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A Review on the Effect of Arginine on Growth Performance, Meat Quality, Intestine Morphology, and Immune System of Broiler Chickens

Review Article

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ABSTRACT

For chickens, arginine considered an essential amino acid due to the lack of urea cycle in birds. Arginine deficiency causes growth retardation, higher prevalence of disease due to the malfunction of immune system, and lower gastrointestinal capacity. However, higher levels of arginine in the diet improved growth performance, muscle hypertrophy, and meat quality. Arginine reduces carcass fat accretion by reducing liver lipogenic enzyme expressions and activities, but it improves muscle fat content. As an immunonutrition, feeding arginine shows some immunostimulatory and thymotrophic role and improves both humoral and cellular immunity. Also, *in ovo* injection of arginine improves both growth and immune function of birds. Arginine also improves insulin, growth hormone, and thyroid hormone secretion and by which, improves growth in a dose dependent manner. Arginine also improves small intestine histomorphology and enzyme activity and then, improves bird digestive system capacity and efficiency. Accordingly, the aim of this review article was to focus on the effects of arginine on growth, immune system, and meat quality of broiler chickens.

KEY WORDS arginine, broiler chicken, growth, immune system, meat quality.

INTRODUCTION

In 1886, arginine was isolated and named; then, in 1895, its presence in animal protein was reported (Evoy *et al.* 1998). Also, the antagonistic effects of arginine and lysine were understood in the 1950's and 1960's (Balnave and Brake, 2002). The impact of arginine on the immune system was demonstrated from 1983 till now (Khajali and Wideman, 2010) and its impact on the carcass fat reduction was proved from 2005 up to now (Tan *et al.* 2011; Ebrahimi *et al.* 2014a). Also, *in ovo* injection of arginine was first used in broiler chickens as a treatment for pulmonary hypertension disease (Pordel *et al.* 2018) and then used as a method for improving the growth of poultry (Foye *et al.* 2006; Foye *et al.* 2007; Abdolalizadeh Alvanegh *et al.* 2017; Omidi, 2018).

As urea cycle in birds is not functional due to the lack or low activity of key enzymes (lack of carbamoyl phosphate synthase I and low activity of arginase and ornithine transcarbamoylase); accordingly, arginine considered an essential amino acid for chickens (Khajali and Wideman, 2010). Also, due to the high growth rate, arginine requirement of broiler chickens is high to support the growth of broilers (Ball *et al.* 2007). Arginine requirement depends on the growth stage and health status (Morris, 2004).

Arginine requirement was also affected by the antagonistic effect of arginine and lysine, which is due to the competence of these two amino acids in gastrointestinal absorption and renal reabsorption (Balnave and Brake, 2002). Although higher levels of lysine cause growth retardation (Balnave and Brake, 2002), increasing dietary arginine higher than suggested levels improved growth performance of broiler chickens (Kidd *et al.* 2001; Ebrahimi *et al.* 2014a).

Past researches demonstrated the importance of arginine supplementation for chickens to support meat quality and growth performance (Ansari Pirsaraei *et al.* 2015; Abdolalizadeh Alvanegh *et al.* 2017; Ansari Pirsaraei *et al.* 2018). Also, the improving effect of arginine on the immune system and intestine histomorphology of chickens was proved (Ebrahimi *et al.* 2014b; Adibmoradi *et al.* 2015; Ebrahimi *et al.* 2016a). Based on our knowledge, there is no review article focused on the effects of using arginine in non-ruminant animals and especially broiler chickens. Therefore, this review article was focused on the effects of arginine on growth, immune system, and meat quality of broiler chickens.

Arginine and growth performance

Previous researches demonstrated the importance of arginine supplementation on growth performance of chickens (Table 1). The dietary supplementation with arginine improved overall body growth with increasing lean deposition, though without increasing fat accretion of broiler chickens (Castro *et al.* 2018). Also, higher levels of arginine (100, 153, and 168% digestible L-arginine based on Ross recommendation) improved growth performance, feed efficiency, and thigh and breast muscles, while it reduced carcass fat accretion in broilers (Ebrahimi *et al.* 2013; Ebrahimi *et al.* 2014a; Ebrahimi *et al.* 2014c). In another study, with supplementing 0.45, 0.90, 1.35, and 1.80% arginine to the basal diet indicated that higher levels of arginine (NRC, 1994) improved daily weight gain and feed conversion ratio (Xu *et al.* 2018). Supplementing 10 g/kg arginine in a maize -soybean basal diet increased body weight gain and relative breast muscle weight, but it decreased carcass abdominal fat pad and skin of ducks (Wu *et al.* 2011). Fernandes *et al.* (2009) with increasing arginine levels (1.490, 1.590, 1.690, and 1.790%) reported a linear increase in breast and breast fillet weight and breast fillet thickness at d 7 of starter period. Al-Daraji and Salih (2012) with dietary adding 0.04% and 0.06% arginine reported an increase in carcass weight, carcass efficiency, and breast and thigh weights. In another study, supplementing arginine in the starter (0, 0.67, 1.37, 2.07, and 2.77%), grower (0, 0.53, 1.1, 1.68, and 2.25%), and finisher (0, 0.52, 1.04, 1.56, and 2.08%) diets increased body weight and feed intake (Emadi *et al.* 2010). Murakami *et al.* (2012) reported that dietary supplementation of arginine (1.390, 1.490, 1.590, 1.690, and 1.790% digestible arginine) in the diet of broiler chickens improved body weight and feed conversion ratio, while had no effect on feed intake of chickens. Kidd *et al.* (2001) reported that dietary supplementing with 120% arginine or lysine based on NRC (1994) recommendation increased body weight gain with adding arginine content of the diet (and without adding lysine content). Gao *et al.* (2017) reported that *in ovo* injection of L-arginine increased body weight gain of broiler chickens during 1-7 days. Though, Omidi (2018) with *in ovo* injection of 0.5% arginine reported no effect on body weight of 24 day-old chickens. Abdolalizadeh Alvanegh *et al.* (2017) with *in ovo* injection of 1 mL solution of different ratios of L-arginine to L-lysine [75.7 (20 mg L-lysine and 15.14 mg L-arginine), 80.7 (20 mg L-lysine and 16.14 mg L-arginine), 85.7 (20 mg L-lysine and 17.14.14 mg L-arginine), 90.7 (20 mg L-lysine and 18.14 mg L-arginine), and 95.7 (20 mg L-lysine and 19.14 mg L-arginine)] reported the improving effect of treatments (up to 90.7 ratio) on chick weight and their carcass traits.

Arginine increases growth performance by several possible mechanisms: 1- arginine is necessary for protein synthesis and growth (Jahanian, 2009; Yao *et al.* 2008). 2- arginine stimulates the release of insulin, GH, and IGF-1, and by which improves feed intake, protein synthesis and growth (Newsholme *et al.* 2005; Jahanian, 2009; Xu *et al.* 2018). 3- polyamines (putrescine, spermidine, and spermine) as a product of arginine have some anabolic functions like improving cell uptake of amino acids and synthesis of proteins (Khajali and Wideman, 2010). 4- nitric oxide as another product of arginine (synthesized by the act of nitric oxide synthase on arginine) stimulate glucose uptake, glucose and fatty acid oxidation, and adipocyte lipolysis (Jobgen *et al.* 2006).

Arginine and meat quality traits

There are few studies in poultry evaluating the effect of arginine on meat quality (Table 1). It was indicated that increasing the dietary arginine levels improved breast muscle crude protein, dry matter, and fat contents (Ebrahimi *et al.* 2014a).

Jiao *et al.* (2010) with evaluating four dietary levels of arginine (80, 100, 120, 140% of NRC recommendation) indicated that increasing dietary arginine improved meat lightness, while decreased meat shear force with no effect on collagen content. Wu *et al.* (2011) indicated that arginine supplementation enhanced intramuscular fat content of duck breast muscle. Also, reducing effect of arginine was observed on shear force and pH of broiler meat (Ebrahimi *et al.* 2015; Ebrahimi *et al.* 2016b). Results of gene expression indicated higher expression of lipogenic genes in muscles (fatty acid synthase and lipoprotein lipase), while lower expression of lipogenic enzymes in adipose tissue (fatty acid synthase and lipoprotein lipase) and liver (acetyl-coenzyme A carboxylase, fatty acid synthase, and malic enzyme), (Ebrahimi *et al.* 2014a; Ansari Pirsaraei *et al.* 2018).

Table 1 Effects of arginine on broiler chickens

Author	Administration of arginine	Growth performance	Meat quality	Intestinal morphology and enzyme activity	Immune system	Blood parameters	Gut microflora
Omidi (2018)	*In ovo* injection	P/L	P/L	P	L	P/L	P
Castro *et al.* (2018)	Feeding	P	–	–	–	–	–
Xu *et al.* (2018)	Feeding	P	–	–	P	P	–
Zhang *et al.* (2018)	Feeding	–	–	P	–	–	P
Gao *et al.* (2017)	*In ovo* injection	P	–	P	–	–	–
Edwards *et al.* (2016)	*In ovo* injection	P	–	P	P	–	–
Nayak *et al.* (2016)	*In ovo* injection	P	–	–	–	–	–
Ebrahimi *et al.* (2015)	Feeding	P	P/L	–	–	P	–
Ebrahimi *et al.* (2014b)	Feeding	P	–	P	P	–	–
Emadi *et al.* (2011)	Feeding	P	–	–	P	P	–
Emadi *et al.* (2010)	Feeding	P	–	–	–	P	–
Jiao *et al.* (2010)	Feeding	P	P	–	–	–	–
Tayade *et al.* (2006)	Feeding	–	–	–	P	–	–
Munir *et al.* (2009)	Feeding	P	–	–	P	–	–

P: stands for positive effect; N: stands for negative effects; L: stands for lacking effect and –: stands for not being evaluated in the article.

In another study, dietary arginine supplementation increased myofiber diameter of broiler chickens (Fernandes *et al.* 2009). On the other hand, *in ovo* injection of 0.5% arginine had no effect on breast meat pH, shear force, and meat color [a* (the index of meat redness), b* (the index of meat yellowness), L* (the index of meat lightness)], (Omidi, 2018). Also, in pig adding 1% arginine increased the antioxidative capacity of skeletal muscle along with increasing intramuscular fat content (Ma *et al.* 2010). Another study in pig indicated that arginine supplementation increased muscle pH and muscle protein, glycogen, and fat contents, while reduced muscle lactate content (Tan *et al.* 2009).

Arginine and intestine morphology

L-arginine plays an important role in intestinal physiology (Table 1), (Rhoads and Wu, 2009). It was indicated that arginine has an improving effect on intestinal absorption and villous recovery after injury (Wang *et al.* 2009). Tan *et al.* (2014) reported that arginine enriched diets reduced damages induced by coccidia (intestinal villous damage, crypt dilation, and goblet cell depletion) in broiler chickens. Also, higher levels of dietary arginine improved small intestine weight and length, villous height, and crypt depth, but these levels decreased villous height to crypt depth ratio, epithelium thickness, and goblet cell number of small intestine of broiler chickens (Ebrahimi *et al.* 2014b; Adibmoradi *et al.* 2015; Ebrahimi *et al.* 2016a). Murakami *et al.* (2012) reported no effect of dietary arginine supplementation on weight and length of small intestine, but an increase in villous height to crypt depth ratio and a decrease in crypt depth of broiler chickens.

In ovo injection of different L-arginine to L-lysine ratios also increased small intestine length, relative weight of small intestine, villous height, and villous height to crypt depth ratio, but it decreased crypt depth of a day old broiler chicks (Ebrahimi *et al.* 2018). Gao *et al.* (2017) with *in ovo* injection of 1% L-arginine reported higher duodenum villous height and villous height to crypt depth ratio, while lower crypt depth of broiler chicks. Also, they reported higher duodenal vasoactive intestinal peptide, ghrelin, and glucagon-like peptide 2 concentrations as well as higher duodenal mucosal enzyme activities (maltase, sucrose, alkaline phosphatase, and inducible nitric oxide synthase) of chicks (Gao *et al.* 2017).

Omidi (2018) with *in ovo* injection of 0.5% L-arginine reported higher jejunum and duodenum villous height to crypt depth ratios of 24 days old broiler chickens. Other studies also indicated improving effect of *in ovo* injection of arginine on small intestine morphology parameters and intestine enzyme activities and so, on the digestive tract capacity of chickens (Foye *et al.* 2007; Edwards *et al.* 2016). Regardless, a study in rats indicated that dietary arginine supplementation reduced small intestine disaccharidase activity (Taboada *et al.* 2006).

Higher villous height and villous height to crypt depth ratio are considered indicators for higher protein synthesis and cellular proliferation of intestinal epithelium (Chang *et al.* 2015). In pigs, Wu *et al.* (2010) reported higher small intestinal growth, villous height, crypt depth, and goblet cell number with feeding diets supplemented with 0.6% arginine. In another study, dietary supplementation of 1% L-arginine increased villous height and vascular endothelial growth factor in duodenal, jejunal, and ileal mucosae (Yao *et al.* 2011).

Part of improving effects of arginine on small intestine morphology may be mediated by polyamines and their effect on protein synthesis, proliferation, and migration of intestinal cells and then, an increase in intestinal villous height and crypt depth (Ruemmele *et al.* 1999; Wang *et al.* 2009; Khajali and Wideman, 2010; Wu *et al.* 2010).

Also, an increase in vascular endothelial growth factor in small intestine may improve the growth of gastrointestinal tract (Yao *et al.* 2011). Tan *et al.* (2010) reported the molecular mechanism by which arginine increases intestinal cells' protein synthesis and reduces protein degradation through activating mammalian target of rapamycin (mTOR) and Toll-like receptor 4 (TLR4) signaling pathways. Pluske *et al.* (1997) reported that higher villous height and lower crypt depth increases performance by increasing the digestive and absorptive capacity of small intestine. Also, it was reported that arginine and nitrite oxide (as one of the arginine product) both stimulate intestinal epithelial cell proliferation and migration (Rhoads and Wu, 2009). Additionally, dietary arginine supplementation stimulated growth hormone, insulin-like growth factors-1, and insulin secretions, which in turn can improve intestinal growth (Xu *et al.* 2018). As intestinal development of broiler chickens occurs during the last stages of incubation, *in ovo* injection of nutrients per se can improve early gastrointestinal development and function of hatchlings, and then cause higher digestion and absorption during the growth period (Ebrahimi *et al.* 2017).

Besides digestion and ingestion, another function of the gastrointestinal tract is a barrier against antigens within the lumen; then, an increase in intestinal permeability causes critical illnesses (Gatt *et al.* 2007). It was indicated that arginine reduced intestinal permeability, while improved intestinal barrier function (Schleiffer and Raul, 1996; Viana *et al.* 2010). Nutrition is an important modulator of gut microbial community structure. L-arginine supplementation had beneficial effects on gut mucosa by improving innate immunity, barrier function, and ileal microbial community, but it suppressed *Clostridium perfringens* colonization and gut injury in broiler chickens (Zhang *et al.* 2017; Zhang *et al.* 2018), (Table 1). Feeding arginine in turkeys also improved *Lactobacillus* of cecum and *Clostridium* and *Coliform* of small intestine (Oso *et al.* 2017). In a study, it was indicated that *in ovo* injection of 0.5% arginine increased cecum *Lactobacillus acidophilus* (gram-positive bacteria), while decreased *Coliforms* and *E. coli* (cecum gram-negative bacteria), (Omidi, 2018).

Arginine and immune system

A practical solution for improving the immune system against pathogens is using nutrients in broiler chickens (Kidd, 2004). Recently, the immunomodulatory effects of arginine on the immune system were proved (Kirk *et al.* 1992), (Table 1). It was indicated that early arginine supplementation improves the development of the immune system (Corzo and Kidd, 2003). D'Amato and Humphrey (2010) reported that the addition of L-arginine in broiler diet improved peripheral blood B cells and the percentage of monocytes. Adding dietary L-arginine in poultry also prevented the impact of oxidative stress during heat stress conditions (Attia *et al.* 2011). It was indicated that high dietary arginine levels increased thymus and spleen relative weights, and skin reaction to phytohemagglutinin P in broiler chickens (Ebrahimi *et al.* 2014b; Ebrahimi *et al.* 2016a; Adibmoradi *et al.* 2015). Tan *et al.* (2007) reported that supplementing 1% arginine reduced the incidence of ascites in broilers exposed to low ambient temperature. Xu *et al.* (2018) reported that dietary arginine supplementation in broiler chickens increased serum concentrations of IgA, IFN-γ, thymus weight, lymphocyte proliferation, antibody titers to Newcastle disease, and serum IgM concentration. Deng *et al.* (2005) reported that high levels of arginine increased antibody levels against sheep red blood cells, while reduced relative bursa weight.

Kwak *et al.* (2001) reported that arginine deficiency decreased nitric oxide production of macrophages. It was indicated that high levels of arginine increased CD8+ cells, the absolute number of heterophils, and the ratio of heterophils to lymphocytes in broiler chickens challenged with infectious bronchitis virus (Lee *et al.* 2002). Emadi *et al.* (2011) reported that higher levels of arginine increased interferon-α, interferon-γ, and immunoglobulin G. High levels of arginine also improved lymphoid organ weights, humoral immunity, and cellular mediated immune response of broiler chicks (Munir *et al.* 2009; Ruiz-Feria and Abdukalykova, 2009).

Although *in ovo* injection of different ratios of L-arginine to L-lysine increased bursa of fabricius weight (Ebrahimi *et al.* 2018), *in ovo* injection of 0.5% arginine had no effect on immune system organs (thymus, spleen, and bursa of fabricius) or antibody titers against Newcastle (Omidi, 2018).

Immunomodulatory actions of arginine mediated by two pathways: 1- arginase pathway, in which polyamines produced as one of the products of arginine; thus, polyamines increase lymphocyte mitogenesis and arginine-dependent macrophage-mediated tumor cell cytotoxicity (Evoy *et al.* 1998), and 2- nitric oxide pathway, which is a product of arginine as a result of nitric oxide synthase (Khajali and Wideman, 2010). Nitric oxide production of macrophages enhances by increasing arginine levels and causes an improvement in weight and function of thymus and mitogenesis of lymphocyte (Evoy *et al.* 1998; Sung *et al.* 1991). Nitric oxide improves coagulation, the immune system, the maintenance of vascular tone, sepsis, hypertension, and cirrhosis (Evoy *et al.* 1998; Jahanian, 2009).

Arginine and some blood parameters

Increasing dietary arginine causes some changes in blood parameters (Table 1). Arginine increases growth hormone (GH) release and stimulates the release of insulin from pancreas (Ebrahimi *et al.* 2013). A blood glucose level also increases with increasing arginine levels, which is as the result of higher gluconeogenesis (Corzo and Kidd, 2003). It was indicated that arginine reduced blood cholesterol, low-density lipoprotein (LDL), and also insulin resistance in diabetes (Mohan and Cas, 1998). Dietary arginine supplementation increased serum concentrations of growth hormone, insulin-like growth factors-I, and insulin of broiler chickens (Xu *et al.* 2018).

Higher levels of arginine in the diet of broiler chickens increased plasma triiodothyronine, thyroxine, and the ratio of triiodothyronine to thyroxine, but decreased plasma cholesterol, triglyceride, and urea concentrations (Ebrahimi *et al.* 2013; Ebrahimi *et al.* 2015; Ansari Pirsaraei *et al.* 2015; Ebrahimi *et al.* 2016b). Emadi *et al.* (2011) reported that arginine supplementation increased albumin and total protein, while decreased aspartate aminotransferase, lactic dehydrogenase, alkaline phosphatase, cholesterol, and triglyceride.

Ansari Pirsaraei *et al.* (2018) with increasing dietary arginine levels (100, 124, 139, and 154%) reported higher blood glucose and high-density lipoprotein (HDL) levels, while lower cholesterol, triglyceride, and low-density lipoprotein (LDL) levels in Arian broilers. *In ovo* injection of different ratios of L-arginine to L-lysine improved serum total protein level, while decreased serum blood urea nitrogen of broiler chicks (Abdolalizadeh Alvanegh *et al.* 2017). On the other hand, 0.5% L-arginine *in ovo* injection had no effect on serum glucose, total protein, cholesterol, and blood urea nitrogen (Omidi, 2018).

CONCLUSION

Arginine considered an essential amino acid for chickens due to the lack of urea cycle and high growth rate. Arginine requirement depends on the growth stage, health status, and dietary lysine level (because of the antagonistic effect of arginine and lysine). Arginine supplementation improved growth performance and meat production of chickens. Increasing the dietary arginine levels also improved meat quality traits (especially meat tenderness and meat fat content). Also, previous studies indicated the improving effect of arginine on intestinal growth, intestinal histology (especially villous height to crypt depth ratio), enzyme activities, and gut microflora community. Furthermore, the stimulatory effects of arginine on the immune system was proved. Arginine supplementation also increased blood GH, insulin, insulin-like growth factors-I, and thyroid hormones. Main effects of arginine mediated by stimulating hormonal secretion and producing polyamines and nitric oxide.

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