth of colon cancer cell in humans as shown by Purup et al (2007). The role of IGF-1 on cancer-genesis may be attributed to its anti-apoptotic effects on pathological cell development [7,9].

Despite the implications of insulin-IGF axis in carcinogenesis, mechanism of how insulin and IGF-1 interact to promote tumour formation exactly and how this process may be regulated by lifestyle changes remains unclear [44]. Research is needed to better understand modifiable determinants of circulating IGF-1, with dietary intake being a plausible candidate for modifying IGF-1 concentrations.

The study aimed to determine the changes in blood and milk IGF-1 levels in first calving Holstein's cows on different sampling days (15, 35, 45), hours (morning-afternoon) and months (February, March, and April).

Materials and Methods

The experimental protocol was approved by the Animals Ethical Committee of Selcuk University and complied with Animal Experimentation (protocol number 2020/40).

The experiment was conducted at the commercial dairy farm included approximately 800 dairy cows in Ankara, Türkiye. Thirty-four healthy Holstein pregnant heifers were

assigned for the study, and these animals were free from infectious and invasive diseases. Heifers received diets as total mixed ration to allow ad libitum feed intake throughout the experiment. Diet was formulated to exceed the NRC (2001) requirements. The feed was offered in two equal portions at 07^{00} and 17^{00} h, and heifers had free access to water. After calving, cows were switched to an early-lactation diet to meet the energy-calorie demands for high milk production.

Blood and Milk Sampling Procedures

Samples of blood and milk were taken in period of February, March, April, and May.

Blood samples were taken from v. jugularis on days 15^{th}, 35^{th} and 45^{th} into vacuum tubes including EDTA after calving, two times a day as before feeding in the morning and before milking in the evening. Plasma obtained after centrifugation (3,000 × g for 15 min, 4 °C) of blood samples were stored -80 ^{0}C until analyses.

The milk samples were manually obtained from a specific breast lobe on the right of all animals on the 15^{th} and 45^{th} days after calving, in three daily periods as morning, afternoon and evening milking and transferred into sterile cups, and then transferred again to -80 ^{0}C until the period of analysis.

Sampling and Analysis

The blood plasma IGF-1 level was determined at the laboratory of the Department of Veterinary Biochemistry, University of Selcuk by enzyme-linked immunosorbent assay using test kits (www.bt-laboratory.com; E0016Bo) and Biotech EL800 plate reader (Agilent Technologies, USA). When setting up the methodology, requirements specified by the test system manufacturer were followed, and all samples were analysed in duplicates.

The milk samples were skimmed by centrifugation at 10000 rpm for 20 min at 4°C and these skimmed samples were diluted twice with distilled water, fraction of casein was removed by bringing the pH to 4.6 using 2 N HCl. Milk serum samples for subsequent studies were centrifuged at 1500 rpm for 15 min.

IGF determination of milk serum was performed by EIA method described as for blood serum IGF-1 analysis above.

Statistical Analysis

The statistically significant differences of means between the groups and sampling periods were evaluated by the paired t- test and general linear model; p values less than 0.05 were considered as statistically significant. Significance levels of between the all data were determined by Tukey-test (SPSS 22 software).

Results

The plasma IGF-1 values, morning-afternoon changes, and seasonal variations (February to May) of samples obtained on the 15^{th}, 35^{th} and 45^{th} days are presented in table 1, milk IGF-1 results were shown in table 2, ambient temperature averages were shown in table 3.

Table 1. Plasma IGF-1 means and statistical significance levels for sampling points in the study.

Plasma IGF-1 (ng/ml)	n	**Day of 15**	**Day of 35**	**Day of 45**	**Significance**
Time		X ± Sx	X ± Sx	X ± Sx	
Morning	34	86,37±2,50 **A**	96,77±2,38 **A**	82,46±2,27**A**	
Evening	34	82,39±2,35**B**	92,15±2,10 **B**	76,29±2,25**B**	
Significance		**P<0.01**	**P<0.01**	**P<0.01**	
Total	**68**	**84.38±1,72 b**	**94,46±1,60 a**	**79,37±1,63 c**	(P<0.001)
Season					
February-March					
Morning	5	75,44±4,19**A**	102,34±3,13**A**	87,91±2,08**A**	
Evening	5	75,22±3,65**A**	98,32±1,45**A**	71,75±2,97**B**	
Significance		P>0.05	P>0.05	P<0.05	
Total	**10**	**75,33±2,62 b**	**100,33±1,76 a**	**79,83±3,19 b**	(P<0.001)
March-April					
Morning	23	83,35±2,40**A**	91,04±2,06**A**	79,47±3,06**A**	
Evening	23	77,91±1,85**B**	86,49±1,88**B**	72,47±2,31**B**	
Significance		P<0.001	P<0.01	P<0.01	
Total	**46**	**80,63±1,55 b**	**88,76±1,42 a**	**75,97±1,76 c**	(P<0.001)
April-May					
Morning	6	107,04±3,56**A**	114,09±6,59**A**	89,40±3,28**A**	
Evening	6	105,55±3,04**A**	108,69±4,21**A**	94,70±3,23**A**	
Significance		P>0.05	P>0.05	P>0.05	
Total	**12**	**106,29±2,24 a**	**111,39±3,81 a**	**92,05±2,34 b**	(P<0.001)

abc, Statistical differences in same lines are significant (P<0.001); AB Statistical differences in same row are significant; P>0.05; P<0.01; P<0.001).

Table 2. Milk IGF-1 means and statistical significance level.

Milk IGF-1 (ng/ml)	**February (n:5)**	**March (n:23)**	**April(n:6)**
	X ± Sx	X ± Sx	X ± Sx
	41,70± 3,94 **b**	49,37±1,84 **b**	62,82±3,60 **a**
Day of 15	43,78±2,98	**A** 51,61±1,87	62,17±3,00
Day of 45	39,62±2,00	**B** 47,13±2,36	63,48±3,07
Significance	P>0.05	P<0.01	P>0.05

a,b; Statistical differences in same lines are significant (P<0.01); AB Statistical differences in same are significant.

Table 3. Environmental temperature means and statistical difference.

Temperature (°C)	n	**Day of 15**	**Day of 35**	**Day of 45**
Time		**X ± Sx**	**X ± Sx**	**X ± Sx**
Morning	34	**C** 4,04±0,37	**C** 7,34±0,35	**B** 9,22±0,32
Afternoon	34	**A** 10,04±0,45	**B** 13,61±0,41	**A** 15,82±0,44
Evening	34	**B** 4,59±0,37	**A** 7,82±0,32	**B** 9,42±0,32

A, B, C; Statistical differences in the same row are significant (P<0.001)

Figure 1, where changes were observed by time (morning, evening) and sampling months (periods of February-March, March-April, April-May), showed that the highest level of plasma IGF-1 levels (94.46 ng/ml) in the 35th day after calving, while the lowest level (79.37 ng/mL) was observed on the 45th day, with a difference in P<0.001 significance. In all sampling days (15th, 35th and 45th) Plasma IGF-1 levels of morning samples were higher (P<0.01) compared to evening samples.

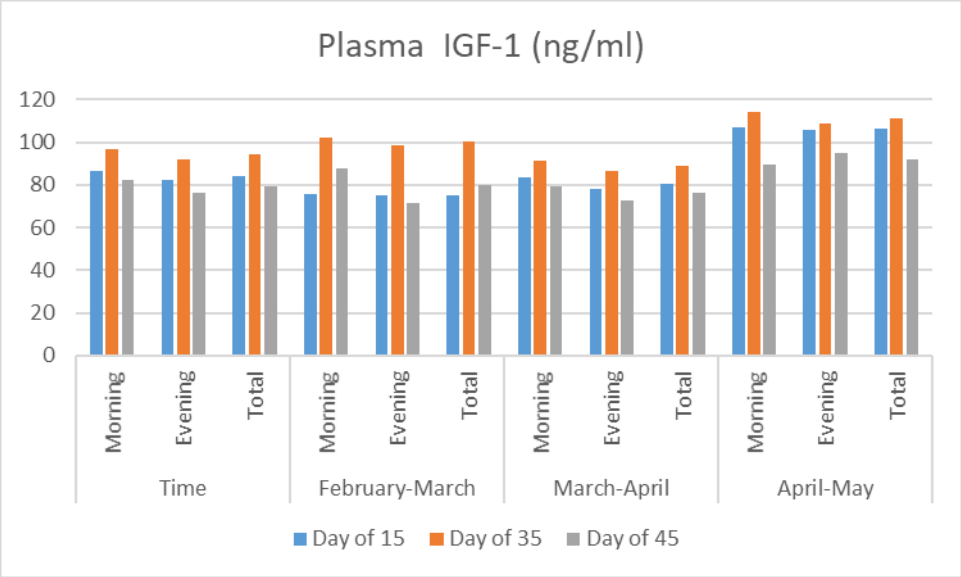

Figure 1. Plasma IGF-1 levels on several sampling points.

The sampling during the experiment covered the months of February-March-April, so the effects of daylight time differences were assessed, and the highest averages were observed in April and on the 35th day of the period, when longer daylight was obtained than others. There was no difference between the samples taken in the morning and in the evening.

When milk IGF-1 values were examined (Figure 2), increasing averages were obtained over the months ($P<0.01$); in milk samples sampled on the 15th and 45th days, milk IGF-1 values peaked in March ($P <0.01$), and decreased by day 15 on the 45th day (51.61 ng/ml versus 47.13 ng/ml).

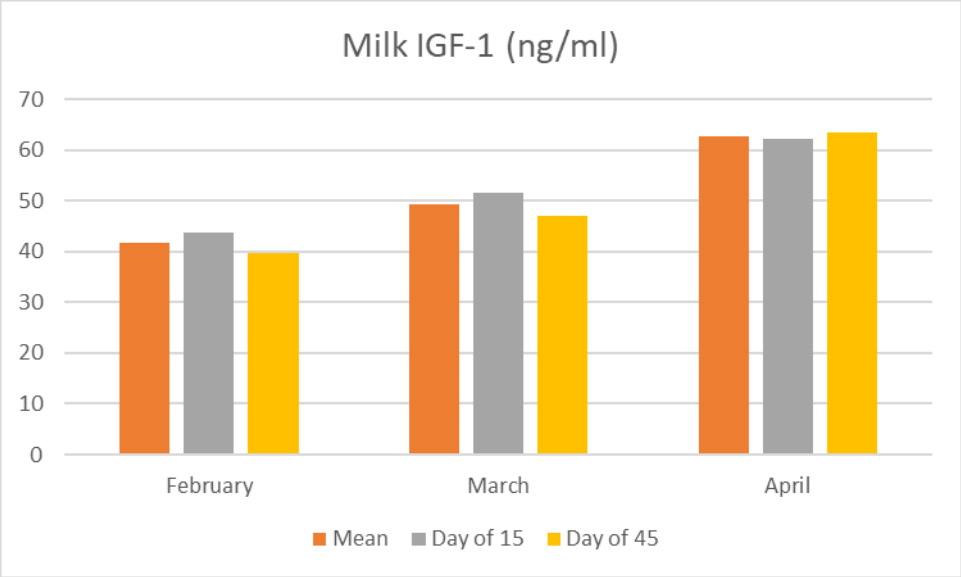

Figure 2. Milk IGF-1 variations on sampling period.

The milk yield values are shown in Figure 2; the total yield was highest on the 45th day after calving (31.2 l) and the highest average yield of milk on all sampling days (15, 35, 45) was observed from morning milking.

Discussion

Growth and development are physiological processes that occurs under the influence of many neuroendocrine hormones such as insulin, growth hormone, IGF-1, thyroid hormones, glucocorticoids, and catecholamines, functionated with the hypothalamus-hypophysis axis [47]. The feeding regimen is known to regulate the GH/IGF-1 ratio specifically on this axis [48,60]. Like its effect on all tissues of live organisms, the development of the mammary gland, especially in milk cows, is sustained by the effect of IGF-1 controlled GH [42].

Indeed, environmental factors such as light, temperature, and humidity also affect the secretion of GH through the mechanisms of the neuroendocrine and the release of IGF-1 in response to this, so IGF-1 is considered a good indicator especially in metabolic progress for milking cows [34,64]. For sustainable levels of plasma IGF-1 levels during pregnancy and lactation, especially at low energy intake, increased blood-binding protein protease activity has been, thereby achieving free-active concentrations of IGF-1 [59]. In cases where increased milk yields caused a metabolic risk, with increased esterified fatty acids (NEFA) in the blood, decreased levels of insulin and IGF-1 are a good indicator [16,22,31]. The present study confirms that the lowest total plasma levels were achieved in the 45th day samples, both in the month and in the morning and evening sampling periods, while the highest average yield of milk was at 45 days reinforcing this relationship.

The seasonal changes in IGF-1 concentrations found in ruminants are mainly driven by photoperiod [12]. In a study in deer (Cervus elaphus), the implantation of melatonin, which has a short-day effect, has suppressed the release of IGF-1 [52]. Another study in cattle found that cattle in the group that were exposed to 16 hours of daily light for 4 months had significantly higher levels of IGF-1 than those in the groups that were illuminated for 8 hours a day [49]. Squires (2003) argues that short-term stress in nonrodent organisms reduces the release of IGF-1, while causing the energy to be shifted more from growth to life-power function.

A study in Saanen cats found that increased photoperiod increases levels of IGF-1 during lactation [32]. In a study in adult male goats, long photoperiod was found to be more effective in increasing plasma levels of IGF-1 in short photoperiod [25].

Comparing the effects of photoperiod and temperature on IGF-1 concentrations in goats, it has been found that the effect of photoperiod is more predominant in relation to the temperature factor, and that the influence of the thermal factor on IGF-1 can be shown more at temperature stress levels [53]. In fact, a study conducted by Hamzaoui et al. (2013) in dairy goats a decrease in IGF-1 levels due to increased temperature stress during lactation.

In dairy cattle, short daylight has been shown to stimulate mammary gland development during the dry period and long daylight in the prenatal process and in lactation [11,56]. The increase in mammary development during the short photoperiod during the dry period is mainly caused by the stimulation of the prolactin hormone, an increase in the synthesis level of IGF-1, and the approaching of the prenatal period in animals, along with the increased IGF-1 level known as the galactopoietic effect of the long day administration, which is known to stimulate the increase in milk synthetics in the developed mammary gland [56]. In fact, in the other study by Dahl et al. (2000) showed that seasonal changes in IGF-1 concentrations were to be driven mainly by photoperiod, and that increased IGF-1 levels during long daylight periods decreased during short day time periods.

In a limited number of studies aimed at determining the effects of temperature and humidity factor on IGF-1 levels in mammals, it has been that there is a negative correlation between ambient temperature and IGF-1 levels, and that during the summer period, IGF-1 levels decrease, while during the period of increasing temperature and day length, IGP-1 levels increase [1,45] and that these increases are due to the effect of long days. Our study suggests that the high IGF-1 values obtained in the April-May period, may have been achieved due to normal ambient temperature and especially long daylight. During three

separate seasonal transitional periods (February-March, March-April, April-May), plasma IGF-1 values have been observed to increase periodically.

In summer, plasma concentrations of insulin, IGF-1 and glucose are lower than in winter. This decline is probably due to decreased feed intake and increased negative energy balance [13,26]. Insulin has a positive effect on the development of the follicles and the quality of the oocytes, and insulin is needed to shape these events. IGF-1 and glucose are essential stimulating factors for follicular development and embryonic implantation [14].

Periodic increases ($P<0.01$) per month were also observed in milk IGF-1 levels like to plasma rates (Figure 2). The differences between the 15th and 45th days were not homogeneous. In a study in pregnant milk cows exposed to high ambient temperatures during pregnancy [29], calves born these animals had the lowest plasma levels of IGF-1, and it has been explained that IGF-1 levels could be influenced by environmental factors even in the intrauterine period.

Again, IGF-1 in cow's milk is protected from the environmental pH or digestive enzymes during human digestion by cows' milk proteins and thus absorbed [28,43]. Studies have shown that IGF-1 in milk is dependent on a complex molecule or protein, which is biologically absorbed by the small intestine in this form.

The levels of IGF-1 contained in cow's and goat's milk, as well as in their composition, are also different, with significantly higher levels in goat milk and colostrum, compared to cow milk [24]. While the IGF-1 contained in goat milk is largely destroyed during pasteurization processes, the cow's milk IGF-1 is not damaged in any way [37].

Whey protein in milk has been found to inhibit the hydrolysis of IGF-1 against enzymes more than the casein fraction and to keep it stable at stomach pH (1-2). In the whey fraction, there are components that can reduce the activity of pepsin and trypsin in simulated digestive conditions and effectively prevent IGF-1 degradation, and these should be detected by further research [62].

Studies in recent years [39,54] indicate that cancer development is accelerated in conditions of high levels of exposure to IGF-1 in different living species, which is due to changes in hormonal imbalances and the continuous influence of high IGF-1, which leads to uncontrolled progress of cell growth.

While low IGF-1 in early pregnancy eliminates the several risks gained by gestation, it has been argued that rising levels of IGF-1 are responsible for preeclampsia, gestational diabetes, hypertension, and breast cancer risks that may develop in later pregnancies. High IGF-1 applications prevent the entry of lacto-albumin into the breast glands, and in conjunction with this, differentiation in the mammal glands progresses towards the development of cancer cells [54].

While it is known to have protective effects against neurodegenerative diseases such as Alzheimer's, dementia, Parkinson's [27], high levels of IGF-1 have been linked to acromegaly, including prostate, premenopausal breast, and colorectal cancers, and shortened life expectancy [7,19,51]. However, studies showing that IGF-1 supports the development of cancer are derived from rodents and cell culture studies, and it is not yet fully clear whether it has the same effect in humans [27].

When the data from the study were examined generally, it was found that the levels of post-lactation blood and milk IGF-1 in dairy cows could vary in relation to the interactions of temperature and daylight. These obtained data are especially important for the management and follow-up of productive and interventional factors affected by changes in IGF-1 levels in the blood, such as pregnancy, embryo development, mammary gland changes, insemination and embryo transfer. The levels of IGF-1, which can be detected in milk, have been found to vary in terms of plasma levels in general. The expected results for plasma and milk IGF-1 concentrations, which would contribute to limited data in this area, could be supported by pre-pregnancy data, as well as by ongoing studies in longer post-lactation periods. Changes in milk IGF-1 concentration, which are thought to occur due to environmental factors, may be important in explaining the neoplastic developments associated with IGF-1 in milk, which have become prominent in recent years and in clarifying the studies to be carried out in this field.

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References

1.Aggarwal A, Upadhyay R: Heat Stress and Animal Productivity. Springer 2013, 79-2-3.

2.Aungier SPM, Roche JF, Diskin M.G, Crowe MA: Risk factors that affect reproductive target achievement in fertile dairy cows. J. Dairy Sci 2014, 97. 3472-3487.

3.Bauman DE, Eppard PJ, DeGeeter MJ, Lanza GM: Responses of high-producing dairy cows to long-term treatment with pituitary somatotropin and recombinant somatotropin. J. Dairy Sci 1985, 68:1352–1362.

4.Brantsæter LA, Olafsdottir AS, Forsum E, Olsen SF, Thorsdottir I: Does milk and dairy consumption during pregnancy influence foetal growth and infant birthweight? A systematic literature reviews. Journal Food & Nutrition Research 2012, 56 (1).

5.Butler WR: Nutritional interactions with reproductive performance in dairy cattle. Anim. Reprod. Sci 2000, 60–61, 449-457.

6.Castigliego L, Li X, Armani A, Mazzi M, Guidi A: An immune-enzymatic assay to measure insulin-like growth factor 1 (IGF-1) in buffalo milk with an IGF binding protein blocking pre-treatment of the sample, International Dairy Journal 2011, 21, 421-6.

7.Clatici VG, Voicu C, Voaides C, Roseanu A, Icriverzi M, Jurcoane S: Diseases of Civilization–Cancer, Diabetes, Obesity and Acne the Implication of Milk, IGF-1 and mTORC1. Mædica 2018, 13(4), 273-281.

8.Clemmons DR: IGF binding proteins, and their functions. Molecular Reproduction and Development 1993, 35, 368 –375.

9.Cohick WS: The role of the IGF system in mammary physiology of ruminants. Domestic Animal Endocrinology 2022, 79, 1-8.

10.Crowe MA, Diskin MG, Williams EJ: Parturition to resumption of ovarian cyclicity: Comparative aspects of beef and dairy cows. Animal 8 (Suppl. s1) 2014, 40-53

11.Dahl GE, Elsasser TH, Capuco AV, Erdman RA, Peters RR: Effects of long day photoperiod on milk yield and circulating insulin-like growth factor-1. J Dairy Sci 1997, 80: 2784–2789.

12.Dahl GE, Buchanan BA, Tucker HA: Photoperiodic effects on dairy cattle: A review. J. Dairy Sci 2000, 83: 885–893.

13.De Rensis F, Marconi P, Capelli T, Gatti F, Facciolongo F, Franzini S: Fertility in postpartum dairy cows in winter or summer following oestrous synchronization and fixed time AI after the induction of an LH surge with GnRH or hCG. Theriogenology 2002, 58(9):1675–1687.

14.De Rensis F, Scaramuzzi RJ: Heat stress and seasonal effects on reproduction in the dairy cow-a review. Theriogenology 2003, 60:1139–1151.

15.Drogan D, Schulze MB, Boeing H, Pischon T: Insulin-Like Growth Factor 1 and Insulin-Like Growth Factor Binding Protein 3 in Relation to the Risk of Type 2 Diabetes Mellitus: Results From the EPIC-Potsdam Study. Am J Epidemiol 2016, 183(6):553-60.

16.Dutta LJ, Nath KC, Deka BC, Bhuyan D, Borah P, Saikia GK, Bharali CAD: Therapeutic management of true anoestrous crossbred cows through nutritional and hormonal intervention. J Entomol Zool Stud 2019, 7, 9-12.

17.Forbes B, McCarthy P, Norton R: Insulin-like growth factor binding proteins: a structural perspective, Frontiers in endocrinology 2012, 3, 38.

18. Gross JJ. Dairy cow physiology and production limits. Animal Frontiers 2023, 13(3): 44-50.

19.Guo, JY, Zhang YQ, Li Y, Li H: Comparison of the difference in serum insulin growth factor-1 levels between chronological age and bone age among children. Clinical Biochemistry 2021, 96, 63–70.

20.Hamzaoui S, Salama KAA, Albanell E, Such X, Caja G: Physiological responses and lactational performances of late-lactation dairy goats under heat stress conditions. J Dairy Sci 2013, 96: 6355–6365.

21.Hart IC. Bines JA, Morant SV, Ridley JL: Endocrine control of energy metabolism in the cow: comparison of the levels of hormones (prolactin, growth hormone, insulin, and thyroxine) and metabolites in the plasma of high- and low-yielding cattle at various stages of lactation. J. Endocrinol 1978, 77:333–345

22.Hayırlı A, Çolak A: İneklerin kuru ve geçiş dönemlerinde sevk-idare ve besleme stratejileri: postpartum süreçte metabolik profil, sağlık durumu ve fertiliteye etkisi. Turkiye Klinikleri J Vet Sci 2011, 2, 1-35.

23.Hoppe C, Udam TR, Lauritzen L, Mølgaard C, Juul A, Michaelsen KF: Animal protein intake, serum insulin-like growth factor I, and growth in healthy 2.5- y-old Danish children. American Journal of Clinical Nutrition 2004, 80, 447–452

24.Hou YL, Zhang FX, Li LZ, Yu LL, Dan Y, Lei FY: Variations of insulin-like growth factor I (IGF-1) in goat milk. Jiangsu Agricultural Sciences 2016, 32(4),843–847.

25.Jin J, Sawai K, Hashizume T: Effects of photoperiod on secretory patterns of growth hormone in adult male goats. Animal Science Journal 2013, 84: 790–797.

26.Jolly PD, McDougall S, Fitzpatrick LA, Macmillan KL, Entwhitsle K: Physiological effect of under nutrition on postpartum anoestrous in cows. Journal of Reproduction and Fertility. Supplement 1995, 49:477–492.

27.Kirovski D, Kneževıć D, Golıć B, Kasagıć D, Jovanovıć L, Bošnjakovıć D, Trıfkovıć J, Sladojevıć Z: Cow Mılk Insulın Lıke Growth Factor-1: Rısk Or Benefıt for Human Health? Proceedings of the XII International Scientific Agricultural Symposium “Agrosym” 2021, 1196.

28.Kirovski D, Lazarević M, Baričević-Jones Ivona, Nedić O, Masnikosa R, Nikolić Judith A: Effects of peroral insulin and glucose on circulating Insulin-like growth factor-I, its binding

proteins and thyroid hormones in neonatal calves, Canadian Journal of Veterinary Research 2008, 72:253-288.

29.Laporta J. Fabris TF, Skibiel AL, Powell JL, Hayen M.J, Horvath K, Miller-Cushon EK, Dahl GE: In utero exposure to heat stress during late gestation has prolonged effects on the activity patterns and growth of dairy calves J. Dairy Sci 2017, 100:2976–2984.

30.Ma J, Giovannucci E, Pollak M, Chan JM, Gaziano JM, Willett W: Stampfer MJ: Milk intake, circulating levels of insulin-like growth factor-I, and risk of colorectal cancer in men. J. Natl. Cancer Inst 2011, 93(17): 1330-1336.

31. Ma J, Kok A, Burgers EEA, Bruckmaier RM, Goselink RMA, Gross JJ, Kemp B, Lam TJGM, Minuti A, Saccenti E, Trevisi E, Vossebeld F, and. van Knegsel ATM: Time profiles of energy balance in dairy cows in association with metabolic status, inflammatory status, and disease J. Dairy Sci. 2024, 107, 9960–9977

32.Mabjeesh SJ, Gal-Garber O, Shamay A: Effect of Photoperiod in the Third Trimester of Gestation on Milk Production and Circulating Hormones in Dairy Goats. J Dairy Sci 2007, 90: 699–705.

33.Malekinejad H, Rezabakhsh A: Hormones in dairy foods and their impact on public health-a narrative review article. Iranian journal of public health 2015, 44(6):742.

34.Mejia-Naranjo W, Yakar S, Bernal R, LeRoith D, Sanchez-Gomez M: Regulation of the splenic somatotropic axis by dietary protein and insulin-like growth factor-I in the rat. Growth Hormone and IGF Research 2003, 13(5):254-263.

35.Melnik B: Milk consumption: aggravating factor of acne and promoter of chronic diseases of Western societies, JDDG: Journal der Deutschen Dermatologischen Gesellschaft 2009, 7(4):364-370.

36.Moyes TE, Stockdale CR, Humphyrs S, Macmillan KL: Differences in plasma concentration of insulin-like growth factor-1 between pregnant and nonpregnant dairy cows. Reproduction, Fertility and Development 2003, 15: 22.

37.Ollikainen P, Muuronen K: Determination of insulin-like growth factor-1 and bovine insulin in raw milk and its casein and whey fractions after microfiltration and ultrafiltration. International Dairy Journal 2013, 28(2):83–87.

38.Olsen SF, Halldorsson TI, Willett WC, Knudsen V, Gillman MW, Mikkelsen TB, Olsen J, Consortium N: Milk consumption during pregnancy is associated with increased infant size at birth: Prospective cohort study. American Journal of Clinical Nutrition 2007, 86:1104–1110.

39.Piñeyrúa JTM, Fariña SR, Mendoza A: Effects of parity on productive, reproductive, metabolic and hormonal responses of Holstein cows. Animal Reproduction Science 2018, 191: 9–21.

40.Purup S, Vestergaard M, Pedersen L, Sejrsen K: Biological activity of bovine milk on proliferation of human intestinal cells. J. Dairy Res 2007, 74(1): 58-65.

41.Qin L, He K, Xu J: Milk consumption and circulating insulin-like growth factor-I level: A systematic literature review. Int. J. Food Sci. Nutr 2009, 60(7): 330-340.

42.Rasouli S, Abdolmohammadi A, Zebarjadi A, Mostafaei A: Evaluation of polymorphism in IGF-1 and IGFBP-3 gEnEs and their relationship with twinning rate and growth traits in markhoz goats. Ann. Anim. Sci 2017, 17:89-103

43.Remaggi G, Saleri R, Andrani M, Satolli F, Rodighiero E, Elviri L: Development and single laboratory validation of a targeted liquid chromatography-triple quadrupole mass spectrometry-based method for the determination of insulin like growth factor-1 in different types of milk samples. Food Chemistry 2022, X, 13.

44.Renehan AG, Frystyk J, Flyvbjerg A: Obesity and cancer risk: the role of the insulin–IGF axis. Trends Endocrinol Metab. 2006, 17: 328-36.

45.Richards MW, Spicer LJ, Wettemann RP: Influence of diet and ambient temperature on bovine serum insulin-like growth factor-I and thyroxine: relationships with non-esterified fatty acids, glucose, insulin, luteinizing hormone and progesterone. Animal Reproduction Science 1995, 37: 267- 279.

46.Šamanc H, Stojić V, Kirovski Danijela, Pušić M, Jakić-Dimić Dobrila, Vujanac I: Insulin-like growth factor-I (IGF-1) and thyroid hormone concentrations in colostrum of Holstein-Friesian cows before and after calving, Acta Veterinaria Beograd 2009, 59, 17-23.

47.Serpek B, Haliloğlu S: Development of an Enzyme Immunoassay for the Determination of Ovine Growth Hormone in Plasma. Turkish Journal of Veterinary & Animal Sciences 2000, 24(2): Article 11.

48.Sferruzzi-Perri AN, Owens JA, Pringle KG, Roberts CT: The neglected role of insulin-like growth factors in the maternal circulation regulating foetal growth. J Physiol 2011, 589:7-20.

49.Spicer LJ, Buchanan BA, Chapin LT, Tucker HA: Effect of 4 months of exposure to various durations of light on serum insulin-like growth factor-1 (IGF-1) in prepubertal Holstein heifers. J. Anim. Sci 1994, 72(1): 178.

50.Squires EJ: Applied animal endocrinology. CABI Publishing, ISBN: 0-85199-594-2, USA. 2003, 234.

51.Sutariya S, Sunkesula V, Kumar R, Shah K: Milk and Milk Products, Insulin-like Growth Factor-1 and Cancer. EC Nutrition 2018, 11, 696–705.

52.Suttie JM, Breier BH, Gluckman PD, Littlejohn RP, Webster JR: Effects of melatonin implants on insulin like growth factor 1 in male red deer (Cervus elaphus). Gen Comp Endocrinol 1992, 87:111–119.

53.Terzi NM, Pehlivan E, Dellal G: Akkeçilerde İnsülin Benzeri Büyüme Faktörü-I'in (IGF-1) Laktasyon Dönemindeki Değişimi. Journal of the Institute of Science and Technology 2019, 9(2):1193-1200.

54.Thordarson G, Slusher N, Leong H, Ochoa D, Rajkumar L, Guzman R, Nandi S Talamantes F: Insulin-like growth factor (IGF)-I obliterates the pregnancy-associated protection against mammary carcinogenesis in rats: evidence that IGF-1 enhances cancer progression through oestrogen receptor-α activation via the mitogen-activated protein kinase pathway. Breast Cancer Research 2004, 6(4), R423-436.

55.Thornton KJ, Kamange-Sollo E, White ME, Dayton WR: Active G protein-coupled receptors (GPCR), matrix metalloproteinases 2/9 (MMP2/9), hepa- rin-binding epidermal growth factor (hbEGF), epidermal growth factor receptor (EGFR), erbB2, and insulin-like growth factor 1 receptor (IGF-1R) are necessary for trenbolone ace- tate-induced alterations in protein turnover rate of fused bovine satellite cell cultures. J Anim. Sci 2016, 94(6): 2332-2343.

56.Wall HE, Auchtung LT, Dhal EG, Ellis ES, McFadden BT: Exposure to Short Day Photoperiod During the Dry Period Enhances Mammary Growth in Dairy Cows. Journal of Dairy Science 2005, 88(6): 1994-2003.

57.Wiley AS, Lubree HG, Joshi SM, Bhat DS, Ramdas LV, Rao AS,Thuse NV, Deshpande VU, Yajnik CS: Cord IGF-1 concentrations in Indian newborns: Associations with neonatal body composition and maternal determinants. Paediatric Obesity 2016, 11(2), 151–157.

58.Wiltbank M, Lopez H, Sartori R, Sangsritavong S, Gumen A: Changes in reproductive physiology of lactating dairy cows due to elevated steroid metabolism. Theriogenology 2006, 65:17–29.

59.Yalçın T, Besler HT: Plasental Hormonların Maternal Metabolizma ve Fetal Büyüme Üzerine Etkisi. Bes Diy Derg 2014, 42 (3):242-251.

60.Yang MY, Fortune JE: Changes in the transcriptome of bovine ovarian corte during follicle activation in vitro. Am J Physiol Heart Circ Physiol 2015, 47, 600-612.

61.Yu H, Rohan T: Role of the insulin-like growth factor family in cancer development and progression. J Natl Cancer Inst 2000, 92(18):1472-89.

62.Zhang F, Xu L, Chen S, Wang B, Shao Y, Zhao A, Han X: Effects of goat milk fractions on the stability of IGF-1 in simulated gastrointestinal conditions. LWT-Food Science and Technology 2018, 91:229–234.

63.Zhu K, Du X, Cowell CT, Greenfield H, Blades B, Dobbins TA, Zhang Q, Fraser DR: Effects of school milk intervention on cortical bone accretion and indicators relevant to bone metabolism in Chinese girls aged 10-12 y in Beijing. American Journal of Clinical Nutrition 2005, 81, 1168–1175.

64.Zulu VC, Nakao T, Sawamukai Y: Insulin-like growth factor-I as a possible hormonal mediator of nutritional regulation of reproduction in cattle. J. Vet. Med. Sci 2002, 64, 657–665.

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