Variation in Plasma Concentrations of Insulin-Like Growth Factor-I in Pasture-Fed Holstein Cows

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ABSTRACT

The objective of this 5-wk study was to determine dietary effects on plasma concentrations of insulin-like growth factor-I (IGF-I), as well as milk production and milk components in pasture-fed dairy cows. Thirty-two Holstein cows 4 to 5 wk postpartum were randomly assigned to 4 dietary subgroups. Feed was provided twice daily ad libitum at 0900 and 1600 h composed of fresh-cut pasture, meadow hay, and pelleted cereal grain to achieve differing levels of DMI and ME density (LL: 16.6 kg of DMI and 174 MJ of ME; HL: 17.3 kg of DMI and 181.1 MJ of ME; LH: 15.4 kg of DMI and 183.1 MJ of ME; HH: 17.9 kg of DMI and 213.3 MJ of ME, with the first letter indicating DMI and the second ME, and with H indicating high and L indicating low, respectively). The first day cows were placed on their diets was designated d 0. Concentrations of IGF-I were measured in frozen-thawed samples of plasma using a verified ELISA. Dietary treatment had affected plasma concentrations of IGF-I by d 7 with cows on high ME diets having greater IGF-I concentrations at d 14 (83.7 vs. 45.6 ng/mL) than cows on the low ME diets. The level of DMI had less effect on plasma concentrations of IGF-I at d 14 (72.2 vs. 57.1 ng/mL). Dietary treatment effects on these concentrations had stabilized by d 21. Day-to-day variation in mean plasma concentrations of IGF-I within each dietary treatment was low during an intensive period of daily sampling for 14 d (from d 22 to 35). Within-cow day-to-day variation was also low compared with that among cows within the same dietary group and was associated with a high repeatability in the day-to-day concentration of IGF-I in individual cows. Intraclass correlation coefficients for IGF-I ranged from 0.56 (± 0.14) to 0.88 (± 0.06) with a combined (pooled) value for the 4 subgroups of 0.77 (± 0.05). The ME and DMI effects (H vs. L) at d 35 were 79.3 vs. 41.4 and 62.0 vs. 55.7 ng/mL, respectively. Although

the ME and DMI differences also affected milk yield and compositional parameters, the effects were not as proportionately great as those measured for IGF-I. Altering the ME or DMI components of the pasture-based diets produced changes in plasma IGF-I concentrations that did not become stabilized for 3 wk, but were then highly repeatable for individual cows within each dietary group. Both observations have relevance to interpreting data related to plasma concentrations of IGF-I in lactating Holstein cows.

Key words: insulin-like growth factor-I, day-to-day variation, pasture-fed, dairy cow

INTRODUCTION

Insulin-like growth factor-I is a small peptide of approximately 7 kDa molecular weight that can affect postnatal growth and reproduction (LeRoith et al., 2001). Bioactivity of IGF-I is regulated by binding with high affinity specific insulin-like growth factor binding proteins (IGFBP; Rajaram et al., 1997; Hwa et al., 1999).

Nutrient intake can influence the levels of circulating IGF-I in dairy cattle. High energy intake, protein intake, or both will increase circulating IGF-I concentrations, whereas levels are reduced by lower protein or energy intake (Thissen et al., 1994; Cohick, 1998). Research in North America has established a link between blood IGF-I concentrations in high genetic merit dairy cows fed a TMR under feedlot conditions and changes in energy balance (Lucy et al., 1992; Beam and Butler, 1998). For instance, energy balance was correlated positively with serum concentrations of IGF-I because lactating dairy cows with positive energy balance had higher circulating concentrations of IGF-I than cows in negative energy balance (NEB; Ronge et al., 1988; Spicer et al., 1990; Beam and Butler, 1998). There is no equivalent information on comparable studies in Australian dairy herds where production systems are based mainly on pasture with strategic feeding of grain-based supplements, especially in early lactation. In addition, information on the effect of nutrient status and

Received August 10, 2007.

Accepted January 13, 2008.

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Table 1. Planned differences in DMI and ME for cows in each treatment group¹

Dietary subgroup	DM intake (kg/cow/d)	ME intake (MJ/cow/d)
LL	16.6	174.0
HL	17.3	181.1
LH	15.4	183.1
HH	17.9	213.3

¹H = high and L = low, where the first letter denotes DMI and the second denotes ME.

energy balance on circulating IGF-I levels has been based mainly on data from the weekly blood sampling of cows fed TMR diets. Data on day-to-day variation in concentrations of IGF-I in blood plasma are limited.

The present study used a commercial IGF-I ELISA kit (Diagnostic Systems Laboratories Inc., Webster, TX; Obese et al., 2008) to test the hypothesis that diets composed of 2 levels of DMI and ME density could affect plasma concentrations of IGF-I. The day-to-day variation in concentrations of IGF-I and individual cow variability in lactating Holstein cows fed pasture during early lactation were also assessed.

MATERIALS AND METHODS

Animals and Experimental Design

The experiment was conducted at the Department of Primary Industry's Ellinbank Dairy Research Institute (38.27 S lat; 145.56 W long) between August and September, 2000. It received approval from the Ethics Committee of the Department of Primary Industries, Ellinbank. Lactating Holstein cows ($n = 32$) in their second or subsequent lactations and from 4 to 5 wk postpartum (initial mean live weight of 504.8 ± 10.0 kg; SEM; range 411 to 621 kg) were treated with an implant of a 6 mg of GnRH-agonist (Deslorelin, Peptech Animal Health, Sydney, Australia), followed by 2 injections of PGF_{2 α} (2 mL of Prosalvin, Intervet, Melbourne, Australia) at 0800 and 1600 h 10 d later. This treatment prevented cows from cycling and producing progesterone as part of a concurrent study to measure the effects of DMI and ME density on metabolic clearance rates of administered progesterone (Rabiee et al., 2001).

The cows were randomly assigned to 4 treatment groups in a 2×2 factorial design after matching on parity, current milk production, and calving date. Feed was provided twice daily at 0900 and 1600 h composed of fresh-cut pasture, meadow hay, and pelleted cereal grain to achieve differing levels of DMI and ME density (Table 1). The study period was for 5 wk composed of a 3-wk adaptation period (designated as the transition phase) followed by 2 wk of intensive sampling (desig-

nated as the stable phase). The first day cows received their allocated diet was designated d 0. Cows were first fed with pelleted cereal grain at 0900 h, followed by pasture in the high ME (**HME**) groups (LH and HH subgroups), or hay and then pasture in the low ME groups (LL and HL subgroups). They were fed indoors in individual stanchions and were individually offered their diets for 5 h after each milking at 0600 and 1500 h. They were then held as a single group in a bare yard after each feeding period but had access to water. Feed allowances were weighed out as well as refusals for grass, hay, and grain so that intakes were measured daily.

Feed Processing and Analysis

Pasture was cut to approximately 40 mm twice daily and harvested using a loader wagon. The DM content of pasture was estimated using a microwave (high for 9 min) so that the correct amount of fresh pasture could be calculated for each cow. A representative sample of each of the feeds offered and refused was dried at 105°C to constant weight to determine the actual DM content. An additional subsample of all feeds offered was bulked on a weekly basis and dried at 65°C for 72 h, ground, and analyzed for in vitro DM digestibility (**DMD**) and N. The DMD was estimated by the method of Clarke et al. (1982). The ME was calculated from DMD $\{[ME = (DMD \times 0.17) - 2]\}$ (SCE, 1990). The nitrogen content was measured by the Kjeldahl method. The CP was calculated from the nitrogen data ($CP = N \times 6.25$). The DMD, ME, and protein content of the various feeds offered are presented in Table 2. The diet composition and actual differences in DM intake of pasture, hay, and pellets and average DM, DMD, ME, and CP of the experimental diets are shown in Table 3.

Blood Sampling Protocol

Blood sampling was by venipuncture from a coccygeal vein into 10 mL of heparinized Vacutainer tubes occurring once weekly at 0700 h after the morning milking on d 0, 7, 21, 28, and 35. Additional samples were collected daily from d 22 to 35 at 0700 h to provide comparative estimates of day-to-day variation during the stable phase of the study. Each blood sample was placed initially on ice and then centrifuged ($1,600 \times g$ for 15 min at 4°C) within 10 min of collection. Plasma was aspirated and stored at -20°C until assayed for IGF-I.

Plasma IGF-I Assay

Plasma IGF-I concentrations were measured using a validated DSL-10-2800 Active Nonextraction IGF-I

Table 2. Chemical analysis of the various feed types in the rations

Item	Digestibility (%)	DM (%)	CP (%)	ME (MJ)
Low energy pellet	75.3	96.8	16.7	11.3
High energy pellet	86.4	96.5	12.9	13.3
Pasture (ryegrass and clover)	77.5	15.4	23.8	11.2
Hay	64.6	82.4	14.1	9.0

ELISA kit (DSL Inc., Webster, TX). The ELISA was validated against an IGF-I RIA in which IGF-I in plasma samples have been dissociated and extracted from IGFBP by size exclusion chromatography under acid conditions (Obese et al., 2008). The intraassay and interassay coefficients of variation of the IGF-I ELISA for plasma were 2.27 and 4.11%, respectively.

Milk Yield and Milk Components

Milk yield was recorded at every morning and evening milking for the 5 wk using a standard herd recording device. A sample of whole milk was preserved with 0.5% bromopol and refrigerated at 4°C for compositional analyses (milk lactose, total protein, and total fat) at weekly intervals using a MilkoScan (Foss Electric, Hillerød, Denmark). These compositional data were used to calculate yields for lactose, protein, and fat.

Statistical Analyses

The effects of DMI and ME on plasma concentrations of IGF-I, milk yield, and milk components, and interaction between DMI and ME density at d 14 of the transition phase and d 35 of the stable phase were analyzed using the GLM procedure in SPSS v. 11.5 (SPSS, 2002). Data for d 0 were obtained before cows had access to their various diets, and these data were used as covariates. The model used was

$$Y = \text{DMI} + \text{ME} + \text{DMI} \times \text{ME} + \text{covariate at d 0},$$

where Y = variable at d 14 or 35. The interaction term was included in the model if its probability was < 0.1. Intraclass correlations (Snedecor and Cochran, 1980) were used to assess the day-to-day variation in plasma concentrations of IGF-I of cows within each group during the 14 d of the stable phase. Calculation of the intraclass correlation coefficient (ICC) of each treatment group used the loneway command software (StataCorp, 2001) in which:

$$\text{ICC} = \frac{\sigma^2_{\text{cow}}}{\sigma^2_{\text{cow}} + \sigma^2_{\text{e}}},$$

where ICC is equal to the proportion of the total variance that is due to the between cow variance, and σ^2_{e} is the error variance. In addition, the Kendall's coefficient of concordance was calculated as a measure of the agreement among rankings of the cows over each of the 14 d of the stable phase for plasma IGF-I measurements (Kendall, 1962).

RESULTS

Changes in Plasma Concentration of IGF-I During the Transition and Stable Phases

Dietary treatments had influenced IGF-I concentrations for each group by d 7 with individual trends continuing to d 21. The changes in IGF-I reflected ME density to a greater degree than DMI (Figure 1). The mean plasma concentrations of IGF-I were highest in cows on the HME diets (LH and HH subgroups) at d 14 ($P < 0.001$) in the transition phase and d 35 ($P < 0.001$) in the stable phase compared with cows on the low ME diets (LL and HL subgroups). The DMI treatment had less influence on the mean plasma concentrations of IGF-I at d 14 ($P = 0.057$) and d 35 ($P = 0.083$). The DMI $\times$ ME interaction for IGF-I concentration was significant at d 14 ($P < 0.047$) in the transition phase because of a spike in concentrations of IGF-I among cows in the HH subgroup. The interaction between DMI and ME was not statistically significant at d 35 ($P = 0.61$).

Table 3. Actual differences in DMI of pasture, hay, and pellets and average DM, DM digestibility (DMD), ME, and CP content of the experimental diets¹

DMI (kg/cow/d)	HL	LL	LH	HH
Pasture	6.3	6.1	10.4	11.0
Hay	4.9	4.3	—	—
Low energy pellet	6.2	6.1	—	—
High energy pellet	—	—	4.9	6.8
Diet composition				
DM (%)	32.5	21.9	21.2	22.8
DMD (g/kg of DM)	73.5	72.8	79.8	80.4
ME (MJ of ME/kg of DM)	10.4	10.5	11.9	11.9
CP (g/kg of DM)	18.6	18.4	20.2	19.5

¹H = high and L = low, where the first letter denotes DMI and the second denotes ME.

Figure 1. Changes in plasma concentrations of IGF-I (mean $\pm$ SE) for 32 cows fed 4 diets ($n = 8$ cows per dietary treatment; HH = high DMI and high ME; HL = high DMI and low ME; LH = low DMI and high ME; LL = low DMI and low ME).

Daily Variation in Plasma Concentrations of IGF-I

The plasma concentrations of IGF-I measured during the 14 consecutive days of sampling in the stable phase showed that levels remained relatively constant for each of the 4 dietary groups (Figure 2). Day-to-day variation within individual cows was less compared with that among cows within the same dietary group. Cows exhibited consistently high, medium, or low plasma concentrations of IGF-I relative to the group mean. Examples of this level of repeatability for cows having the highest and the lowest plasma concentrations of IGF-I in the HH and LL groups are shown in Figure 3. The ICC as a measure of the proportion of the total variance that was due to between-cow variance were 0.56 ± 0.14 , 0.75 ± 0.11 , 0.81 ± 0.09 , and 0.88 ± 0.06 for the subgroups HL, HH, LH, and LL, respectively, and was 0.77 ± 0.05 for the 4 groups combined (pooled ICC), based on the deviations from each group mean. Similarly, there was a high level of agreement among rankings of cows within a group over each of the 14 d of plasma IGF-I measurement as indicated by Kendall's coefficients of concordance (HL = 0.65; HH = 0.78; LH = 0.86; LL = 0.93; each $P < 0.001$), and 0.84 for the combined groups

Figure 2. Daily plasma concentrations of IGF-I (mean $\pm$ SE) in 32 cows fed 4 diets ($n = 8$ cows per dietary treatment; HH = high DMI and high ME; HL = high DMI and low ME; LH = low DMI and high ME; LL = low DMI and low ME).

Figure 3. Plasma IGF-I profiles of individual cows with the highest and lowest plasma concentrations of IGF-I within the dietary subgroups with high DMI and high ME (HH), and low DMI and low ME (LL).

(pooled over all groups and using the deviations from the group means).

protein concentrations for the diets with the higher ME density ($P < 0.001$; Table 5).

Milk Yield and Milk Composition During the Transition and Stable Phases

Dietary treatment influenced mean milk yield during the 5-wk study. Cows in the HH group had the highest milk production, while those in the LL group had the lowest (Figure 4). The mean daily milk yield at d 0 was 28.9 l, ranging from 27.8 l for the LH group to 30 l for the HL group ($P > 0.05$). There was no correlation between cow yield and IGF-I concentrations across dietary treatment ($r = 0.058$, $P = 0.754$). Overall means for daily yields of lactose, milk fat, and protein were 1.34 ± 0.04 , 1.29 ± 0.04 , and 0.82 ± 0.02 kg/cow. Mean composition statistics were 4.99 ± 0.03 , 4.85 ± 0.12 , and $3.04 \pm 0.03\%$ for lactose, fat, and protein. Daily milk yields at d 35 were affected by DMI and ME concentration ($P < 0.001$; Table 4). The interaction between these 2 dietary components was also significant ($P < 0.001$; Table 4); the effect of the high ME density was only apparent with the higher DMI. Similar interactive effects of diet were also observed with daily yields of lactose and protein at d 35 ($P < 0.001$), but not with milk fat. Statistically significant milk compositional effects at d 35 only involved increases in lactose and

DISCUSSION

The results from this study have demonstrated that changes in diets based on fresh pasture resulted in

Figure 4. Daily milk production (mean $\pm$ SE) in 32 cows fed 4 diets ($n = 8$ cows per dietary treatment; HH = high DMI and high ME; HL = high DMI and low ME; LH = low DMI and high ME; LL = low DMI and low ME).

Table 4. Unadjusted subgroup means, least squares (LS) means, and probability values for milk yield at d 14 and 35¹

Parameter	Unadjusted subgroup means				LS means					
	LL	HL	LH	HH	LDMI	HDMI	SEM	LME	HME	SEM
Milk yield (d 14), L	23.8	26.2	27.3	28.2	25.2	27.6	0.8	25.4	27.3	0.8
Milk yield (d 35), L	23.8	24.7	24.1	31.5	23.8	28.3	0.8	24.5	27.6	0.8
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	P-value									
	Milk yield (d 14)				Milk yield (d 35)					
Model	<0.001				<0.001					
Intercept	0.283				<0.001					
DMI	0.040				<0.001					
ME	0.095				0.001					
Covariate	<0.001				0.015					
DMI × ME	—				<0.001					

¹LDMI = low DMI; HDMI = high DMI; LME = low ME; HME = high ME; LL = low DMI and low ME; HL = high DMI and low ME; LH = low DMI and high ME; HH = high DMI and high ME.

changes in plasma concentrations that were occurring by d 7 but continued for a further 2 wk (to d 21) before stabilizing at 4 different levels. The ME density of the diet affected circulating IGF-I concentrations to a greater degree than DMI. Cows receiving the HME rations (HH and LH; Figure 1) increased their average plasma IGF-I concentrations from d 0 to 21 and maintained these higher concentrations from d 22 to 35 (Figure 2). The interaction between DMI and ME density at d 14 may have reflected the greater impact of a high ME diet when combined with higher DM intake. The ME density effect is consistent with other studies indicating higher plasma concentrations of IGF-I in dairy cows (Lucy et al., 1992; Andersen et al., 2004) and heifers (Armstrong et al., 2001) offered high energy diets.

The average IGF-I concentrations for the 4 diets ranged from 29.1 to 96.4 ng/mL (Figure 1). Since the influence of diet was so profound, comparisons with other studies involving different diets not based on pasture are limited. Nonetheless, comparable ranges of 25 to 76 ng/mL, 44 to 92.8 ng/mL, and 40 to 75 ng/mL have been reported for Holstein cows on TMR by Vega et al.

(1991), Abribat et al. (1990), and Spicer et al. (1993), respectively. The concentrations on the pasture-based diets used in the present study were lower than those reported by Snijders et al. (2001) for Holstein cows of high genetic merit (120 to 130 ng/mL) or average genetic merit (130 to 150 ng/mL).

The repeatability in average plasma concentrations of IGF-I for each group during the intensive sampling from d 22 to 35 was high (Figure 2). The levels in individual cows remained relatively constant and did not fluctuate appreciably from day to day, with cows having either consistently high, medium, or low IGF-I concentrations relative to their group means (Figure 3). The ICC of 0.77 ± 0.05 and a Kendall's coefficient of concordance of 0.84 over the 4 groups were indicative of a marked cow component in the variation in IGF-I concentrations. This high repeatability with respect to day-to-day variation in plasma concentrations of IGF-I in individual Holstein cows may be genetically influenced. Its heritability in young dairy cattle was estimated as 0.35 (Grochowska et al., 2001), with values ranging from 0.31 to 0.59 reported in beef cattle (Davis and

Table 5. Unadjusted subgroup means, least squares (LS) means and probability values for milk components at d 35¹

Parameter	Unadjusted subgroups means				LS means							
	LL	HL	LH	HH	LDMI	HDMI	SEM	SIG	LME	HME	SEM	P-value
Lactose (%)	4.88	4.94	4.94	5.03	4.96	4.93	0.03	NS	4.84	5.03	0.03	***
Lactose yield (kg)	1.18	1.22	1.19	1.58	1.17	1.40	0.04	***	1.20	1.38	0.04	***
Protein (%)	2.90	2.96	3.13	3.21	3.05	3.05	0.03	NS	2.92	3.18	0.03	***
Protein yield (kg)	0.70	0.73	0.75	1.01	0.72	0.87	0.02	***	0.72	0.88	0.02	***
Fat (%)	5.15	5.16	4.99	4.41	5.04	4.82	0.22	NS	5.01	4.85	0.23	**
Fat yield (kg)	1.23	1.28	1.20	1.39	1.22	1.33	0.07	NS	1.25	1.30	0.07	NS

¹LDMI = low DMI; HDMI = high DMI; LME = low ME; HME = high ME; LL = low DMI and low ME; HL = high DMI and low ME; LH = low DMI and high ME; HH = high DMI and high ME.

***P < 0.01; **P < 0.001.

Simmen, 1997, 2000; Johnston et al., 2001; Yilmaz et al., 2004). Another possible reason for the low fluctuation in IGF-I concentrations within individual cows may relate to the relatively long half-life of IGF-I in the blood as a result of binding with specific IGFBP in the blood (Zapf et al., 1986; Comin et al., 2002). Because daily plasma concentrations of IGF-I for individual cows were similar to those for weekly samples for the same cow, animals should be able to be sampled at weekly intervals to ascertain any changes in IGF-I concentrations provided they remain on the same diet. If dietary intake or composition is altered, then plasma concentrations of IGF-I may continue to change for at least 3 wk (as shown in Figure 1).

The average daily yields of milk throughout the trial were similar to those reported for Holstein cows in commercial herds in the Ellinbank region that had seasonally concentrated calving patterns and received pasture-based diets supplemented with some grain (Auld et al., 2007). Only the cows receiving the HH diet increased daily milk yields over the 35 d, but the change was from 29 to 31 L. The level of DMI as well as dietary ME density both affected yields of milk (Table 4), lactose, and protein at d 35 and involved a significant interaction (Table 5). These effects clearly differed from the dietary effects observed on plasma concentrations of IGF-I.

CONCLUSIONS

The plasma concentrations of IGF-I in cows reflected diet composition and nutritional status with daily intakes of ME having a greater effect on plasma IGF-I concentrations than DMI. The changes in these concentrations were apparent within 7 d of introducing each diet, but separate trends continued for a further 14 d. Thereafter, average daily concentrations for each dietary group became stabilized. Interanimal variation in plasma concentrations of IGF-I was higher than within-animal variation in each of the dietary groups from d 22 to 35 of the stable phase. The study has demonstrated that IGF-I concentrations remain fairly constant and do not change appreciably between days in individual cows fed pasture-based diets as long as they remain on a constant diet. The initial slow rate of change combined with the eventual limited amount of variation for individual animals should have implications for experimental designs in studies investigating the effect of nutritional status or energy balance on changes in plasma concentrations of IGF-I. Results from this study suggest that changes in plasma concentrations of IGF-I for individual cows over a designated period of time may be more important than simply comparing group means, especially when diets may differ.

ACKNOWLEDGMENTS

Appreciation is expressed to the University of Melbourne, Dairy Australia, Primegro Ltd. (Adelaide) and the Cooperative Research Centre for Tissue Growth and Repair (Adelaide) for supporting the project.

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