



## Optimization of Marbling Through Vitamin A Management at Different Stages of Production Cycle in Beef Cattle

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**Abstract:** Marbling or intramuscular fat (IMF) is one of the major quality attributes of beef. Intramuscular adipocytes develop later than subcutaneous, visceral, and intermuscular fat depots during early development. The variation in developmental timing among fat depots can be leveraged as a targeted strategy to enhance marbling. Vitamin A regulates cell proliferation and differentiation via its active metabolite retinoic acid. Recent studies indicate that vitamin A supplementation to beef cattle during the late gestation and neonatal stages promotes the formation of IMF adipocytes (adipogenesis/adipocyte hyperplasia), which provide sites for IMF accumulation during the fattening stage. On the other hand, vitamin A promotes lipid oxidation, and its restriction during the finishing stage increases IMF deposition and achieves a higher ratio of prime-grade carcasses. In conclusion, the stage-specific vitamin A management strategy can be effectively utilized to maximize IMF deposition and improve beef quality.

**Key words:** beef, marbling, quality, yield, tenderness, vitamin A, gestation, neonatal stage

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### Introduction

Intramuscular fat (IMF), known as “marbling,” is a major determinant of meat palatability (Duarte et al., 2013). Marbling fat appears as white flecks of fat interspersed between muscle fibers and primary muscle bundles (Lee et al., 2018). Abundant marbling is correlated with improved tenderness, juiciness, enhancement of desirable flavor, and visual appearance of meat that cumulatively increase consumer satisfaction (Bonny et al., 2015; Stewart et al., 2021). However, it is a significant challenge for optimizing IMF deposition in beef cattle, because IMF has a lower nutrient partitioning priority compared to subcutaneous, intermuscular, and visceral depots, which are negatively associated with carcass yield (Mann, 2022; Wang et al., 2016). Therefore, selectively enhancing the development and deposition of IMF

without promoting the others is complex but economically important.

The marbling fat is affected by genetics, sex, and the availability of nutrients during the various developmental stages. Cattle breeds like Wagyu (>30% IMF) and Hanwoo (>12% IMF) generally exhibit higher fat content in their longissimus muscle; on the other hand, cattle with *Bos indicus* background, like Brahman, have lower IMF% (Beak et al., 2021; Nguyen et al., 2021; Yamada et al., 2020). Heifers exhibit higher IMF content than bulls, potentially due to the negative impact of male hormone testosterone and dihydrotestosterone on adipogenesis (Picard et al., 2019). Nutritional management at different stages of the life cycle has been effective in facilitating IMF accumulation in beef cattle (Mwangi et al., 2019; Park et al., 2018; Pogge and Hansen, 2013). Using a high-concentration diet rather than grass

during the finishing stage is one of the most popular strategies to increase IMF in Angus. In addition, several vitamins, including A, C, and D at different stages of the production cycle, were used as a strategy to improve IMF% in beef cattle due to their regulatory effect on adipogenesis (Harris et al., 2018; Pogge and Hansen, 2013; Pogge et al., 2015; Sarah et al., 2024).

Vitamin A and its metabolite retinoic acid promote the formation of new adipocytes (hyperplasia) during the early developmental stage, which can enhance IMF content in beef (Sarah et al., 2024; Wang et al., 2007; Yu et al., 2022). However, retinoic acid also promotes lipid oxidation, which may reduce adipocyte hypertrophy in finishing cattle (Knutson et al., 2020; Maciel et al., 2022; Pickworth et al., 2012a; Wang et al., 2018). Thus, restriction of vitamin A in finishing cattle has been utilized to enhance marbling and quality grade (Knutson et al., 2020).

In this review, we summarized the impacts of vitamin A supplementation at different stages of the production cycle of beef cattle on hyperplasia and hypertrophy of intramuscular adipocytes, as well as on beef yield. We aim to clarify the window of vitamin A management during the beef cattle production cycle for optimal IMF deposition and yield based on accumulating research findings.

## Vitamin A Metabolism in Beef Cattle

Vitamin A is a major fat-soluble vitamin that exists in several forms during its metabolic pathway, including retinol (circulatory form), retinyl esters (storage form), retinaldehyde, and retinoic acid (active form), collectively known as retinoids (Carazo et al., 2021). It is well established that ruminants can't synthesize the fat-soluble vitamins except vitamin D, and they entirely rely on the dietary supply of vitamin precursors to convert them into a metabolically active form. In ruminants, forages constitute the primary source of vitamin A precursor carotenoids, particularly  $\beta$ -carotene, which is enzymatically converted into active retinoids or stored in the liver (Shastak and Pelletier, 2024). The absorption of dietary  $\beta$ -carotenes takes place in the proximal part of the small intestine upon digestion, which is around 65 to 75% of dietary intake (Shirakami et al., 2012). The absorption is affected by dietary fat content due to its lipophilic nature, as well as the status of intestinal health and vitamin A status (Yao et al., 2023). Absorbed  $\beta$ -carotene is cleaved by  $\beta$ -carotene 15,15'-oxygenase 1 (BCO1) to generate retinol,

the immediate precursor of vitamin A. Retinol is also esterified to form retinyl esters, which are incorporated into chylomicrons for transport primarily to the liver and to other tissues such as adipose tissue for storage (Kim et al., 2011). Ruminal microbes play a major role in the degradation of  $\beta$ -carotene and retinol esters. Around 60% of  $\beta$ -carotene degradation occurs in the rumen. However, the variable nature of  $\beta$ -carotene 15,15'-oxygenase 1 activity in cattle impacts the efficiency of the bioconversion of  $\beta$ -carotene into the circulatory retinol or liver storage (Kim et al., 2011). Therefore, dietary supplementation of  $\beta$ -carotene alone may not be sufficient to ensure a proportional increase of circulatory retinol or liver storage.

Liver store majority of retinol in the body, around 80 to 85%, with the rest in adipose tissue, lungs, and kidneys in the form of retinyl esters (Shirakami et al., 2012). When required, free retinol can be delivered to the target tissues upon cleavage into retinol and the sequential oxidation by retinol dehydrogenases and retinal dehydrogenases (Kedishvili, 2016). Free retinol conjugates with retinol-binding protein and reaches the target tissue via circulation (Kedishvili, 2016). Restriction of retinol and  $\beta$ -carotene intake depletes liver storage within 40 d for light feeder steers, 120 d in finishing cattle, and 150 d in mature cows, indicating lower liver retinol storage in young animals relative to older (Wellmann et al., 2020). The availability of  $\beta$ -carotene in forages fluctuates due to seasons, the maturity level of forage, harvesting time, and storage duration. Fresh forage contains 5 times higher  $\beta$ -carotene than corn silage and 10 times higher than hay due to its susceptibility to oxidation (Pickworth et al., 2012b). Therefore, the actual intake of  $\beta$ -carotene varies greatly for cattle, completely dependent on forage diet, and retinol supplementation is required to maintain liver storage when fed on silage or haylage to prevent deficiency.

## Requirement of Vitamin A at Different Stages of The Production Cycle

### *In pregnant and lactating cows*

The cow-calf operation is the first stage in the beef cattle production system. Profitability of the cow-calf operation greatly depends on the reproductive efficiency of cows and the growth efficiency of calves. Because muscle development and intramuscular

adipocyte formation are actively ongoing, the prenatal stage, especially the mid to late fetal stage, is critical for enhancing offspring productivity (Du et al., 2013). Maternal nutritional status at this stage greatly influences the offspring's myogenesis, fibrogenesis, and adipogenesis (Hossain et al., 2025; Hossain et al., 2024). By regulating the proliferation and lineage-specific differentiation of progenitor cells, vitamin A is essential for the maintenance and formation of numerous tissues, including adipose tissue, skeletal muscle, and immune cells (Alosilla et al., 2007; Du, 2023; Jin et al., 2024). Beef production depends heavily on pastures, and the quality and quantity of grass in the pasture depend on the weather and geographical location. In the yearly reproduction cycle of cattle, pregnant cows frequently experience vitamin A deficiency, which occurs due to no or few availability of fresh forage during the winter and early spring, profoundly limiting  $\beta$ -carotene intake, and the increased nutrient demands due to the rapidly growing fetuses during the mid to late gestation (Weiss, 2018), which completely rely on maternal circulation for retinol (Sapin et al., 2000; Spiegler et al., 2012). Calves born to a vitamin A-deficient dam have low liver retinol storage and compromised immune functionality (Spiegler et al., 2012). Vitamin A supplementation to dams robustly enhances immune response and antibody concentration in offspring (Palmer et al., 2015).

While studies about vitamin A supplementation for beef cows are limited, there are several studies in dairy cows. To meet vitamin A demands, a supplementation of 110 IU/kg body weight is recommended for lactating dairy cows, or approximately 75,000 IU/day for a cow producing 75lb milk/day and consuming 60% forage with little or no fresh forage (NRC, 2001). The vitamin A supplementation during the dry period increases plasma retinol concentrations of calves and retinol concentration in the first colostrum (Puvogel et al., 2008). For cows producing over 75lb of milk, an additional supplementation of 450 IU/lb of milk can recover the loss of vitamin A via milk (according to the National Academies of Sciences, Engineering, and Medicine (NASEM), 2021). At the start of lactation, there is a significant loss of plasma retinol via colostrum; however, there is insufficient data about the requirement for additional vitamin A supplementation during this period.

### ***In neonate calves***

Neonatal calves have a greater risk of deficiency relative to cows, as they are born with low liver retinol

storage (Speer et al., 2024; Zanker et al., 2013). The critical role of retinoic acid in immune system development has been well established (West et al., 1989). Calf born with vitamin A deficiency have enhanced susceptibility to respiratory disease and calf scour due to immune deficiency (McGill et al., 2019). In humans, vitamin A supplementation remains widely used in developing countries to reduce the incidence of diarrhea and respiratory diseases in offspring (Imdad et al., 2011; Lie et al., 1993; Sommer et al., 1986). In addition to immune function, vitamin A plays a crucial role in vision. Lower vitamin A is associated with impaired weight gain, exophthalmos, and blindness in calves (Kang et al., 2017; van der Lugt and Prozesky, 1989). Altered skeletal growth was reported in a vitamin A-deficient calf (Gallina et al., 1970). Major skeletal growth occurs during the early stage of life, and vitamin A assists in bone development by stimulating the proliferation of osteoblasts and bone resorption (Yee et al., 2021). Early vitamin A deficiency manifests as staggering gait, lameness or stiffness in joints, swelling of legs and brisket (Olson and Hollis, 2007). Taking these immune and developmental functions into consideration, vitamin A deficiency can result in serious health outcomes as well as impaired growth.

Colostrum is the primary source of vitamin A. In addition, liver storage and plasma retinol concentrations rapidly increase in neonatal calves after intake of the first colostrum (Puvogel et al., 2008). For the first 2 to 3 mos of extrauterine life, calves depend greatly on the quality and quantity of colostrum that they absorbed in the first day of life to train their nascent immune system (Nowak et al., 2012; Osorio et al., 2013). Calves born with an adequate level of vitamin A acquire additional vitamin A from colostrum to meet calves' requirements (NASEM, 2021). However, calves with a deficient vitamin A level can be supplemented with a 5,000,000 IU vitamin A injection for an initial boost to retinol level. Liver or plasma retinol level should be assessed before injection to avoid hypervitaminosis and associated impairment of bone growth (Woodard et al., 1997). The NASEM recommendation for calves receiving milk replacer is 11,000 IU/kg milk replacer till the age of 3 mos, and calves on dry starter feed is 3,700 IU/kg DM (NASEM, 2021). However, calves born with severe developmental deformities, with muscle incoordination, will not be reversed by vitamin A supplementation.

Feeder cattle undergo a critical transition process from pasture to a grain-based diet in a feedlot specially in the first 3 to 4 wks. Vitamin A deficiency may develop after the feeder calves are on a ration

containing adequate retinol or vitamin A, due to replacing yellow corn with grain containing lower  $\beta$ -carotene, entering feedlot from winter pasture, using younger animals with lower liver retinol storage, or grazing on forages with drought or excessive use of nitrogen fertilizer (Mitchell et al., 1967). Younger animals deplete their liver storage more easily and are more likely to express the deficiency symptoms sooner than the older animals when on a vitamin A-deficient diet (Wellmann et al., 2020). Cattle with vitamin A deficiency exhibit reduced feed intake, poor weight gain, ataxia, convulsions, rough and dull hair coat, hair loss, and scale or scurf on the skin, night blindness, and total blindness in young and growing animals (Booth et al., 1987). For growing cattle, the requirement of vitamin A is 3,700 IU/kg of DM (NASEM, 2021). Incoming feeders and growing cattle under stress or coming from winter pasture can be supplemented with 500,000 to 1 million IU vitamin A via intramuscular, intra-ruminal injection or via drinking water to recover from the deficiency. However, monitoring plasma retinal level or liver storage by biopsy is required for the early identification of deficiency and timely vitamin A supplementation.

In finishing cattle, studies focused on vitamin A restriction due to its role in enhancing lipid oxidation. However, the NESAM recommendation of vitamin A for finishing cattle is 2,200 IU/kg DM, and cattle maintained on this recommended level of vitamin A supplementation exhibited higher average daily gain compared to those fed 3 and 5 times higher supplementation or completely vitamin A-restricted cattle (Gorocica-Buenfil et al., 2007; Pyatt et al., 2005; Zinn et al., 1996). On the other hand, finishing cattle without vitamin A supplementation for 120 d didn't exhibit symptoms of night blindness or other complications and showed no alteration in carcass characteristics (Bryant et al., 2010; Wellmann et al., 2020). These data suggest the relatively higher tolerance of finishing cattle compared to young calves to vitamin A deficiency.

## Development of The IMF in Beef Cattle

### *Origins and timeline of adipocyte formation in different fat depots of beef cattle*

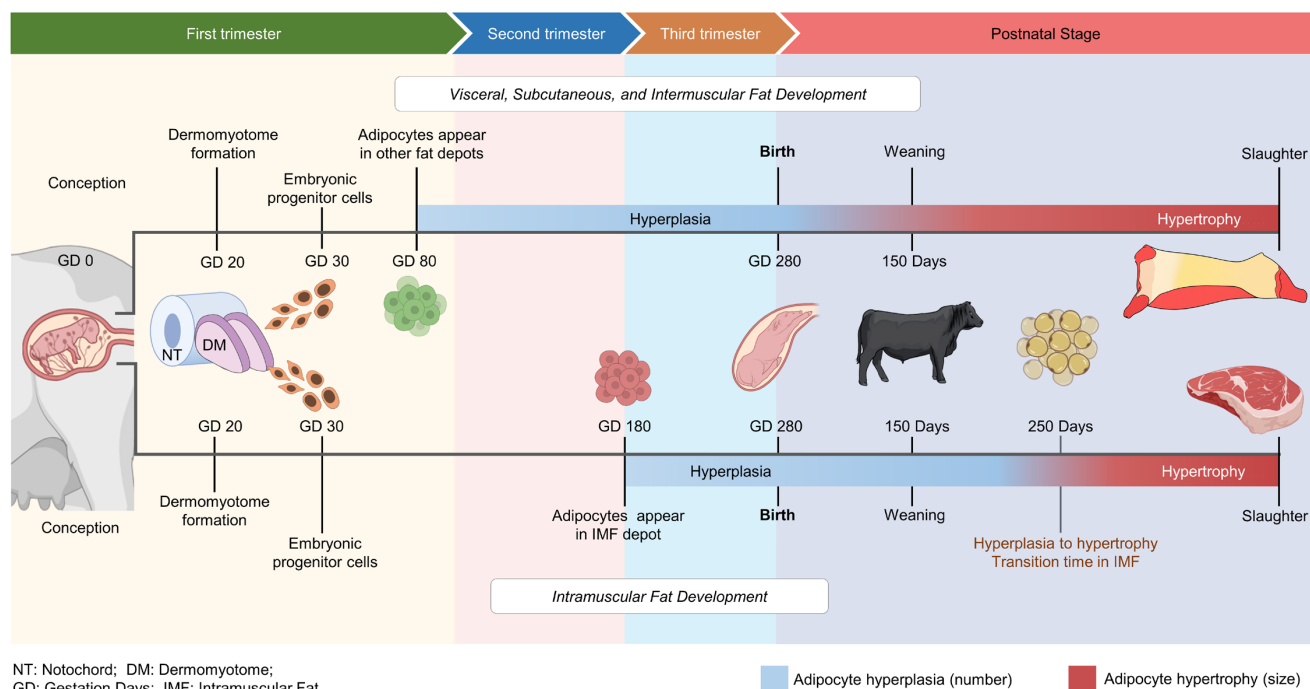
The development of visceral, subcutaneous, intermuscular, and intramuscular fat depots begins at different time points of the embryonic and fetal stages. During early development, somites, the segmented structures of

embryos, split into sclerotomes and dermomyotomes around gestational day (GD) 20. The dermomyotomes further develop into myogenic and nonmyogenic multipotent progenitor cells at approximately GD 30 in beef cattle (Du et al., 2017). The visceral adipose tissue progenitor cells and preadipocytes are the first to appear, mainly from non-myogenic cells of the dermomyotome at GD 80 (Du, 2023; Vernon, 1986). The de novo formation of new adipocytes in visceral fat continues during the neonatal stage. The subcutaneous and intermuscular adipocytes appear following the visceral depot, and their formation continues until the early pre-weaning period, after which it becomes progressively limited (Figure 1) (Keogh et al., 2021). The intramuscular adipocytes are the last ones to appear at approximately GD 180 of the fetal stage and continue till about 250 d of age, when it wanes (Du, 2023).

### ***Proliferation and adipogenic differentiation of progenitor cells***

The formation of new adipocytes occurs through 2 distinct phases: commitment of progenitor cells to adipogenic lineage and differentiation of committed cells into mature adipocytes (Nguyen et al., 2021). The sequential expression of several transcription factors and lineage-specific genes regulates adipogenic commitment of mesenchymal progenitor cells, followed by the differentiation process. The proliferation and pluripotency of these mesenchymal progenitor cells are regulated by several transcription factors, including Krüppel-like factor 2 (KLF2), SRY-related HMG-box 9 (SOX9), and preadipocyte factor 1 (PREF-1) (Table 1). They express highly in undifferentiated embryonic stem cells and promote their proliferation. The higher abundance of progenitor cells allows the formation of more adipocytes in the later stages of life. The expression *Klf2* downregulates during differentiation, accompanied by loss of cell pluripotency (da Silva et al., 2020; Sun et al., 2022; Vietor et al., 2023; Wang et al., 2016b).

Zinc-finger protein 423 (ZFP423) is the first transcription factor expressed during the commitment of progenitor cells to adipogenesis. In bovine stromal vascular cells, *Zfp423* expression correlates with their adipogenic potential (Gupta et al., 2012; Hepler et al., 2017; Huang et al., 2012). In the same steer, *Zfp423* expression varies across different muscles and was correlated with the IMF abundance (Martinez Del Pino et al., 2020). These findings suggest *Zfp423* as a regulator of muscle-specific differences in adipogenic potential.



**Figure 1.** Timeline of intramuscular, visceral, subcutaneous, and intermuscular fat development in Angus cattle. The times for adipocyte hyperplasia and hypertrophy are approximate (Du, 2023; Du et al., 2017; Keogh et al., 2021; Vernon, 1986). NT: notochord; DM: dermomyotome; GD: gestation days; IMF: intramuscular fat. Created with BioRender.com

The further differentiation of committed adipocytes is mediated by a cascade of adipogenic regulatory factors, including CCAAT/enhancer-binding proteins (C/EBPs) family and peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) (Park et al., 2016; Tang et al., 2021). C/EBP $\beta$  and C/EBP $\delta$  appear during the early stage of adipogenesis and form a heterodimer complex that induces the expression of the terminal differentiation marker *Ppar $\gamma$*  and *Cebpa* (Table 1) (Malibary, 2023; Park et al., 2016). PPAR $\gamma$  also enhances *Cebpa* expression to facilitate the terminal differentiation of adipocytes (Rosen et al., 1999). In addition, sterol regulatory element-binding protein 1c (SREBP1C) is another crucial regulatory factor of adipogenic differentiation, which is induced by the C/EBP $\beta$  and C/EBP $\delta$  dimer and enhances the formation of PPAR $\gamma$  ligands, which facilitates the terminal differentiation of adipocytes (Payne et al., 2009; Wang et al., 2016a). Collectively, adipocyte differentiation is a complex and highly coordinated process involving multiple transcription factors that interact, regulate one another, and fine-tune each other's activity.

### Regulation of lipid accumulation in adipocytes

Following adipogenic differentiation, adipocytes accumulate lipids to increase in size, a process referred

to as adipocyte hypertrophy. This accumulation occurs by the uptake of free fatty acids that are released from the circulating lipoprotein by lipoprotein lipase and by *de novo* fatty acid (FA) synthesis inside adipocytes (Goldberg et al., 2009). Fatty acid translocase (CD36), fatty acid transporter protein 1 (FATP1), and intercellular fatty acid binding protein 4 (FABP4) are involved in the transportation of FA into adipocytes (Table 1) (Goszczynski et al., 2017; H. Li et al., 2022). The *Fabp4* abundance is correlated with IMF deposition and cattle breeds such as Wagyu, renowned for their high IMF, which highly express this gene (Goszczynski et al., 2017). During *de novo* FA synthesis, acetyl-CoA carboxylase converts acetyl-CoA to malonyl-CoA, which is then used for fatty acid chain elongation by fatty acid synthase. Stearoyl-CoA desaturase (SCD) subsequently introduces double bonds into saturated fatty acyl chains to produce monounsaturated fatty acids. Esterification of these FA with glycerol backbone forms triacylglycerol (TAG), the neutral lipid stored as lipid droplets inside adipocytes (Xue et al., 2017). Adipocytes in ruminants can effectively utilize acetate as a substrate to synthesize fatty acids (Nguyen et al., 2021). Glucose transporter 4 (GLUT4), an insulin-dependent glucose transporter, facilitates the uptake of glucose into cells, and glucose is used for producing the glycerol backbone. Importantly, propionic acid produced during rumen fermentation is a major

**Table 1.** Role of different genes involved in the development of intramuscular adipose tissue in beef cattle

Genes	Function	References
<b>Proliferation</b>		
<i>Klf2</i> (Krüppel-like factors-2)	Promotes proliferation of adipogenic progenitor cells.	(Wang et al., 2016b; Wang and Sul, 2009)
<i>Sox9</i> (SRY-related HMG-box 9)	Maintain their undifferentiated state by downregulating the genes involved in differentiation.	(da Silva et al., 2020; Sun et al., 2022; Vietor et al., 2023; Wang et al., 2016b)
<i>Pref-1/ Dlk1</i> (Preadipocyte factor 1)		
<b>Commitment</b>		
<i>Zfp 423</i> (Zinc-finger protein 423)	<ul style="list-style-type: none"> <li>• Reduces thermogenic gene expression and maintains white adipose tissue identity, which may enhance fat deposition</li> <li>• Expression correlates with their adipogenic potential</li> </ul>	(Gupta et al., 2012; Hepler et al., 2017; Huang et al., 2012)
<b>Differentiation</b>		
<i>Cebpb</i> (CCAAT/enhancer-binding protein β)	Expresses in the early stage of adipogenesis and induces the expression of later-stage differentiation markers of <i>Pparγ</i> and <i>Cebpa</i> .	(Park et al., 2016; Tang et al., 2021).
<i>Cebpδ</i>	<ul style="list-style-type: none"> <li>• Expresses along with <i>Cebpb</i> at early stage of adipogenic differentiation</li> <li>• Forms heterodimer with <i>Cebpb</i> and induces the expression of <i>Pparγ</i> and <i>Cebpa</i></li> </ul>	(Malibary, 2023; Park et al., 2016)
<i>Sox6</i> (SRY-related HMG-box 6)	Inhibits adipogenic differentiation.	(Park et al., 2016; Tang et al., 2021)
<i>Pparγ</i> (Peroxisome proliferator-activated receptor γ)	Enhances <i>Cebpa</i> expression to facilitate the terminal differentiation of adipocytes.	(Rosen et al., 1999)
<i>Cebpa</i> (CCAAT/enhancer-binding protein α)	Forms a complex with C/EBPβ and C/EBPδ dimer to promote terminal differentiation.	(Guo et al., 2015; Park et al., 2016)
<i>Srebp1c</i> (Sterol regulatory element-binding protein 1c)	<ul style="list-style-type: none"> <li>• Enhances the formation of PPARγ ligands</li> <li>• Facilitates the terminal differentiation of adipocytes</li> </ul>	(Payne et al., 2009; Wang et al., 2016a)
<i>Cfd</i> (Complement Factor D)	Encodes Adipsin, which is correlated with adipogenic differentiation and IMF deposition in cattle.	(Wang et al., 2023)
<i>Nab2</i> ( <i>Ngfi-a binding protein 2</i> )	<ul style="list-style-type: none"> <li>• Facilitates the expression of <i>Cfd</i></li> <li>• Is highly expressed in Wagyu cattle</li> </ul>	(Wang et al., 2023)
<b>Lipid Accumulation</b>		
<i>Cd36</i> (Fatty acid translocase)	Involved in the transportation of fatty acids into adipocytes.	(Goszczynski et al., 2017; Li et al., 2022)
<i>Fatp1</i> (Fatty acid transporter protein 1)	Enhances the cellular uptake of long-chain fatty acids and lipid accumulation.	(Wu et al., 2006)
<i>Fabp4</i> (Fatty acid binding protein 4)	Facilitates the transportation of fatty acids across cell membranes. Regulates glucose homeostasis.	(Goszczynski et al., 2017).
<i>Glut4</i> (Glucose transporter 4)	An insulin-dependent glucose transporter facilitates the uptake of glucose into cells, and glucose is used to produce the glycerol backbone.	(Maldini and Allen, 2019)
<i>miR-424</i> (microRNA)	Promotes adipogenesis by upregulating Liver Kinase B1, involved in the AMP-activated protein kinase pathway.	(Wang et al., 2020; Yue et al., 2022)
<i>Lkb1</i> (Liver Kinase B1)	Negatively associates with adipogenesis and enhances the expression of genes associated with thermogenesis and lipolysis in cattle, including <i>Pgc1a</i> , <i>Ppara</i> , <i>Ucp1</i> , <i>Atgl</i> , <i>Hsl</i> , and <i>Lpl</i> .	(Wang et al., 2020; Yue et al., 2022)
<i>Acta1</i> , <i>Tnnt1</i> and <i>Mdh2</i>	Negatively associated with IMF deposition.	(Shin and Chung, 2016)

source of glycerol for TAG synthesis in cattle (Maldini and Allen, 2019). Once TAG is formed, perilipin-1 (PLIN1) coats the lipid droplets to make them stable

inside adipocytes. On the other hand, lipolysis, catalyzed by hormone-sensitive lipase, hydrolyzes TAG and releases FFA and glycerol. Then, FFA is broken

down into acetyl-CoA in mitochondria for  $\beta$ -oxidation and energy production (Houten and Wanders, 2010).

Greater IMF deposition is correlated with the higher capability of synthesizing saturated fatty acids and monounsaturated fatty acids (MUFA) in cattle (Nguyen et al., 2021). Stearoyl-CoA desaturase catalyzes the synthesis of MUFA, a major component of IMF, which enhances beef flavor (Oh et al., 2013). Cattle such as Wagyu and Hanwoo that exhibit higher IMF compared to Angus, Holstein, and other beef breeds highly express *Scd* (Gotoh and Joo, 2016), which catalyzes MUFA production (Chung et al., 2021). In addition, MUFA can act as a PPAR $\gamma$  ligand and enhance PPAR $\gamma$  activity (Moreno et al., 2010), which likely can promote adipogenesis.

## Vitamin A Stage-Specifically Regulates Adipogenesis

### *Vitamin A promotes the proliferation of adipogenic progenitor cells*

Retinoic acid, the active metabolite of vitamin A, is a major regulator of adipogenesis. Retinoic acid binds to retinoic acid receptor (RAR) and retinoic acid X receptor, which form a dimer and bind with specific retinoic acid response elements located in the promoters of their target genes (Cunningham and Duester, 2015; Malibary, 2023). Retinoic acid regulates adipogenesis by influencing cellular differentiation, proliferation, and lipid accumulation; however, its regulatory effects and outcomes vary depending on the stage of adipogenic development.

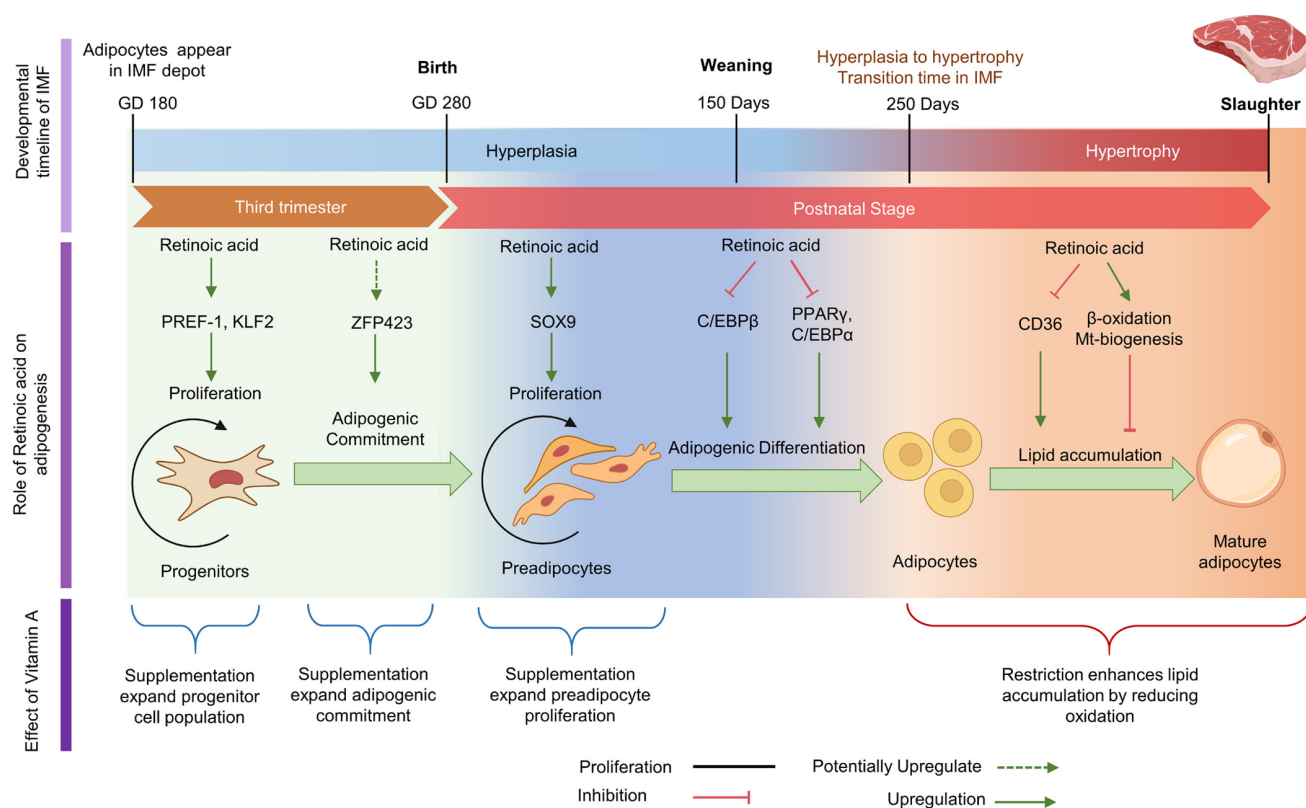
As a potent regulator, retinoic acid regulates the proliferation and commitment of progenitor cells. In adipogenic progenitor cells, *Pref1* and *Klf2* expression increase shortly after retinoic acid exposure (Jim et al., 2024). Retinoic acid upregulates *Pref-1* expression by activating the cellular retinoic acid binding protein type II (CRABP-II)/ RAR $\gamma$  (Noy, 2013). Another gene, *Sox9*, is a downstream target of PREF-1 become activated after retinoic acid exposure. By activating *Sox9* and *Klf2*, Retinoic acid enhances progenitor cell proliferation and expands the progenitor cell pool (Berry et al., 2012). Retinoic acid-mediated expansion of the progenitor cell population during the embryonic stage may increase the number of cells available for differentiation later in development (Figure 2).

### *Vitamin A enhances adipogenic commitment*

As a key developmental gene, *Zfp423* is highly expressed in committed adipogenic progenitor cells in both rodents and cattle (Gupta et al., 2012; Harris et al., 2018; Huang et al., 2012; Jin et al., 2024). *In vivo* retinoic acid treatment in adipogenic progenitor cells initially increased cell proliferation and *Zfp423* expression, but its expression downregulated with the progression of differentiation (Hepler et al., 2017; Jin et al., 2024; Wang et al., 2017). As *Zfp423* is expressed in the very early stage of adipogenesis during commitment, the early upregulation enhances the adipogenic commitment and downregulates with the advancement of adipogenesis, likely due to retinoic acid-mediated inhibition of differentiation (Berry et al., 2012). Collectively, these data indicate the positive effects of vitamin A on *Zfp423* expression and adipogenic commitment.

### *Vitamin A inhibits adipogenic differentiation*

Transcription factors PPAR $\gamma$  and CEBP $\alpha$  are two master regulators of adipogenic differentiation, preceded by early differentiation marker C/EBP $\beta$ . Retinoic acid signaling suppresses the expression of both early and terminal differentiation markers. Retinoic acid upregulates SMAD3, the downstream of transforming growth factor (TGF)  $\beta$  signaling pathway, which alters the DNA binding ability of C/EBP $\beta$  through its Mad homology 1 (MH1) domain (Hossain et al., 2024; Marchildon et al., 2010). Retinoic acid inhibits the GSK3 $\beta$ -mediated phosphorylation activity at Thr188 of C/EBP $\beta$  and decreases its DNA binding capability (Ayala-Summano et al., 2016; X. Li et al., 2009). Downregulation of C/EBP $\beta$  delays the expression of terminal differential regulators *Ppar $\gamma$*  and *Cebpa*, inhibiting adipogenic differentiation (Guo et al., 2015). In addition, retinoic acid can directly inhibit PPAR $\gamma$  and CEBP $\alpha$  activity. *In vivo* retinoic acid treatment induces the expression of Fos-related antigen 1 (FRA1) that directly binds with the *Ppar $\gamma$*  promoter to downregulate its expression (Xie et al., 2020). In addition, C/EBP homologous protein (CHOP) is upregulated in preadipocytes after retinoic acid exposure. CHOP forms a heterodimer with C/EBP $\beta$ , sequestering its ability to stimulate C/EBP $\alpha$  expression and delay the terminal differentiation (Chikka et al., 2013; Gery et al., 2004). Thus, retinoic acid inhibits both early and late stages of adipogenic differentiation.



**Figure 2.** Potential role of retinoic acid on adipocyte hyperplasia and hypertrophy at different stages of development in beef cattle. Both hyperplasia and hypertrophy are continuous processes, and the hypothetical timeline only shows the dominant mechanism at that stage (Ayala-Sumano et al., 2016; Berry et al., 2012; Harris et al., 2018; Huang et al., 2012; Jin et al., 2024; Lim et al., 2006; Tourniaire et al., 2015; Xie et al., 2020). KLF2: Krüppel-like factors-2; SOX9: SRY-related HMG-box 9; PEF-1: Preadipocyte factor 1; ZFP423: Zinc-finger protein 423; C/EBP: CCAA T/enhancer-binding proteins, PPAR $\gamma$ : peroxisome proliferator-activated receptor  $\gamma$ ; CD36: Fatty acid translocase. Created with [BioRender.com](https://www.biorender.com)

## Vitamin A suppresses lipogenesis and enhances fatty acid oxidation

Retinoic acid suppresses lipogenesis and impairs adipocyte hypertrophy. Fatty acid translocation into cells is regulated by *Cd36*, the expression of which is stimulated by PPAR $\gamma$ , a key marker for terminal adipogenic differentiation (Lim et al., 2006). By inhibiting *Ppar $\gamma$*  expression, retinoic acid delays *Cd36* expression, reduces fatty acid transport into mature adipocytes, and thereby suppresses lipogenesis (Amengual et al., 2018). In addition, retinoic acid promotes lipid catabolism and enhances energy expenditure in the body. Retinoic acid upregulates *Ppara*, a key gene promoting  $\beta$ -oxidation (Mandard et al., 2004). Retinoic acid also acts as a ligand for PPAR $\beta/\delta$ , further enhancing peroxisomal fatty acid  $\beta$ -oxidation (Levi et al., 2015; Shaw et al., 2003). In addition, retinoic acid activates transcription of Peroxisome-proliferator-activated receptor- $\gamma$  coactivator-1 (PGC-1 $\alpha$ ), in coordination with PPAR $\alpha$ , activates the other key genes, including Carnitine palmitoyl transferase 1A (CPA-1a), to upregulate  $\beta$ -oxidation (Song et al., 2010). Furthermore, retinoic acid enhances the browning of

white adipose tissue by facilitating mitochondrial biogenesis and inducing *Ucp1* expression (Tourniaire et al., 2015; Wang et al., 2017; Wang et al., 2018). Collectively, retinoic acid inhibits adipocyte hypertrophy through enhancing fatty acid  $\beta$ -oxidation and suppressing adipocyte hypertrophy.

To summarize, the impact of retinoic acid on adipose development is stage-specific. It enhances the proliferation and self-renewal of the adipogenic progenitor cells and commitment of preadipocytes; however, it inhibits differentiation and lipid accumulation (Figure 2).

## Stage-Specific Vitamin A Management to Improve Imf Deposition in Beef Cattle

### Vitamin A management in late gestation

Adipocyte progenitor cells begin to appear in the intramuscular area during the mid to late gestation, around GD180, whereas in other fat depots they appear

**Table 2.** Effect of vitamin A supplementation during the prenatal stage on beef yield and quality

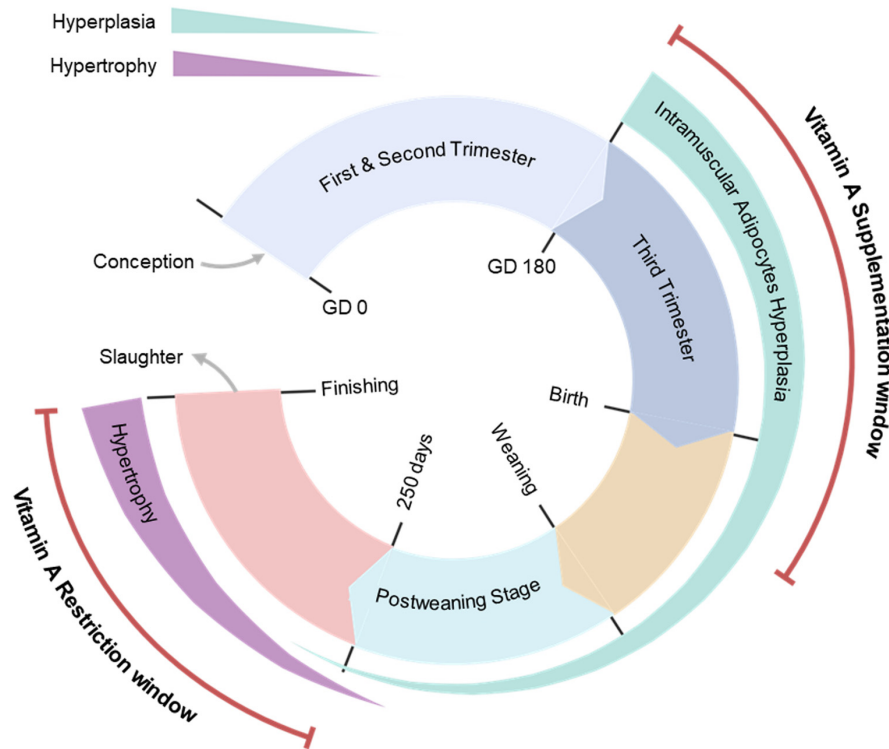
Breed	Vitamin A treatment	Effect on Beef Yield	Effect on Beef quality	References
Angus-Simmental	Supplementation of vitamin A with feed • 12,200 IU/kg DM from 180 d of gestation to parturition	At 480 d of age • No significant change in body weight and size of ribeye area	At 480 d of age • Around 41% percentage increase in IMF in offspring	(Sarah et al., 2024)
Hanwoo	Supplementation of vitamin A with feed • 3,508 IU/kg DM from 150 to 225 days of gestation • 9,508 IU/kg DM from gestational day 225 until parturition.	At 31 d of age • Increased birth weight of offspring • Upregulated expression of Myogenic marker genes	At 31 d of age • Increased preadipocyte marker gene <i>Klf2</i> , but the comparative quantification of preadipocytes was not reported	(Jo et al., 2020)
Angus - Nellore	Single dose of vitamin A injection at 2,000,000 IU/hd • At 250 d of gestation in the cow • At birth and 60 days of age in calves	At 297 d of age after finishing • Steers exhibited higher body weight • No effect on heifer	At 297 d of age after finishing • Steers exhibited a greater ribeye area and marbling • No effect on heifer	(Ladeira et al., 2024)

earlier (Figure 2) (Du, 2023). As discussed above, retinoic acid promotes the proliferation of adipogenic progenitor cells, which provides an opportunity to effectively increase the IMF progenitor cell pool with less effect on other depots. Consistently, retinoic acid treatment to Angus-Simmental cows from GD180 till parturition increased IMF deposition without a significant effect on the subcutaneous fat thickness and Kidney Pelvic Heart (KPH) fat (Table 2) (Sarah et al., 2024). On the other hand, retinoic acid treatment during this period didn't affect muscle development (Sarah et al., 2024). In another study, retinoic acid treatment of Hanwoo cows from GD150 to parturition affected both myogenesis and intramuscular adipogenesis. The *longissimus dorsi* muscle showed higher expression of *Klf2*, indicating an increased proliferation rate of progenitor cells, as well as elevated expression of myogenic marker genes *Myod* and *Myf5* (Jo et al., 2020). Since secondary myogenesis in beef cattle is actively ongoing around GD150, retinoic acid treatment during this period may enhance muscle development (Du et al., 2017). However, adipogenesis in subcutaneous, visceral, and intermuscular fat depots is also active during this time, meaning that retinoic acid treatment could potentially increase adipocyte progenitor cell population in these depots, a possibility that was not assessed in the study (Jo et al., 2020). Furthermore, because myogenic and adipogenic cells originate from the same progenitor pools, early embryonic retinoic acid treatment might shift the balance of progenitor cell fates toward myogenesis (Song et al., 2024). While the impact of this early retinoic acid treatment on final body weight and intramuscular fat content in finishing cattle needs to be thoroughly examined, available studies point to promising results. In Angus-Nellore cows, vitamin A treatment on GD 250 resulted in higher body

weight and ribeye area. In addition, it increased both IMF percentage and backfat thickness, with steers surprisingly exhibiting greater improvements than heifers in all parameters (Ladeira et al., 2024). Therefore, vitamin A supplementation during the last trimester of gestation has the potential for enhancing IMF development, with steers showing a better response than heifers (Figure 3).

### Vitamin A management in the neonatal stage

The hyperplasia of intramuscular adipocytes continues after birth until approximately 250 d of age, whereas the hyperplasia of other fat depots gradually declines after the neonatal stage (Du et al., 2017). Therefore, retinoic acid treatment of calves in the neonatal stage has been used as a strategy to improve IMF content in beef. In Angus steer calves, vitamin A injection of 150,000 IU administered twice at birth and at one month of age increased IMF by approximately 18–24%, along with marbling score, without altering other fat depots at 438 d of age, and showed greater efficiency than a 300,000 IU injection (Table 3) (Harris et al., 2018; Yu et al., 2022). *Biceps femoris* muscle at 2 mos of age from vitamin A-treated calves exhibited increased population of adipose tissue *Pdgfra* positive adipose progenitor cells, as well as an upregulation of angiogenic genes *Vegfa* and *Vegfr2*. Similarly, intramuscular injection of vitamin A in Montana-Nellore calves resulted in a ~25.4% increase in IMF in the *longissimus thoracis* muscle without alteration in body weight and ribeye area (Maciel et al., 2022). Additionally, combined vitamin A treatment during late pregnancy and the neonatal stage in Hanwoo cattle increased body weight gain and the expression of the preadipogenic marker gene



**Figure 3.** Proposed vitamin A management windows to optimize intramuscular fat deposition in beef cattle. In the prenatal vitamin A supplementation window, vitamin A is supplemented at 12,200 IU/kg DM from GD180 to parturition (based on prenatal treatment on Angus x Simmental cows or neonatal injection of 150,000 IU/hd to calf at birth and 1 mo of age (Harris et al., 2018; Sarah et al., 2024; Yu et al., 2022)). During the vitamin A restriction window at the finishing stage, cattle are provided 600 to 1103 IU/kg DM vitamin A (Based on vitamin A restriction treatment of Angus x Simmental and Angus Steers for 5 and 10 mos, respectively, from Knutson et al., 2020; Kruk et al., 2018). GD: gestation day.

**Note: High doses of vitamin A intake or injection during pregnancy may lead to teratogenic effects in offspring for both humans and animals (Rothman et al., 1995). Serum retinol level should be monitored, and animals with a serum retinol level lower than the minimum required level (22.5 ng/mL) should not enter vitamin A restriction treatment due to health complications of vitamin A deficiency.**

*Pref1*, indicating a potential increase in adipogenic progenitor population and yield in finishing cattle (Peng et al., 2020). However, in this study, the final IMF percentage and carcass weight of the cattle were not evaluated. Overall, these findings suggest that vitamin A treatment during the neonatal stage, alongside prenatal administration, can be effective in enhancing IMF in beef cattle.

Comparing vitamin A treatment during prenatal and neonatal stages provided important insights into the relative effectiveness of vitamin A treatment. Vitamin A treatment in cows during the last month of pregnancy, compared to treatment of calves at birth and 2 mos of age, revealed that prenatal administration resulted in greater increases in IMF percentage and ribeye area in steers than neonatal treatment (Ladeira et al., 2024). However, vitamin A treatment at either stage did not result in differences in final body weight or dressing percentage among steers. While neonatal vitamin A treatment produced a ~18–25.4% increase in IMF in carcasses, prenatal supplementation to cows achieved a substantial ~41% increase (Maciel et al.,

2022; Sarah et al., 2024; Yu et al., 2022). Overall, evidence suggests that both prenatal and neonatal vitamin A treatments can improve IMF in beef cattle without increasing the mass of other fat depots or negatively impacting growth performance and carcass yield, while prenatal treatment during the last trimester (GD180 to parturition) can be more effective.

### **Vitamin A management in growing and finishing heifers and steers**

During the growing and finishing stages, the adipogenic capacity of the intramuscular fat depot wanes, and lipid accumulation in existing adipocytes becomes a major factor in marbling fat accumulation. While vitamin A supplementation during early developmental stages increases IMF adipocyte number, which provides sites for marbling fat deposition, vitamin A during the growing and finishing stages enhances lipid oxidation to suppress marbling fat accumulation. Therefore, vitamin A restriction has been used to increase IMF deposition, particularly in steers

**Table 3.** Effect of vitamin A supplementation in the neonatal stage on beef yield and quality

Breed	Vitamin A Supplementation	Effect on Beef Yield	Effect on Beef quality	References
Angus	Single dose of vitamin A Injection of 150,000 and 300,000 IU/hd to calves <ul style="list-style-type: none"> <li>• At birth</li> <li>• At 1 mo age</li> </ul>	At 438 d of age 150,000 IU vitamin A injection <ul style="list-style-type: none"> <li>• No impact on overall growth performance</li> </ul>	At 438 d of age vitamin A injection <ul style="list-style-type: none"> <li>• Increased 18% IMF</li> <li>• Increased marbling scores</li> </ul>	(Harris et al., 2018)
Hanwoo	Oral supplementation of vitamin A <ul style="list-style-type: none"> <li>• From day 220 to parturition, 100,000 IU/hd/d to the cow</li> <li>• From day 5 to 2 mos of age, 25,000 IU/hd/d to calves</li> </ul>	At 2 mos of age <ul style="list-style-type: none"> <li>• Promoted myogenic marker gene expression in <i>longissimus dorsi</i> muscle</li> </ul>	At 2 mos of age <ul style="list-style-type: none"> <li>• Vitamin A promoted preadipocyte development</li> </ul>	(Peng et al., 2020)
Angus	Vitamin A injection of 150,000 IU/hd to calves <ul style="list-style-type: none"> <li>• At birth</li> <li>• At 1 mo of age</li> </ul>	No data available about carcass weight or dressing percentage	At 308 d of age <ul style="list-style-type: none"> <li>• Vitamin A-treated cattle had around 24% increase in IMF</li> </ul>	(Yu et al., 2022)
Montana: Nellore Calves	Vitamin A injection (IM) of 300,000 IU/hd <ul style="list-style-type: none"> <li>• At Birth</li> </ul>	At 390 d of age <ul style="list-style-type: none"> <li>• No effect on final body weight and ribeye area</li> </ul>	At 390 d of age <ul style="list-style-type: none"> <li>• Increased 25.4% IMF in <i>longissimus thoracis</i> muscle</li> </ul>	(Maciel et al., 2022)
Angus: Nellore	Vitamin A injection 2,000,000 IU/hd <ul style="list-style-type: none"> <li>• At day 250 of gestation in the cow</li> <li>• At birth and 60 d of age in calves</li> </ul>	At 297 d of age after finishing <ul style="list-style-type: none"> <li>• Steers from vitamin A-injected cows exhibited higher body weight than neonatal injection</li> </ul>	At 297 d of age after the finishing <ul style="list-style-type: none"> <li>• Steers from Vita A injected cows exhibited higher IMF % than neonatal injection</li> </ul>	(Ladeira et al., 2024)

(Table 4) (Knutson et al., 2020; Kruk et al., 2018; Pickworth et al., 2012a; Wellmann et al., 2020).

The recommended level of vitamin A by the NASEM is 2,000 IU/Kg DM (NASM, 2016) for feedlot cattle. Supplementation of vitamin A to the recommended level or higher level (11,000 IU/kg DM) in vitamin A-depleted steers for a shorter period of time during the finishing stage in 7 to 8-mo-old Angus cattle didn't impact the carcass yield or quality, including IMF, KPH, and marbling score (Wellmann et al., 2020). However, supplementation for a long time (~10 mos) in Angus reduced IMF percentage and back-fat thickness, without reducing the density of adipocytes (Kruk et al., 2018; Pickworth et al., 2012a). In yearling and 2-year-old Limousin-Luxi cattle, a higher dose of vitamin A (4,000 IU/kg DM) reduced the meat tenderness (Wang et al., 2007). Furthermore, retinoic acid enhances collagen synthesis by fibroblasts, accompanied by reduced lipid accumulation, which might explain the increase in shear force of beef from the higher vitamin A intake group (Zasada and Budzisz, 2019).

On the other hand, complete restriction of vitamin A to Angus steers during feedlot for 6 mos increased the number of USDA Choice and Prime carcasses in the finished cattle (Pickworth et al., 2012b). Lower vitamin A supplementation (723 IU/kg DM) for ~5 mos to Simmental and Angus Steers with depleted liver retinol storage and to Angus steers with (600 IU/kg DM) regular liver retinol level for ~10 mos increased IMF %, and the number and size of marbling

flecks increased by 22% (Knutson et al., 2020; Kruk et al., 2018). Yearling steers typically have sufficient retinol stores for about 3 mos, and exposure to a low-vitamin A basal diet for longer than 3 mos depletes liver retinol stores, reflected in reduced serum retinol levels (Bryant et al., 2010; Wellmann et al., 2020). As hypertrophy becomes prominent during this stage, low retinol levels reduce lipid oxidation, which promotes lipid storage and marbling fat accumulation (Tourniaire et al., 2015). Therefore, vitamin A restriction throughout the entire finishing stage can effectively promote adipocyte hypertrophy and IMF deposition in beef cattle (Figure 3).

### Sex-specific effects of vitamin A supplementation on marbling

The sex-specific impact of vitamin A treatment during neonatal stages in terms of marbling is ambiguous from the available studies. All the neonatal vitamin A treatment trials were conducted on Angus cattle, where the IMF content was measured after finishing on steers only (Harris et al., 2018) (Yu et al., 2022) (Maciel et al., 2022). In Hanwoo cattle, both male and female calves were treated with oral vitamin A supplementation and the genes related to preadipocyte development at 2 mos of age; however, the sex-specific comparisons were not carried out (Peng et al., 2020). The only vitamin A trial that evaluated its sex-specific effect on both the prenatal and neonatal stages was conducted on Nellore × Angus crossbred cattle, and the

**Table 4.** Effect of vitamin A treatment in growing and finishing steers on beef yield and quality

Breed/Type	Age (Mos)	Vitamin A Supplementation	Effect on Beef Yield	Effect on Beef Quality	References
Angus	Feedlot	Vitamin A restriction and and 3750 IU/kg DM of vitamin A for 184 d in the feedlot	No effect on body weight gain	Restriction of vitamin A supplementation <ul style="list-style-type: none"> <li>Increased % of USDA Choice+ and Prime quality grade</li> <li>Increased backfat thickness</li> </ul>	(Pickwort et al., 2012a)
Angus Steers	7m	Supp. of vitamin A at 0, 2,200, and 11,000 IU/kg DM for 119 d to vitamin A-depleted steers	No difference in hot carcass weight, ribeye area, carcass yield	Vitamin A restriction and 11,000 IU/kg DM supplementation both lowered the marbling score; however, they were not significant	(Wellmann et al., 2020)
Simmental and Angus Steers	8m	Supp. of vitamin A at 723 IU/kg DM for 156 d (Vitamin A restriction)	No effect on body weight gain	Restriction of vitamin A intake <ul style="list-style-type: none"> <li>Increased IMF percentage</li> <li>Increased ribeye area</li> <li>Increased number of prime carcasses</li> </ul>	(Knutson et al., 2020)
Angus Steers	12m	Supp. of vitamin A at 600 IU/kg DM for 10 mos (Vitamin A restriction)	No effect on overall weight gain	Restriction of vitamin A intake <ul style="list-style-type: none"> <li>Increased IMF by 46%</li> <li>Number of marbling flecks increased by 22%</li> </ul>	(Kruk et al., 2018)
Angus Steers	12m	Suppl. of vitamin A at 1,103, 2,205, 4,410, and 8,820 IU/kg DM for 142 d	Animals that met daily requirements had a higher dressing percentage	Marbling fleck size increased by 14% <ul style="list-style-type: none"> <li>Animals that met daily requirements had higher ribeye area and marbling area; however, the difference was not significant</li> </ul>	(Bryant et al., 2010)
Limousin X Luxi Steers	12m	At 1,100, 2,200, and 4,000 IU/kg DM For 3 mos For 6 mos	Supp. of 4000 IU/kg DM <ul style="list-style-type: none"> <li>Reduced average daily gain</li> </ul>	Supp. of 4000 IU/kg DM <ul style="list-style-type: none"> <li>No effect on marbling</li> <li>Reduced meat tenderness</li> </ul>	(Wang et al., 2007)
Steers	24m	At 1,100, 2,200, and 4,000 IU/kg DM For 3 mos	No effect on overall weight gain	No effect on marbling <ul style="list-style-type: none"> <li>High dose (4000 IU) reduced tenderness</li> </ul>	

overall difference of IMF content between steers and heifers was not significant, and the stage-specific difference between the two sex groups was not consistent (Ladeira et al., 2024). In brief, available studies indicate that vitamin A treatment enhanced the IMF deposition, particularly in steers; however, the impact on heifers or sex-specific effect is not conclusive due to a lack of comprehensive studies involving both steers and heifers.

## Conclusion

Vitamin A is an essential fat-soluble vitamin required for the optimum growth and production of beef cattle at their different stages of the production cycle. Available studies suggest the stage-specific effects of vitamin A supplementation on IMF, with prenatal and postnatal supplementation enhancing the proliferation of mesenchymal and adipogenic progenitor cells, which expand the sites for IMF deposition, whereas vitamin A suppresses adipocyte differentiation and adipocyte hypertrophy in growing and finishing stages.

The later appearance of adipocyte progenitor cells in the intramuscular depot than the subcutaneous and intermuscular depots suggests the late fetal stage as an effective window to selectively increase their number by vitamin A supplementation without impacting the other fat depots. Accumulated studies also suggest that neonatal supplementation of vitamin A is effective in enhancing the number of preadipocytes, as the hyperplasia of intramuscular adipocytes continues at this stage.

In contrast, vitamin A restriction during the finishing stage promotes IMF deposition by reducing the hepatic retinol reserve and attenuating retinoic acid signaling, which promotes adipocyte hypertrophy in finishing with sufficient liver retinol stores. However, the hepatic retinol storage of feedlot cattle is influenced by  $\beta$ -carotene content of forage, intestinal absorption capability, and the enzyme required for the bioconversion of  $\beta$ -carotene to metabolizable form. Although mature cattle are relatively immune to vitamin A deficiency syndromes due to their larger amount of liver storage, it is essential to assess hepatic retinol status before vitamin A restriction treatment to avoid the impact of vitamin A deficiency on production efficiency.

Collectively, the available studies suggest that the supplementation of vitamin A in late gestational and/or neonatal stages promotes adipocyte progenitor cell

population, while restriction during the finishing stage facilitates lipid accumulation. However, further studies are required to understand the underlying mechanisms and accurately delineate the stage-specific supplementation strategy to maximize carcass quality without negative effects or even improve growth efficiency.

## Declaration of Competing Interest

No conflict of interest is associated with this study.

## Author Contribution

Md Nazmul Hossain: Writing – original draft, Writing – review & editing; Min Du: Conceptualization, Supervision, and Writing – review & editing.

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