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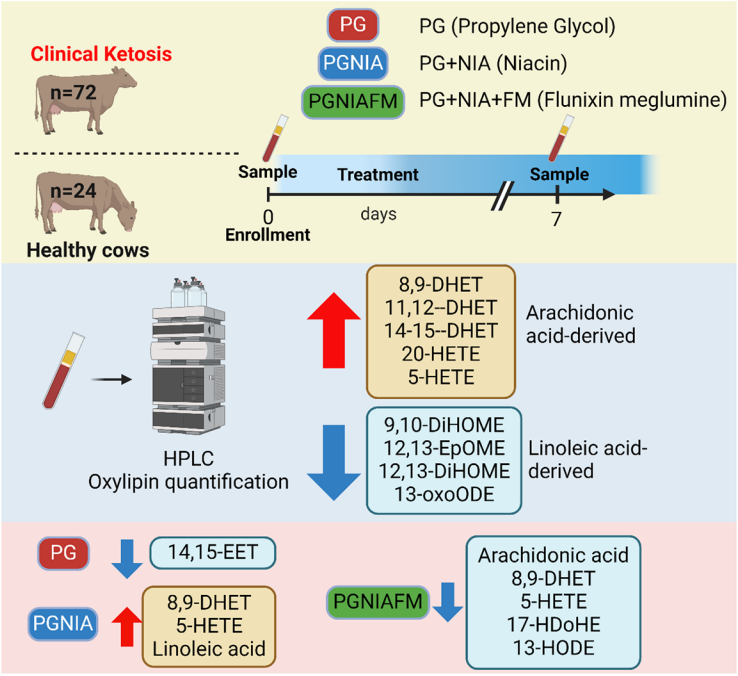
Short Communication
Health, Welfare, and Behavior

Oxylipin dynamics in dairy cows during clinical ketosis and after treatment with niacin and flunixin meglumine

Miguel Chirivi, Daniela Cortes-Beltran, Jeff Gandy, and G. Andres Contreras*

Graphical Abstract

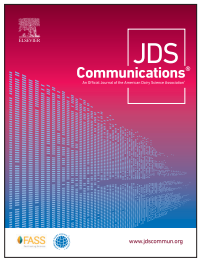


Summary

Dairy cows with clinical ketosis (CK) develop intense adipose tissue lipolysis. However, it is unknown whether this leads to alterations in the synthesis of lipid mediators of inflammation, including oxylipins. This study evaluated oxylipin profiles during CK and its treatment with propylene glycol (PG) and lipolysis inhibitors niacin (NIA) and flunixin meglumine (FM). Seventy-two CK cows (blood β-hydroxybutyrate > 1.2 mmol/L) were enrolled and randomly assigned to (1) PG, (2) PGNIA, and (3) PGNIAFM. The CK cows had elevated arachidonic- and reduced linoleic-derived oxylipins. PGNIAFM restored plasma oxylipins in CK to profiles similar to those observed in healthy cows. Inhibiting lipolysis may regulate oxylipin biosynthesis during CK.

Highlights

- CK increases plasma levels of oxylipins derived from arachidonic acid (ARA).
- Oxidized linoleic acid metabolite biosynthesis is reduced during CK in dairy cows.
- ARA was identified as the top canonical pathway activated during CK.
- Treating CK with lipolysis inhibitors restored oxylipin profiles by reducing ARA metabolism.



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Oxylipin dynamics in dairy cows during clinical ketosis and after treatment with niacin and flunixin meglumine

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Abstract: Dairy cows with clinical ketosis (CK) exhibit metabolic changes, including intense adipose tissue (AT) lipolysis and systemic insulin resistance, that increase plasma BHB and free fatty acids (FFA). Cows with CK also have systemic inflammation, predisposing them to inflammatory and infectious diseases. This inflammatory process is modulated in part by oxidized fatty acids (oxylipins) that regulate all aspects of inflammation. Oxylipin profiles have been characterized in healthy periparturient cows, but their dynamics during CK are unknown. Clinical ketosis is an acute metabolic disease requiring clinical therapy, commonly including propylene glycol (PG) as a gluconeogenic agent. Recently, we showed that including lipolysis inhibitors such as niacin (NIA) and flunixin meglumine (FM) improved CK recovery. These drugs may modulate oxylipin biosynthesis by regulating the release of PUFA (oxylipin substrates) and cyclooxygenase activity. However, their impact on oxylipin profiles in cows with CK is unknown. The objective of this study was to determine the dynamics of specific linoleic and arachidonic acid-derived oxylipins during CK and following therapy with PG, NIA, and FM. Multiparous Jersey cows (n = 72; 7.1 DIM) with CK from a commercial dairy were sampled. Inclusion criteria were CK symptoms (lethargy, depressed appetite, and reduced rumen fill) and blood BHB ≥ 1.2 mmol/L. The CK cows (n = 24/treatment) were randomly assigned to one of the 3 treatments: (1) PG: 310 g orally once daily for 5 d, (2) PG + NIA (PGNIA): 24 g orally once daily for 3 d, (3) PG + NIA + FM (PGNIAFM): 1.1 mg/kg i.v. once daily for 3 d. Healthy control cows (HC; n = 24) matched by lactation and DIM (±2 d) were also included. Plasma oxylipins were quantified at enrollment and 7 d later using HPLC-MS/MS. At enrollment, CK had higher concentrations of arachidonic acid (ARA)-derived 5- and 20-HETE, 8,9-, 11,12-, and 14–15-DHET, and lower concentrations of linoleic acid (LA)-derived 12,13-EpOME, 13-oxoODE, 9,10- and 12,13-DiHOME. Integrated analysis of biological pathways and oxylipin profiles using Ingenuity Pathway Analysis revealed ARA metabolism as the top pathway activated during CK. By d 7, treatment with PGNIAFM restored plasma PUFA and oxylipins to profiles similar to HC. Ingenuity Pathway Analysis showed that PGNIAFM activated the zinc transporter SLC30A7, associated with reduced activation of the ARA pathway. Results indicate that higher FA availability during CK, driven in part by dysregulated lipolysis, increases the pool of substrates for oxylipin biosynthesis. These oxylipins may play a role in both metabolic dysregulation and restoring homeostasis during CK. Inhibiting lipolysis and cyclooxygenase activity with NIA and FM can alter ARA- and LA-derived oxylipin biosynthesis. These findings underscore the potential use of lipolysis inhibitors NIA and FM in CK therapeutics and highlight the importance of understanding oxylipin pathways in the pathogenesis of CK.

During the periparturient period, cows enter a state of negative energy balance due to reduced appetite and enhanced energy requirements for fetal growth and lactogenesis (Contreras et al., 2017b). To meet energy demands, periparturient cows mobilize free fatty acids (**FFA**) from triglycerides (**TG**) in adipose tissue (**AT**) via lipolysis. In the liver, FFA can be oxidized to generate ATP, re-esterified into TG for export or storage, or metabolized into ketone bodies. These ketones, including acetone, acetoacetate, and BHB, contribute 5% to 20% of total energy needs in mammals (Mooli and Ramakrishnan, 2022). However, when ketogenesis exceeds the systemic capacity to use ketones, blood ketone levels rise, resulting in ketosis.

Periparturient cows are highly susceptible to clinical ketosis (**CK**), defined by reduced appetite, decreased milk yield, lethargy, and the presence of a positive urine ketone test, along with BHB in blood >1.1 mmol/L (Seifi et al., 2011; Suthar et al., 2013). Blood glucose below 2.0 mmol/L triggers CK symptoms, which can be life-threatening if untreated (Sun et al., 2014). Intense and protracted lipolysis, common in CK, is considered an inflammatory event due to AT remodeling. This remodeling includes immune cell infiltration, alterations in AT extracellular matrix, and the synthesis of inflammatory mediators, including oxylipins, derived from PUFA (Gartung et al., 2016).

Lipases and phospholipases release PUFA from TG and phospholipids that can be oxidized by cyclooxygenases (**COX**), lipoxygenases (**LOX**), and cytochrome P450 (**CYP450**) into oxylipins. Nonenzymatic reactions triggered by reactive oxygen species released from mitochondrial respiration and inflammatory processes can also oxidize PUFA to produce oxylipins (Sordillo, 2018). These lipid mediators have inflammatory, anti-inflammatory, and vasoactive effects (Gabbs et al., 2015). Oxylipin profiles in cattle vary by lactation stage and health status (Kuhn et al., 2017). For instance, cows with coliform mastitis have higher PUFA and LOX-derived oxylipins in plasma (Mavangira et al., 2015). Oxylipin profiles during CK in dairy cows are not yet defined. Given the higher PUFA availability and systemic inflammation in ketotic cows, we

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hypothesize that cows with CK present a pro-inflammatory oxylipin profile that can be modified by inhibiting lipolysis. Thus, the objective of this study was to define oxylipin dynamics in CK and healthy cows enrolled in a randomized clinical trial (**RCT**) that evaluated the use of lipolysis inhibitors, niacin (**NIA**) and flunixin meglumine (**FM**), and propylene glycol (**PG**) to treat the disease (Chirivi et al., 2023).

Michigan State University's Institutional Animal Care and Use Committee (#202100139) approved all procedures. In the present study, CK was defined by the following *inclusion criteria:* multiparity, 2–21 DIM, depressed appetite, reduced rumen fill, and lethargy. Only cows showing the above clinical signs were tested for hyperketonemia (BHB ≥ 1.2 mmol/L; n = 80) using the Precision Xtra meter. *Exclusion criteria:* diagnosis of a concurrent disease (e.g., metritis, lameness) within 14 d postenrollment. Healthy control cows (**HC**) were multiparous, 2–21 DIM, plasma BHB <1.2 mmol/L. The HC were matched to CK cows by parity and DIM to establish a baseline for oxylipin profiles in nonketotic healthy cows. Animals in this study were part of a larger study and details on sample size determination, number of animals, and data analysis methods are found in the RCT report (Chirivi et al., 2023).

At d 0, treatments were assigned as follows: **PG**: 310 g propylene glycol orally 1×/d for 5 d (Interstate Chemical Company, USA), n = 26. **PGNIA**: PG and 24 g NIA orally 1×/d for 3 d (Balchem, USA), n = 27. **PGNIAFM**: PG, NIA, and 1.1 mg/kg of BW intravenous FM 1×/d for 3 d (Merck Animal Health, USA), n = 27. **HC**: no treatment, n = 24. Details on treatment and the blinding protocols are in the RCT report.

Blood samples were collected on d 0, 3, 7, and 14 for measuring metabolic and inflammatory markers (results in RCT report). Oxylipins were quantified in plasma collected on d 0 and 7. Plasma was harvested at the farm, added with an antioxidant, and then flash-frozen in liquid nitrogen (Putman et al., 2019). Samples were then transported (−20°C, less than 2 h) and stored (−80°C) until further processing. Oxylipins were extracted and analyzed using HPLC-MS/MS. Oxylipin concentration results were imported into the Ingenuity Pathway Analysis (**IPA**) Software (Qiagen, Redwood City, CA), which identifies oxylipins by their PubChem number. Ingenuity Pathway Analysis uses databases to predict regulatory networks associated with a lipid metabolite expression list, determining a statistical Z-score for each network. This Z-score predicts how the network is altered by the given lipidomic profile. Canonical pathways and functional regulatory networks of upstream regulators were identified by the prediction algorithms and the hypergeometric distribution algorithm. Pathway significance was set at $P < 0.05$, and network significance at $P < 0.01$. Irrelevant diseases and processes specific to other species were removed. To complement the IPA analysis, oxylipin concentrations were also analyzed with the lipid enrichment analysis (LIPEA) algorithm (Biomedical Cybernetics Group, Germany).

Only animals that completed the 14-d sampling period were included in the analysis (n = 24/treatment). Statistical analyses were performed using JMP Pro17 (SAS Institute Inc., Cary, NC). The normality of the variables was checked using the Shapiro-Wilk test ($P < 0.05$). Data were $\log_{10}$ transformed, and model fit was reassessed. A nonparametric Mann-Whitney test determined statistical differences between CK and HC at d 0. Significance was set at $P \leq 0.05$. At d 7, treatment effects were evaluated by Friedman's 2-way ANOVA test, using d 0 data as covariate, and Tukey's post hoc adjustment was used for pairwise comparisons.

Seventy-two cows with CK and 24 HC completed the RCT. In the CK group, cows were enrolled (d 0) at 7.05 (SD = 3.61) DIM and had a parity mode of 3. The HC animals were enrolled at 7.03 (SD = 4.47) DIM with a parity mode of 3. Detailed study population characteristics are included in the RCT report.

The present study corroborates previous findings indicating intense and protracted AT lipolysis in dairy cows with CK, leading to elevated plasma FFA and BHB, and hypoglycemia (Dervishi et al., 2021). In the present study, at enrollment, CK had high plasma FFA, hyperketonemia, reduced plasma cholesterol, hypoinsulinemia, and hypoglycemia. Blood chemistry profiles are presented in the RCT report.

During the first week of lactation, dairy cows had high plasma PUFA, including arachidonic acid (**ARA**), linoleic acid (**LA**), α-linolenic acid (**ALA**), and eicosapentaenoic acid (**EPA**; Contreras et al., 2017a). These FA come from cellular membrane phospholipids, TG in lipid droplets, and de novo lipogenesis. Phospholipase-A2 releases ARA and LA from cell membranes. Elongases and desaturases synthesize ARA from LA, the PUFA preferentially mobilized around calving (Contreras et al., 2010). Adipose tissue's neutral lipases, such as adipose triglyceride lipase (**ATGL**), hydrolyze TG to release ARA (Schreiber and Zechner, 2014). The companion article focused on AT function during CK shows that the activity of hormone-sensitive lipase activity, the rate-limiting enzyme of demand lipolysis, is increased in CK cows' adipocytes (Chirivi et al., 2024). Therefore, TG hydrolysis could be a significant PUFA source during CK in dairy cattle. While phospholipase A also contributes to ARA production, assessing its activity is beyond this study's scope and should be prioritized for future research. Once released, PUFA are highly prone to oxidation into oxylipins by enzymatic and nonenzymatic reactions (Sordillo, 2018).

The CYP450 oxylipins include hydroxides (hydroxyeicosatetraenoic acids; **HETE**), epoxides (epoxyeicosatrienoic acids [**EET**] and epoxyoctadecanoic acids [**EpOME**]), and diols (dihydroxyeicosatrienoic acids [**DHET**] and dihydroxyoctadecenoic acids [**DiHOME**]) (Kuhn et al., 2021). In this study, 20-HETE was higher in CK than HC (Figure 1a). In humans, plasma 20-HETE increases in nonalcoholic fatty liver disease (Li et al., 2020), a disorder that shares many features with hepatic lipidosis in cattle (Gröhn et al., 1983). 20-HETE is also synthesized in inflamed tissues and supports vascular responses to sepsis and endotoxemia (Theken et al., 2011). Notably, 72.2% of CK cows in this RCT had high endotoxin and bacterial DNA in plasma (RCT report). Although speculative, higher plasma 20-HETE in CK could be related to responses to endotoxemia during the disease.

The CYP450 products 14,15-EET and 8,9-, 11,12-, 14,15-DHET were also higher in CK versus HC. The EET are converted to DHET by epoxide hydrolases. In fatty liver diseases in rodents and humans, plasma DHET increase, indicating higher hepatic CYP450 activity (Wells et al., 2016). Given hepatic dysfunction in CK, EET and DHET levels may indicate liver dysfunction in CK cows.

The ARA-derived 5-HETE also increased during CK (Figure 1a). This oxylipin, synthesized by 5-LOX, is an early predictor of hepatic steatosis in humans (Maciejewska et al., 2015) and an AT inflammation biomarker in women with insulin resistance (Heem-

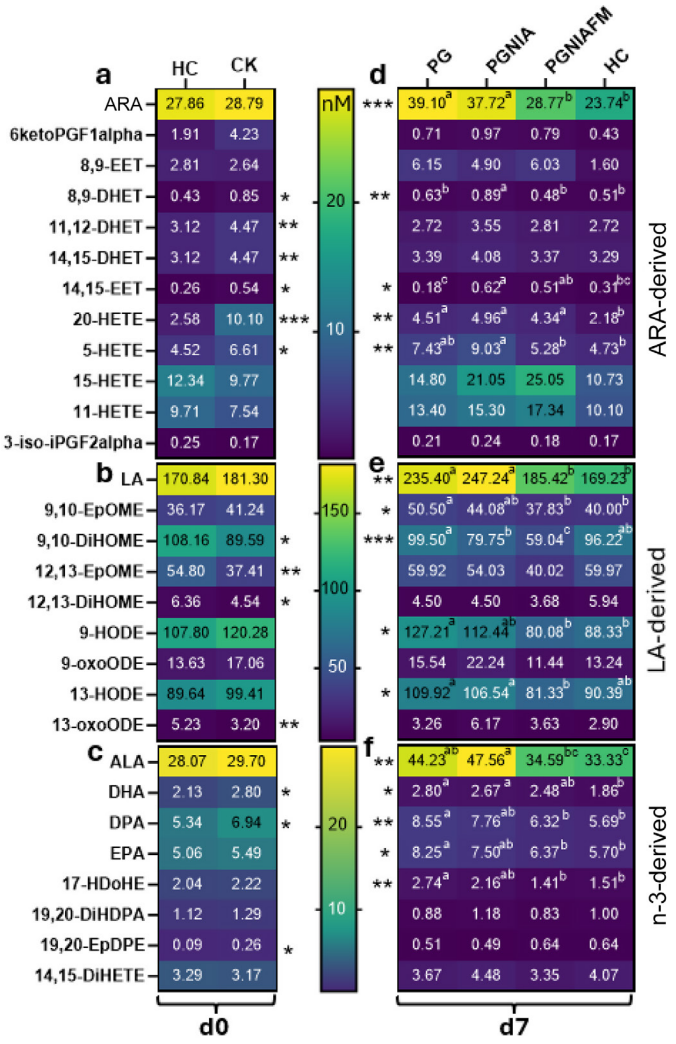

Figure 1. Arachidonic acid (ARA), linoleic acid (LA), and n-3-derived oxylipin concentrations in cows with clinical ketosis (CK) and healthy cows (HC). The CK cows (BHB ≥ 1.2 mmol/L, n = 72) were treated with propylene glycol (PG), PG + niacin (PGNIA), or PGNIA + flunixin meglumine (PGNIAFM). Healthy controls (HC; n = 24) with no sign of disease and normoketonemia (BHB < 1.2) were selected to assess basal oxylipin levels in this farm. Plasma oxylipin content was measured at enrollment (d 0, a–c) and 7 d after treatment (d 7, d–f). Values are least squares means of derived oxylipin concentrations (n*M*). Mean values within the same row that are marked with different letters (a–c) are significantly different ($P \leq 0.05$). Significance levels are indicated as follows: *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$. ALA = alpha linoleic acid; DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; EPA = eicosapentaenoic acid.

skerk et al., 2015). 5-HETE, a leukotriene precursor, may reduce inflammatory responses if its production is limited (Maciejewska et al., 2015). The dynamics of 5-HETE biosynthesis in dairy cattle are unknown, requiring more research on its potential as a liver steatosis and CK biomarker.

Linoleic acid–derived CYP450 products 12,13-EpOME and 9,10-, and 12,13-DiHOME were lower in CK compared with HC (Figure 1b). These oxylipins are peroxisome proliferator-activated receptor γ (PPARγ) ligands stimulating adipogenesis, lipogenesis, and oxidative phosphorylation in AT and liver (Hildreth et al., 2020). Reduced levels of these oxylipins may lower the signals that suppress lipolysis and promote AT adipogenesis, thus reducing lipid accumulation during CK. Since 12,13-DiHOME is a product of 12,13-EpOME hydrolysis by soluble epoxide hydrolase (**sEH**), its decrease was expected. A reduction in 9,10-DiHOME but not its parent compound 9,10-EpOME in CK cows could be due to several physiological mechanisms, including reduced sEH or enhanced 9,10-DiHOME degradation. Notably, both 12,13- and 9,10-DiHOME are PPARγ ligands and, therefore, promote fatty acid uptake in adipocytes by facilitating FATP1 and CD36 translocation (Lynes et al., 2017). In humans, higher levels of these DiHOME are associated with improved metabolic health and are promising targets for metabolic disease. It is unknown if a similar response occurs in periparturient cows during high metabolic activity, warranting further investigation.

Among the LA-derived LOX oxylipins, CK exhibited lower 13-oxo-ODE than HC (Figure 1b). This ketone product of 13-HODE is a potent PPARγ ligand. Our results show CK coincides with reduced biosynthesis of oxylipins that are PPARγ ligands. This change may impair PPARγ mechanisms that prevent excessive lipolysis and limit lipotoxicity from lipolysis-derived products during CK.

Cows with CK had higher plasma DHA and DPA than HC (Figure 1c). Among the 5 DHA and EPA-derived oxylipins detected, only DHA-derived 19,20-EpDPE rose during CK (Figure 1c). In rodent models of fatty liver disease, 19,20-EpDPE reduced hepatic macrophage trafficking and aggregation (Aoki et al., 2023). Aoki and colleagues suggested that 19,20-EpDPE biosynthesis is enhanced early in liver disease, possibly in response to high circulating FFA. Future research should evaluate 19,20-EpDPE as a biomarker of liver function in dairy cattle.

Oxylipin networks using IPA revealed ARA metabolism as the top pathway activated during CK versus HC at d 0 (Figure 2A). The other activated pathways were transcriptional regulation of adipocyte differentiation and regulation of lipid metabolism by PPARα. These findings reflect increased ARA-derived oxylipins content and high AT lipolytic activity in CK. Similarly, LIPEA analysis identified ARA metabolism, PPAR signaling, and inflammatory mediator regulation of TRP channels as top pathways ($P < 0.05$, Benjamini correction).

Additionally, IPA identified SLC30A7, EPHX2, and PNPLA8 as upstream pathway regulators. SLC30A7 is a zinc transporter protein crucial for zinc homeostasis, affecting enzymes involved in lipid metabolism and FA transporters like FABP3 and CD36 (Huang et al., 2018). Zinc also regulates insulin signaling and glucose metabolism, influencing ketosis by affecting substrate availability and insulin sensitivity. Epoxide hydrolase 2 (EPHX2) converts anti-inflammatory epoxides (e.g., 12,13-EpOME) into diols (e.g., 12,13-DiHOME) lacking these properties. EPHX2 inhibitors are being considered for treating fatty liver and metabolic complications (Warner et al., 2020). Our results provide initial evidence for EPHX2 as a possible therapeutic target in CK. Finally, PNPLA8 is a patatin-like phospholipase that promotes hepatocyte autophagy in response to lipid overload (fatty liver). Upstream PNPLA8 activation may indicate a response to lipid accumulation in CK cows' liver and other organs.

This is the first study evaluating plasma oxylipin dynamics after using PG, NIA, and FM to treat CK. As reported in Chirivi et al.

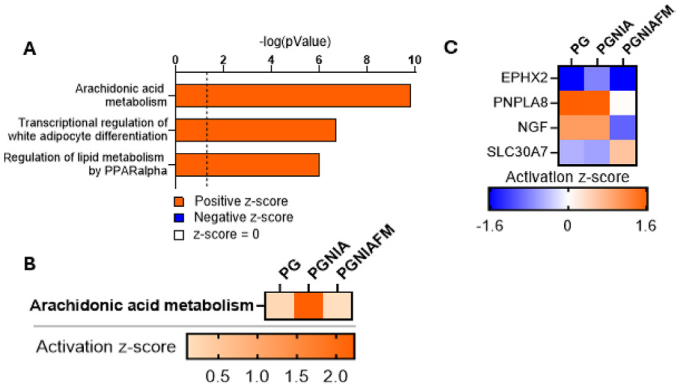

Figure 2. (A) Effects of clinical ketosis (CK) on upstream regulators and biological functions as predicted by IPA analysis at d 0. The dashed line indicates a threshold of $P = 0.05$. (B) Effects of treating clinical ketosis (CK) with propylene glycol (PG), propylene glycol + niacin (PGNIA), or propylene glycol + niacin + flunixin meglumine (PGNIAFM) on biological function pathways as predicted by IPA analysis at d 7. Network analyses combined differentially expressed oxylipins with upstream regulators and physiological functions to identify factors related to the activation or inactivation of biological processes ($P \leq 0.05$). (C) Upstream pathway regulators activated at d 7 ($P \leq 0.05$).

(2023), PGNIAFM reduced lipolysis and inflammation, shown by lower FFA and acute-phase proteins compared with PG and PGNIA. Consequently, by d 7 plasma ARA, LA, EPA, and DPA were reduced in PGNIAFM compared with other treatments (Figures 1d–f). This likely reflects the antilipolytic action of NIA upon binding to GPR109A reducing the production of cAMP. Flunixin meglumine, a nonselective COX inhibitor, reduces inflammatory activators of lipolysis like prostaglandin E2, TNFα, and IL-6 (Kenéz et al., 2014; Inazumi et al., 2020).

The PGNIAFM treatment lowered 9,10-DiHOME, and LOX-derived 13-HODE compared with other treatments, and reduced 8,9-DHET, 9,10-EpOME, and 9-HODE compared with PG (Figure 1d, 1e). Except for 9,10-DiHOME, these reductions aligned their levels with those in the HC group. The reduction in HETE and HODE, generally recognized as pro-inflammatory oxylipins, suggests lower inflammation in cows treated with PGNIAFM, which aligns with the lower systemic and AT inflammation described in Chirivi et al. (2023, 2024). However, 20-HETE levels remained high across all treatments compared with HC ($P < 0.01$), indicating possible inflammation after d 7 in cows recovering from CK.

The PGNIA treatment induced minimal alterations in the oxylipin profile compared with PG. Plasma ARA, LA, ALA, DHA, DPA, and EPA levels were similar between PG and PGNIA (Figure 1d-f). Arachidonic acid–derived 8,9-DHET was more abundant in PGNIA cows than in other treatments and HC, whereas 14,15-EET was higher in PGNIA than in PG and HC (Figure 1d). The PG-treated cows had the highest 9,10-DiHOME levels, whereas PGNIAFM cows had the lowest (Figure 1e). Higher DHET, EET, and EpOME levels may indicate a persistent pro-inflammatory profile in CK cows treated with PG or PGNIA. Among n-3-derived oxylipins, only 17-HDoHE was affected, with the PG group having higher levels than PGNIAFM and HC (Figure 1f).

Further investigation is needed to clarify the precise roles of these oxylipins in CK. Notably, PGNIAFM cows had an oxylipin profile similar to HC, suggesting faster resolution of CK-related inflammation than PG and PGNIA. Future studies should explore any interaction between NIA and FM, as this study did not include a separate PG+FM treatment group.

Next, we assessed the effect of lipolysis inhibitor treatment on canonical pathways at d 7 using IPA. The ARA metabolism pathway activity was reduced by PG and PGNIAFM compared with PGNIA (Figure 2B). Lipolysis inhibition did not affect transcriptional regulation of adipocyte differentiation and PPARα pathways (Z-scores not shown). Upstream pathway regulators activated at d 0 were affected by lipolysis inhibitors by d 7 (Figure 2C). The PGNIA treatment had limited EPHX2 activity downregulation compared with PG and PGNIAFM. PNPLA8 and NGF were strongly activated by PG and PGNIA (Figure 2C). In contrast, SLC30A7 was activated in PGNIAFM compared with the other treatments (Figure 2C). Although there is no specific evidence of how PG, NIA, and FM directly activate SLC30A7, FM's anti-inflammatory properties could indirectly affect zinc levels, as zinc is a negative acute-phase reactant and reducing inflammation increases plasma zinc (Jung et al., 2015).

This study provides lipidomics data showing elevated ARA-derived and reduced LA-derived oxylipins during CK in dairy cows, as well as the dynamics of oxylipins following treatment with gluconeogenic and antilipolytic agents. Our results identified ARA-derived 5- and 20-HETE, as well as LA-derived 13-oxoODE, 12,13-EpOME, and 9,10- and 12,13-DiHOME, as potential biomarkers of CK. Understanding the role of oxylipins and other byproducts of lipolysis and inflammation during ketosis could enhance our comprehension of the mechanisms underlying CK development.

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Notes

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Nonstandard abbreviations used: ALA = alpha linoleic acid; ARA = arachidonic acid; AT = adipose tissue; ATGL = adipose triglyceride lipase; CK = clinical ketosis; COX = cyclooxygenase; CYP450 = cytochrome P450; DHA = docosahexaenoic acid; DHET = dihydroxyeicosatrienoic acid; DiHOME = dihydroxyoctadecenoic acid; DPA = docosapentaenoic acid; EET = epoxyeicosatrienoic acid; EPA = eicosapentaenoic acid; EpOME = epoxyoctadecanoic acid; FFA = free fatty acid; FM = flunixin meglumine; HC = healthy control cows; HETE = hydroxyeicosatetraenoic acid; IPA = Ingenuity Pathway Analysis; LA = linoleic acid; LIPEA = lipid enrichment analysis; LOX = lipoxygenase; NIA = niacin; PG = propylene glycol; PGNIA = PG and 24 g NIA orally 1×/d for 3 d; PGNIAFM = PG, NIA, and 1.1 mg/kg of BW intravenous FM 1×/d for 3 d; RCT = randomized clinical trial; sEH = soluble epoxide hydrolase; TG = triglyceride.