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Associations between bone and energy metabolism in cows fed diets differing in level of dietary cation-anion difference and supplemented with cholecalciferol or calcidiol

R. M. Rodney,*† N. P. Martinez,‡ P. Celi,†§ E. Block,# P. C. Thomson,† G. Wijffels,‖ D. R. Fraser,† J. E. P. Santos,‡ and I. J. Lean*†[1]
*Scibus, Camden, New South Wales, Australia 2570
†School of Life and Environmental Sciences, The University of Sydney, Camden, New South Wales, Australia 2570
‡Department of Animal Sciences, University of Florida, Gainesville 32611
§DSM Nutritional Products, Animal Nutrition and Health, Columbia, MD 21045
#Arm & Hammer Animal Nutrition, Princeton, NJ 08543
‖CSIRO Agriculture, St. Lucia, Queensland, Australia 4067

ABSTRACT

Bone-derived hormones play an important role in metabolism. This study examined the hypothesis that interactions between bone and energy metabolism, particularly those involving osteocalcin, are present in dairy cattle and have feedback mechanisms over time. Associations between metabolites in blood were examined in 32 Holstein cows blocked by parity and milk yield and randomly allocated to diets containing either 0.27 mg/kg dry matter (DM) calcidiol or cholecalciferol for an anticipated intake of 3 mg/d (120,000 IU/d) at 11 kg of DM, and positive (+130 mEq/kg DM) or negative (−130 mEq/kg DM) dietary cation-anion difference (DCAD) from 252 d of gestation to calving. Blood was sampled every 3 d, from 9 d prepartum to 30 d postpartum, and plasma concentrations of vitamin D_3, 25-hydroxyvitamin D_3, adiponectin, C-telopeptide of type 1 collagen (CTX1), glucose, insulin-like growth factor 1 (IGF1), insulin, undercarboxylated osteocalcin (uOC), and carboxylated osteocalcin (cOC) were determined. Feeding calcidiol compared with cholecalciferol increased plasma concentrations of 25-hydroxyvitamin D_3 pre- (264.2 ± 8.0 vs. 61.3 ± 8.0 ng/mL) and postpartum (170.8 ± 6.2 vs. 51.3 ± 6.2 ng/mL) but decreased concentrations of vitamin D_3 pre- (1.2 ± 0.6 vs. 14.5 ± 0.6 ng/mL) and postpartum (1.9 ± 0.4 vs. 3.2 ± 0.6 ng/mL). Prepartum, cows fed the negative DCAD diet had reduced concentrations of vitamin D_3 and glucose compared with cows fed a positive DCAD. The combination of negative DCAD and cholecalciferol reduced IGF1 concentrations prepartum. The DCAD treatment had no effect on postpartum concentrations of metabolites. Nulliparous cows had increased concentrations of OC, CTX1, IGF1, glucose, and insulin compared with parous cows. Time series analysis identified associations between metabolites on the same day and over 3-d lags up to ±9 d that suggest feedback between 25-hydroxyvitamin D_3 and vitamin D_3 in the negative lags, indicating that 25-hydroxyvitamin D_3 may exert feedback on vitamin D_3 but not vice versa. We found evidence of a feedback mechanism between vitamin D_3 and IGF1, with positive effect size (ES) on the same day and 3 d later, and negative ES 9 d later, that was more evident in cholecalciferol-fed cows. This suggests an important role of IGF1 in integrating bone metabolism with energy and protein metabolic pathways. Evidence of feedback was found between uOC and particularly cOC with IGF1, with positive ES on the same day but negative ES 6 d before and 6 d after. An association between uOC or cOC and IGF1 has not been previously identified in cattle and suggests that both uOC and cOC may have marked biological activity. Associations between OC and insulin identified in mice were not observed herein, although associations between OC and glucose were similar to those between IGF1 and glucose, supporting associations between glucose, OC, and IGF1. We provide further statistical evidence of crosstalk between vitamin D compounds, bone hormones, and energy metabolism in cattle. In particular, associations between uOC or cOC and IGF1 may provide links between prepartum diets and observations of prolonged increases in milk production and allow better control of peripartum metabolism.

Key words: dietary cation-anion difference, IGF1, osteocalcin, vitamin D

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[1]Corresponding author: ianl@scibus.com.au

INTRODUCTION

The interplay between bone and energy metabolism has been identified in murine models (Lee et al., 2007), and associations between bone markers and energy metabolism have been demonstrated in humans (Wolf, 2008). We have postulated a specific role for bone metabolism, and links to energy metabolism, in the adaptation of dairy cows to lactation (Lean et al., 2014) and anticipated that these associations are influenced by prepartum dietary interventions. Such interventions have had profound and long-lasting effects on productivity, health, and fertility of cows (Lean et al., 2014; Martinez et al., 2018b).

Lee et al. (2007) identified actions of the osteoblast-derived hormone osteocalcin (**OC**) that created a feedback loop between bone and energy metabolism. Osteocalcin is produced by mature osteoblasts and undergoes vitamin K-dependent γ-carboxylation, resulting in carboxylated OC (**cOC**) that increases the affinity of the molecule for Ca and hydroxyapatite in bones and plays a role in bone accretion in numerous species, including bovine (Van Mosel and Corlett, 1990). A smaller fraction of OC remains undercarboxylated (**uOC**) and interacts with the G-protein coupled receptor GPRC6A in numerous tissues (Wei and Karsenty, 2015). In a influential paper, Lee et al. (2007) conducted a series of experiments that demonstrated that OC promoted pancreatic β-cell proliferation and insulin secretion, independently increased peripheral tissue insulin sensitivity, and stimulated adiponectin secretion by adipocytes. On the other hand, adiponectin has been shown to increase osteoblast proliferation and differentiation (Berner et al., 2004), bone deposition (Kanazawa et al., 2007), and glucose uptake by skeletal muscle, and it may suppress hepatic gluconeogenesis (Yamauchi et al., 2002). Insulin acts to directly inhibit osteoblast activity, thereby enhancing bone resorption (Lee et al., 2007). Associations have been made between obesity and Ca metabolism in cattle (Heuer et al., 1999; DeGaris et al., 2010) and induced subclinical hypocalcemia resulted in transient insulin resistance based on increased blood glucose and reduced plasma insulin concentrations in dairy cattle (Martinez et al., 2014).

Diets with negative DCAD enhance the response to parathyroid hormone in dairy cows, which increases concentrations of 1,25-dihydroxyvitamin D_3 and Ca in blood of cows (Goff et al., 2014). The increased concentrations of 1,25-dihydroxyvitamin D_3 in cows fed acidogenic diets are presumed to be caused by increased renal synthesis of the vitamin (Goff et al., 1991, 2014). Furthermore, acidogenic diets increase blood concentrations of total and ionized Ca on the day of calving and in the following days (Oetzel et al., 1991; Phillippo et al., 1994; Rodney et al., 2018), likely because of increased concentrations of 1,25-dihydroxyvitamin D_3 and increased responsiveness of target tissues to the vitamin (Goff and Horst, 1997). Vitamin D plays a crucial role in the absorption of minerals from the gastrointestinal tract including the forestomachs (Sidler-Lauff et al., 2010), and it is essential for bone metabolism, regulating the activity of osteoblasts and osteoclasts (Tanaka and DeLuca, 1971). Complementary to vitamin D, acidogenic diets enhance Ca flux from the mucosal to the serosal side of the gastrointestinal tract of ruminants (Wilkens et al., 2016) and have been shown to improve Ca and Mg retention in dairy cows (Abu Damir et al., 1994). Vitamin D responsive elements have been identified in the OC gene *BGLAP* (Terpening et al., 1991), and 1,25-dihydroxyvitamin D_3 and other vitamin D metabolites can activate the gene and stimulate OC synthesis (Uchida et al., 1994). Dietary interventions that influence mineral and vitamin D metabolism might also influence energy metabolism in dairy cows as part of the homeorhetic adaptations to lactation (Bauman and Currie, 1980).

Establishing associations with potential feedback loops among mineral–bone–energy metabolism in transition dairy cows can create a novel hypothesis on the mechanisms by which nutrients and dietary interventions influence adaptations to lactation. This cross-talk and integration of metabolism has been elegantly demonstrated in murine models (Lee et al., 2007), and may apply to humans (Wolf, 2008) and possibly dairy cattle (Lean et al., 2014). We hypothesized that associations between bone-derived compounds and those involved in energy metabolism would be evident. The objectives were to use time series analysis to identify associations over time between plasma compounds involved in bone, mineral, and energy metabolism in transition dairy cows fed diets differing in level of DCAD and source of supplemental vitamin D.

MATERIALS AND METHODS

Throughout the manuscript, sources of vitamin D fed to cows prepartum will be referred as cholecalciferol (**CH**) and calcidiol (**CA**), whereas vitamin D metabolites measured in plasma will be referred to as vitamin D_3 and 25-hydroxyvitamin D_3.

Cows, Diets, and Treatments

All procedures were approved by the University of Florida Institutional Animal Care and Use Committee (protocol number 201408331). This study is part of a series of experiments conducted to evaluate the effects of level of dietary DCAD and source of supplemental