Feeding Methionine on Broiler Chickens' Biological Functions: Review

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Abstract: Methionine is the first limiting amino acid in all poultry corn-soybean based diets, which plays many important metabolic functions in broilers such as protein synthesis, the production of other sulfur AAs and protect cells against oxidative stress. Methionine sources (DL- methionine, DL-2-hydroxy-4- butanoic acid and Betaine) has a main role the performance of growth, feed conversion ratio, breast meat, immune and detoxification functions. Contrast, the lack of methionine in the body results in reduced synthesis of protein, alters the mTOR/S6K1 signaling pathway and affected by the oxidative status of the cell. There is a difference in the requirements of broilers for the methionine by strain and age.

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1. Introduction

Balanced diets in modern broiler chickens are very important where become very complex to provide all their requirements, so the essential amino acids (EAA) are added to the diets, because that poultry are not able to synthesize EAAs, so must be supplemented in the diet (Stradiotti et al. 2016). Methionine (Met) is the first limiting amino acid (AA) in broilers, which acts as an EAA for protein synthesis (Fu et al. 2016), as the major AA for initiation of translation (Zhang et al. 2016). In addition, Met contributes to the provision of methyl groups, these groups play an essential role in the synthesis of other sulfur amino acids (SAA) such as creatine, choline, betaine and especially cysteine (Cys) via converted to S-adenosylmethionine (SAM) (Brosnan and Brosnan 2006). Therefore, Met has a role indirect of against oxidative stress by Cys (Cys is required for the synthesis of glutathione and taurine), which are essential compounds against oxidative stress. (Métayer et al. 2008). Met also affects the metabolism of lipid via stimulating the oxidative demolition of fatty acids through its role in the synthesis of carnitine (Nukreaw et al. 2011).

Met is added to broiler chickens diets as a free AA or AA analogue (Conde-Aguilera et al. 2016). Several studies have indicated that Met with various sources has the main role in improving growth performance of broilers (Yang et al. 2016; Powell et al. 2016). In addition, the Met has regulatory effects on growth performance and breast meat yield in broilers (Ahmed and Abbas 2011). While a study by Conde-Aguilera et al (2013) reported that broiler chickens fed on low levels of the Met leads to reduction growth and breast meat quality.

The dietary Met influence on mRNA expression and DNA methylation of myostatin as reported in many studies, where the growth of muscle is regulated by myostatin; this confirms that Met first limited AA in broiler diets (Tesseraud et al. 2011).

In this review, through recent studies to describe source, requirements and metabolic pathway of the Met in the body. After that, the focus on the effect of the Met on breast muscle and alters myogenic gene expression.

2. Sources and Alternatives of Methionine (Met)

Methionine (Met) is one of the essential amino acids (EAA), which supplemented in broiler diets from several natural sources (protein sources of animal or plant) to meet the needs of the broilers (Stradiotti et al. 2016). In recent years, it is prohibiting the use of animal protein sources (meat and bone meal) because of the potential risks, as well as a decline it in fishmeal, this led to increased need for a plant protein source (Chadd et al. 2002). In addition, synthetic of Met is used in dietary to the meet Met requirement (Bunchasak 2009). Met sources commercially available are used in two forms (powder and liquid), DL- Met (DLM: powder form) and DL-2-hydroxy-4-methylthio butanoic acid (LMA: liquid form) (Conde-Aguilera et al. 2016).

A complex chemical synthetic process produces DLM; 3-carbon aldehyde is the first material for its production and derived from propylene (Aldrich 2007). The reported study by Dilger and Baker (2007) obtained that 1- Met and DLM no difference in effectiveness in poultry. Despite that DLM is used more efficiently under Met deficiency in the diet compared with LMA, whereas LMA is used more efficiently when provided to meet the recommended requirement (Gonzales-Esquerra et al. 2007).

DLM and LMA found in two forms, that consist of an L- and D-isomers at 1: 1 ratio, the Met in tissues occurs on the L-form (active), whereas the D-form is not biologically active (Bunchasak 2009). In the metabolism of poultry 70—100% of the D-isomer (not active) of DLM or LMA is converted to L-isomer (active) (Hasegawa et al. 2005). Used a corn-soybean meal in base broiler diets, which they are poor in the Met, so synthetic DL-Met or its analog supplemented to meet the requirement of broilers (Fu et al. 2016).

As a result of the high cost of synthetic DL- Met used in chicken diets, there is a tendency to look for alternatives DL-Met. Including betaine is one of the compounds which a naturally occurring via the methylated derivative of glycine, betaine contains about 3.75 times the methyl groups (on a molecular weight basis) compared with the Met (Rao et al. 2011). Betaine may either take the place of Met by providing the methyl group necessary for the reconversion of homocysteine to the Met (McDevitt et al. 2000). Kalbande et al (2009) show that herbal Met can replace DL-Met high efficiency at 1 g/kg of broiler chicken diet. While, Igbasan et al (2012) found that herbal Met is not an effective substitute for the synthetic Met on the performance of broilers. So, confirmed that the synthetic Met replacement has led to lower broiler performance (Demattê et al. 2016).

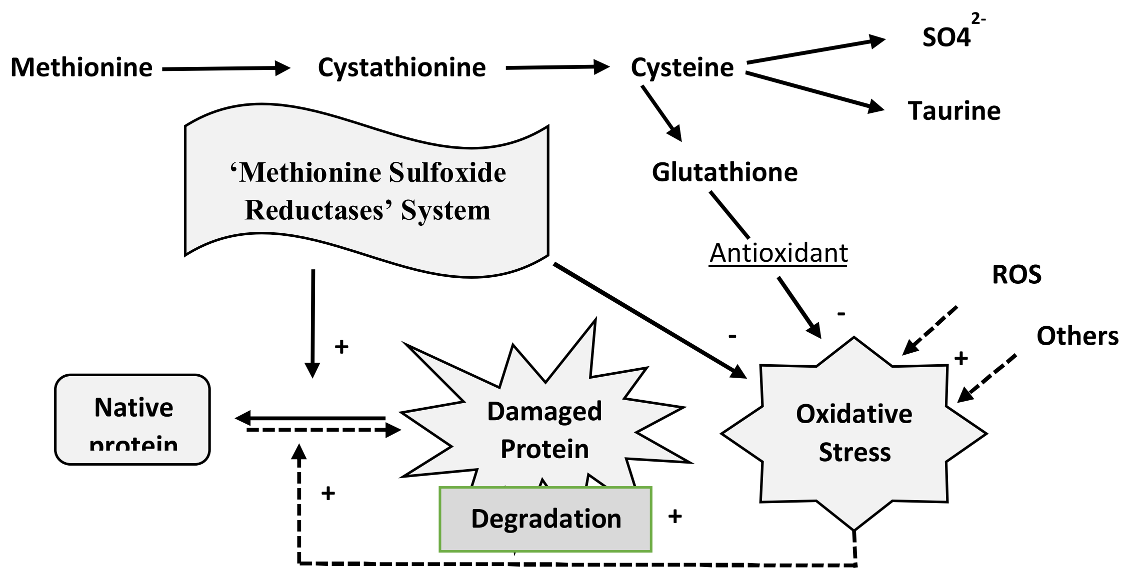

Fig. 1. The control of oxidative status via Met **(Métayer et al. 2008).**

3. Metabolism of Methionine (Met)

Met is an essential sulfur-containing AA ($C5H11NO2S$), where interacts with other nutrients involved in metabolism (Bunchasak 2009) and as reported in a review by Jankowski et al (2014) that essential AAs, especially the Met play a role in protein synthesis. Also, plays an important role in the body through: involved in protein synthesis and the production of other SAAs such as homocysteine. Which product indirect by methylation and transsulfuration (Troen 2003); and helping protect cells against oxidative stress due to Met acting as a precursor of carnitine and glutathione (Li et al. 2007). Which reduces ROS and thus maintains cells from oxidative stress as shown in Figure 1 (Métayer et al. 2008).

Figure 2. Demonstrates the metabolic pathway of the Met in the body as indicated by studies (Waterland 2006; Dunlevy et al. 2006; Wu et al. 2012). Metabolism pathways of Met as following: (1) Convert activation of Met into S adenosylmethionine (SAM) -transferase by ATP. (2) S-adenosylmethionine (SAM) demethylation into S-adenosylhomocysteine (SAH) together with convert the acceptor R into RCH3R. (3) Alternative demethylation catalyzed by glycine N-methyltransferase, which changes over glycine (Gly) into sarcosine (CH3Gly). (4) Hydrolysis of SAH into homocysteine (HCYS) and adenosine by SAH hydrolase. (5) HCYS reaction with serine (Ser) converted to shape cystathionine (CTT) through helping vitamin B6-inferred pyridoxal-5'- phosphate-dependent CTT β-synthase. (6) Conversion of CTT into cysteine (Cys) and α-ketobutyrate in the presence of vitamin B6. (7) 5-methyltetrahydrofolate (5-methylTHF) demethylation into THF and HCYS re-methylation into Met by methionine synthase through

helping vitamin B12. (8) In the liver, re-methylation of HCYS by betaine-homocysteine methyltransferase within the sight of choline-inferred betaine. (9) Synthesis of N5, 10-methylenetetrahydrofolate (5, 10-methyleneTHF) from THF combined with the change of Ser into Gly through the activity of pyridoxal-5'-phosphate-subordinate serine hydroxymethyltransferase. The decrease of 5, 10-methyleneTHF into 5-methylTHF catalyzed by N5, 10-methylenetetrahydrofolate reductase (MTHFR).

Halsted and Medici (2011) revealed that changeless bonds are shaped amongst Met and serine amid transsulfuration, which requires CBS and B6 as the essential assistant component. Additionally, HCYS is used back to Met within the sight of B12. Re-methylation requires the nearness of MTHRF and folic corrosive (Grimble 2006). SAM arranges transsulfuration and re-methylation forms by going about as a CBS activator or inhibitor of MTHRF (Brosnan and Brosnan 2006).

4. The Relationship of Methionine (Met) with Cysteine (Cys) and Sulfur

Many metabolic pathways and other nutrients such as cysteine, choline, betain involve Met (Bunchasak, 2008). Poultry are requires to both Met and cysteine (Cys) for protein synthesis and major providers of organic sulfur within the body, which play an important role in connective tissue support (Fanatico 2010). Given the strong relationship between the Met and Cys, they are usually called total sulfur AA (TSAA) (Burley et al. 2016). TSAA act as a sulfur donor (Bunchasak 2009). However, when the formulation of broiler diets, the Met and TSAA levels must always be considered together, where are found that increase Cys in TSAA deficient diets can cause reduced broiler performance (Baker and Dilger 2008).

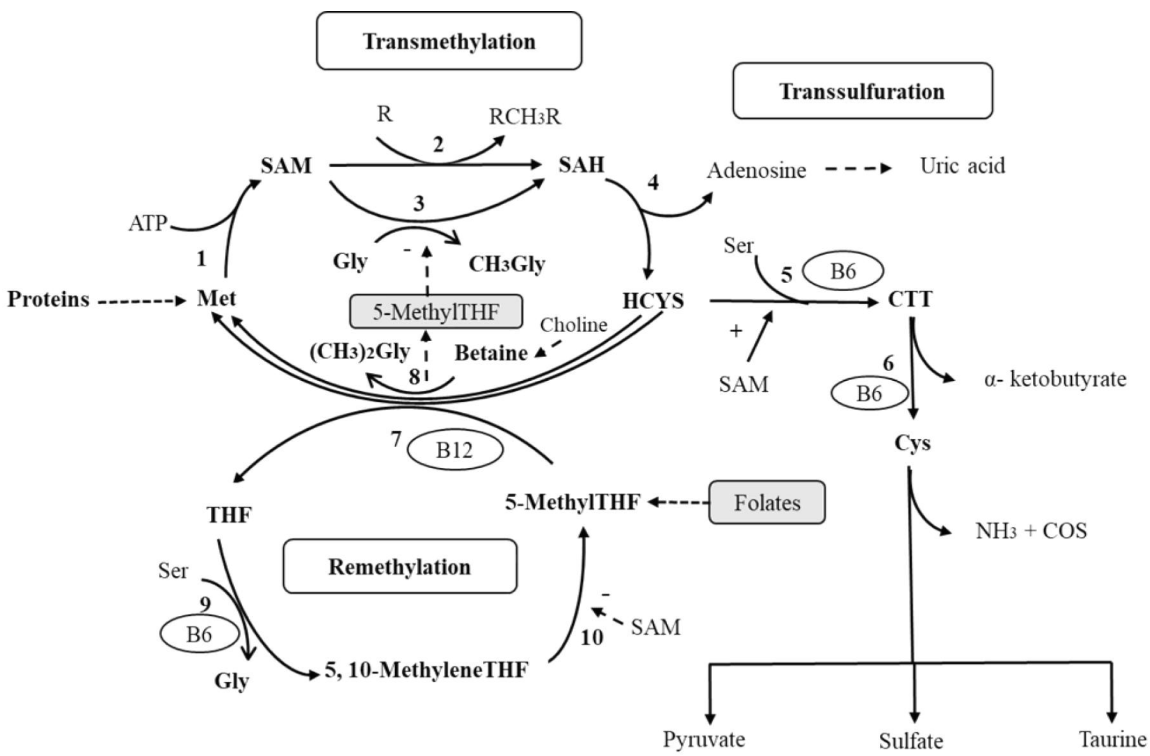

Figure 2. Methionine metabolism **(Durand *et al.*, 2001)**; MS – methionine synthase; 5,10-MTHF – 5,10-methylenetetrahydrofolate; 5-MTHF 5-methylenetetrahydrofolate; MTHFR- methylenetetrahydrofolate reductase; BHMT – betaine-homocysteine S-methyltransferase; CBS – cystatione-β-synthase.

In addition, there is a relationship between Met, betaine and choline, which are all involved in methyl group as donors in methylation reactions (Pillai et al. 2006). On the other hand, the effect of the Met is unique which that methyl donors from betaine and choline could not substitute for the Met in broilers fed diets marginally deficient in TSAA (McDevitt et al. 2000). However. Attia et al. (2005) reported that the Met level could be decreased to 0.37% of the diet when 0.07% of betaine is added.

5. Effects of Methionine (Met) Deficiencies and Requirements of Broiler Chickens Functions

Met has a numerous of biological functions, including protein metabolism, oxidative stress, and methylation (Tesseraud et al. 2009). Therefore, Met deficiency leads to reduce protein synthesis, alters the mTOR/S6K1 signaling pathway and influence the cell oxidative status (Métayer-Coustard et al. 2010). Met deficiency inhibits IPEC-1 cell autophagic responses (Tang et al. 2015). Autophagy is the mechanism of cell survival during the nutrient deficiency (Deretic and Levine 2009). On the other hand, effects of a deficient Met supply in diets on the chemical composition of different tissues and breast meat quality of broiler chickens (Conde-Aguilera et al. 2013). Also, Bunchasak et al. (2006) found that Met deficiencies in the diet lead to decreased feed intake of broiler chickens due to AA imbalances. However, chickens lose the ability to adjust feed intake to satisfy their AA requirements due to AA imbalances, so positive effect of Met supplementation may be due to the improved feed intake via the AA balance (Bunchasak 2009). Met is the first limiting AA when fed broiler on commercial diets of a corn-soybean meal, so the diet is supplemented with Met to meet the requirements of TSAA (Dozier and Mercier 2013). The requirements of commercially recommended Met are higher than the recommendation of the NRC (1994). The Met requirement (%) of diet decreases when chicks are grown up, while Met requirement as relative to lysine tends to increase as shown in Table 1 (Bunchasak 2009). Bunchasak (2009) reported that strains require different amounts of the Met, may be due to genetic diversity, which is affected ability on Met utilization (Table 1). Whereas, Kalinowski et al. (2003) show that no significant difference between strain and Met requirement. Burley et al. (2016) report that use an average age in the inclusion rate of the Met to diet is very important, which may allow to better provide for Met throughout various phases of growth since the requirements of the broilers change with age. The Met requirement in the feed is highest in starter both commercial diets and NRC then declines as the chicken ages.

Table 1. Recommendations of methionine (Met) and total sulfur amino acid (TSAA) for broiler strains according to the nutrition guide

Strain	Stage	Nutritional recommendation (%)				Relative to lysine	
		TSAA[5]		Met		TSAA	Met.
		Total	Digest	Total	Digest		
Ross 308[1]	Starter	1.07	0.94	0.51	0.47	74	38
	Grower	0.95	0.84	0.45	0.42	76	38
	Finisher	0.60	0.76	0.41	0.38	78	39
Cobb[2]	Starter	0.98	0.86	0.56	0.50	74	38
	Grower	0.96	0.84	0.53	0.48	75	40
	Finisher1	0.88	0.77	0.48	0.43	78	41
	Finisher2	0.80	0.7	0.44	0.40	78	41
ArborAcres[3]	Starter	0.97	0.86	0.53	0.46	71	39
	Grower	0.85	0.75	0.46	0.41	72	39
	Finisher1	0.78	0.69	0.42	0.37	73	39
	Finisher2	0.77	0.68	0.42	0.37	76	41
NRC[4]	Starter	0.90	-	0.50	-	82	46
	Grower	0.72	-	0.38	-	72	38
	Finisher	0.60	-	0.32	-	71	38

Source: Bunchasak (2009).

[1]Starter (0-10 days), grower (11-24 days) and finisher (25-slaughter).

[2] Starter (0-10 days)‹ grower (11—22 days)‹ finisher 1 (23-42 days) and finisher 2 (42-slaughter).

[3]Starter (0-14 days), grower (15-28 days), finisher l (29—36 days) and finisher 2 (37-slaughter (.

[4]Starter (0-21 days), grower (22-42 days) and finisher (43-56 days).

[5]TSAA= Total sulfur amino acids.

Therefore, the age of the chicken impacts on the level of Met needed in the diet to support optimal performance. The results showed by Lumpkins et al. (2007) that no difference of Met requirements between male and female broilers in optimal performance. TSAA or Met requirement depends on dietary protein level (Vieira et al. 2004). While, Si et al. (2004) reported that no significant interaction between Met and protein levels when male broiler chicks were fed diets with CP (16, 18, 20, or 22%) and NRC recommendations (100 or 110%).

6. Effect of Feeding Methionine (Met) on Growth and Meat Quality of Broiler Chickens

The different levels of the Met have an effect on growth performance and breast meat yield of broiler chickens as reported by many studies (Ahmed and Abbas 2011; Bouyeh and Gevorgyan 2011). Therefore, the study showed by Wen et al. (2014b) that the Met level 0.43% (control) was inadequate for optimal growth rate (GR) and feed efficiency (FE) of broilers compared to Met level 0.53%, and they indicates that Met promotes broiler growth by regulating the development of the breast muscle. These results are consistent with Zhai et al. (2012), who reported that breast meat yield was greater when increasing the level of the Met from 0.41% to 0.51% in broiler diets. Furthermore, diet supplementation with Met lead to increased growth rate and improved meat quality (Zhai et al. 2016). Muscle growth may be due to increase protein deposition (myofibrillar and sarcoplasmic hypertrophy) by the Met (Nagao et al. 2011). Whereas, that Met level 0.86% in diets may be above to the requirement of broilers (Wen et al. 2016). Wen et al. (2014a) showed that the increasing of Met in the diet has positively improved in the BWG and breast muscle yield, may be due to increase cell size and enhanced activity tissue cell through alterations of myostatin transcription (DNA), phosphorylation of mTOR and FoxO4 in the breast muscle. Additionally. Zhan et al. (2006) reported that Met supplementation increased breast in muscle yield and decreased abdominal fat content.

Nierobisz et al. (2007) hypothesised that the Met addition to feed lead to increase cell mitotic activity in the muscle of growing chicks. On the other hand, proved that cell activity is greatly weakened by reducing Met availability in broiler diet (Powell et al. 2013, 2014) and lower protein accretion in breast muscle (Goulart et al. 2011). As well the supplementing Met in the Low-CP diet improved the feed and protein conversion ratios, reduced fat accumulation, and reduced the production cost of broiler chickens with regard to fat deposition (Jariyahatthakij et al. 2018). Met has no effect on the morphological structure or fat deposition of the breast muscle (Powell et al. 2016).

The results by Yang et al. (2016) indicated that optimal dietary supplementation of the Met could increase growth performance. Similarly, L-Met or DL-Met supplementation improved growth performance of male broilers (Zhang et al. 2016). The Met supply was affected on performance and tissue weights, but not effect by the Met source, whereas reducing the Met content in the diet led to increasing the redness value of breast muscle in broilers (Conde-Aguilera et al. 2016). In addition, Agostini et al. (2016) concluded that Met sources (DL- Met and hydroxy- Met) lead to similar performances response when compared with TSAA values around the broiler requirement level.

7. Effect of Feeding Methionine (Met) on Myogenic Gene Expression in Broiler Chickens

Skeletal muscle development through many Myogenic regulatory factors (genes), which include myogenic differentiation factor 1 (myoD1), myogenic factor 5 (myf5), myogenin, the myocyte enhancer factor 2 (MEF2), and muscle regulatory factor 4 (MRF4) (Townley-Tilson et al. 2010). However, little is known about the effects of Met on the expressions of these genes (Tesseraud et al. 2011). Wen et al. (2014a) who concluded that inclusion of Met in broiler diets improved breast muscle yield via increased mRNA expression of Myf5 and MEF2B. Zhang et al. (2018) have shown that supplementing Met in the broiler chickens diet influenced the transcriptional regulation and activity of Met oxidases in a tissue and age-specific manner. Met oxidases may thus act as a determining factor in the bioefficacy of different dietary supplemental Met sources. On the other hand, myostatin is the negative regulator of muscle growth by inhibition increased muscle mass (Wang and McPherron 2012). A study also reported that raising the level of the Met from 0.21 to 0.61% in dietary broiler chickens (4 to 8 wk) led to promoted the methylation of myostatin from 46 to 84% in muscle, which was negatively correlated with its gene expression (Liu et al. 2006).

DNA methylation can be affected by nutrition, leading to changes in gene expression (Anderson et al. 2012). The methyl groups transferred in DNA methylation reactions are derived from Met; therefore, high Met intake of dietary might be result increase DNA methylation (Waterland 2006).

8. Effect of Feeding Methionine (Met) on Immune and Other Function of Broiler Chickens

Met has a role in immune function of broilers (Ruan et al. 2017), through effects on the innate and adaptive immune function (Zhang and Guo 2008). Grimble (2006) reported that the role of Met is in the process of synthesis and catabolism in the immune system. Many studies, discoverd that birds fed on high levels of Met in broilers dietary may increasing in weight of Fabricius bursa and spleen as percentage of body weight (Mirzaaghatabar et al. 2011), higher in antibody titer when infected broilers by coccidium (Jin et al. 2005), and Newcastle disease virus (Bouyeh 2012). However, deficiency of Met may inhibit the proliferation and differentiation of B-lymphocytes, and increase apoptotic cells (Wu et al. 2013). Study by Tang et al. (2009) pointed out that Met could improve intestinal humoral immune function by activity of lysozyme, total iron binding capacity and the IgM content. Met is is important in synthesis of choline. Nevertheless, choline and acetylcholine play key roles in the metabolism of leukocyte (Kim et al. 2006).

Met has a protective role on aflatoxin (Istiqomah et al. 2017). This was confirmed by a study by Sharma et al. (2015) who noted that the inclusion of Met into dietary contaminated with aflatoxin resulted in improved performance of the broilers compared to the contaminated diet without Met. Met sources may be prevent the occurrence of NE outbreaks through inhibitor effect against *C. perfringens* in the intestinal tract of broiler chickens (Dahiya et al. 2007). Both L-Met or DL-Met supplementations have shown to have a positive effect on villus with increased GSH and TAC production as well as decreased protein oxidation in the duodenum when compared to control group but L-Met had a better function on redox status, development of the gut and growth response than chicks fed diets with DL-Met (Shen et al. 2015).

9. Conclusions

Based on recent experimental studies that both synthetic DL-Met, Betaine and herbal Met can replace several natural sources of Met to meet the needs of the broilers. Met plays many important metabolic and biological functions via protein metabolism, oxidative stress, immune function and methylation and regulate key metabolic pathways to improve growth, thus found that Met effects on body weight gains, feed conversion ratio and meat quality. Broiler chickens requirements of Met vary depending on the breed and age to support optimal performance. Also, the results of studies indicate that the Met has to do with other nutrients (Cysteine and betaine and choline).

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Conflict of interest declaration:

There is no conflict of interest.

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Reference

1. Agostini, P.; Dalibard, P.; Mercier, Y.; Van der Aar, P.; Van der Klis, J., 2016: Comparison of methionine sources around requirement levels using a methionine efficacy method in 0 to 28 day old broilers. Poultry Science 95, 560-569.
2. Ahmed, M. E.; Abbas, T. E., 2011: Effects of dietary levels of methionine on broiler performance and carcass characteristics. International Journal of Poultry Science 10, 147-151.
3. Aldrich, G., 2007: DL-methionine: several vital functions. Available Source: http: / / www. petfoodindustry. Com/ViewArticle. aspx?id = 18526, October 29.
4. Anderson, O. S.; Sant, K. E.; Dolinoy, D. C., 2012: Nutrition and epigenetics: an interplay of dietary methyl donors, one-carbon metabolism and DNA methylation. The Journal of nutritional biochemistry 23, 853-859.
5. Attia, Y.; Hassan, R.; Shehatta, M.; Abd-El-Hady, S. B., 2005: Growth, carcass quality and serum constituents of slow growing chicks as affected by betaine addition to diets containing 2. Different levels of methionine. International Journal of Poultry Science 4, 856-865.
6. Baker, D. H.; Dilger, R. N., 2008: Excess cyst (e) ine and L-methionine precursor utilization. Paper presented at the Proceedings of Mid Atlantic nutrition conference. Baltimore 1, 82-88.
7. Bouyeh, M., 2012: Effect of Excess Lysine and Methionine on Immune System and Performance of Broilers. Annals of Biological Research 3, 3218-3224.
8. Bouyeh, M.; Gevorgyan, O. K., 2011: Influence of excess lysine and methionine on cholesterol, fat and performance of broiler chicks. Journal of Animal and Veterinary Advances 10, 1546-1550.
9. Brosnan, J. T.; Brosnan, M. E., 2006: The sulfur-containing amino acids: an overview. The Journal of nutrition 136, 1636-1640.
10. Bunchasak, C.; Sooksridang, T.; Chaiyapit, R., 2006: Effect of adding methionine hydroxy analogue as methionine source at the commercial requirement recommendation on production performance and evidence of ascites syndrome of male broiler chicks fed corn-soybean based. International Journal of Poultry Science 5, 744-752.
11. Bunchasak, C., 2009: Role of dietary methionine in poultry production. International Journal of Poultry Science 46, 169-179.
12. Bunchasak, C., 2008: Using synthetic amino acids in broiler chicken diet. In: Proceedings of Satellite Symposium, International Symposium on the Future and Practical Usage of Amino

Acids for Animal Production. Animal Science Congress 7-18.
13. Burley, H.; Anderson, K.; Patterson, P.; Tillman, P., 2016: Formulation challenges of organic poultry diets with readily available ingredients and limited synthetic methionine. Journal of Applied Poultry Research 25, 443-454.
14. Chadd, S. A.; Davies, W. P; Jason, M. K., 2002: Practical production of protein for food animals. In: Proceedings of Protein Sources for the Animal Feed Industry, Expert Consultation and Workshop Bangkok, FAO Animal Production and Health. Available Source: http://www.fao.org/docrep/007/y5019e/y5019e07.htm#bm07.
15. Conde-Aguilera, J.; Cholet, J.; Lessire, M.; Mercier, Y.; Tesseraud, S.; Milgen, J., 2016: The level and source of free-methionine affect body composition and breast muscle traits in growing broilers. Poultry Science 95, 2322-2331.
16. Conde-Aguilera, J. A,; Cobo-Ortega, C.; Tesseraud, S.; Lessire, M.; Mercier, Y.; Van Milgen, J., 2013: Changes in body composition in broilers by a sulfur amino acid deficiency during growth. Poultry Science 92, 1266-1275.
17. Dahiya, J. P.; Hoehler, D.; Van Kessel, A. G.; Drew, M. D. 2007: Effect of different dietary methionine sources on intestinal microbial populations in broiler chickens. Poultry Science 86, 2358-2366.
18. Demattê, F. L. C.; de Oliveira, P. D. C.; Do, P. G. D. V.; Beutner, C. G., 2016: Effect of an unusual source of methionine on the performance of organic chickens. Organic Agriculture 6, 191-197.
19. Deretic, V.; Levine, B., 2009: Autophagy, immunity, and microbial adaptations. Cell Host and Microbe 5, 527–549.
20. Dilger, R.; Baker, D., 2007: DL-Methionine is as efficacious as L-methionine, but modest L-cystine excesses are anorexigenic in sulfur amino acid-deficient purified and practical-type diets fed to chicks. Poultry Science 86, 2367-2374.
21. Dozier, W.; Mercier, Y., 2013: Ratio of digestible total sulfur amino acids to lysine of broiler chicks from 1 to 15 days of age. Journal of Applied Poultry Research 22, 862-871.
22. Dunlevy, L. P.; Burren, K. A.; Mills, K.; Chitty, L. S.; Copp, A, J.; Greene, N. D., 2006: Integrity of the methylation cycle is essential for mammalian neural tube closure. Clinical and Molecular Teratology 76, 544-552.
23. Fanatico, A., 2010: Organic poultry production: providing adequate methionine: ATTRA.
24. Fu, Q.; Leng, Z.; Ding, L.; Wang, T.; Wen, C.; Zhou, Y., 2016: Complete replacement of supplemental DL-methionine by betaine affects meat quality and amino acid contents in broilers. Animal Feed Science and Technology 212, 63-69.
25. Gonzales-Esquerra, R.; Vázquez-Añón, M.; Hampton, T.; York, T.; Feine, S.; Wuelling, C.; Knight, C., 2007: Evidence of a different dose response in turkeys when fed 2-hydroxy-4 (methylthio) butanoic acid versus DL-methionine. Poultry Science 86, 517-524.
26. Goulart, C. C.; Costa, F. G. P.; Silva, J.; Souza, J.; Rodrigues, V. P.; Oliveira, C., 2011: Requirements of digestible methionine+ cystine for broiler chickens at 1 to 42 days of age. Revista Brasileira de Zootecnia 40, 797-803.
27. Grimble, R. F., 2006: The effects of sulfur amino acid intake on immune function in humans. The Journal of Nutrition 136, 1660-1665.
28. Halsted, C. H.; Medici, V., 2011: Aberrant hepatic methionine metabolism and gene methylation in the pathogenesis and treatment of alcoholic steatohepatitis. International journal of hepatology 1-7.
29. Hasegawa, H.; Shinohara, Y.; Akahane, K.; Hashimoto, T., 2005: Direct detection and evaluation of conversion of D-methionine into L-methionine in rats by stable isotope methodology. The Journal of Nutrition 135, 2001-2005.
30. Igbasan, F. A.; Ibrahim, A. M.; Osho, B. I., 2012: Comparative efficacy of herbal and synthetic methionine on performance of some haematological and biochemical parameters in domestic laying hens. African Journal of Biotechnology 11, 10617-10625.
31. Istiqomah, L.; Damayanti, E.; Julendra, H.; Suryani, A. E.; Sakti, A. A.; Anggraeni, A. S., 2017: Effect of methionine and lactic acid bacteria as aflatoxin binder on broiler performance. In AIP Conference Proceedings 1854, 1-7.
32. Jankowski, J.; Kubińska, M.; Zduńczyk, Z., 2014: Nutritional and immunomodulatory function of methionine in poultry diets–a review. Annals of Animal Science 14, 17-32.
33. Jariyahatthakij, P.; Chomtee, B.; Poeikhampha, T.; Loongyai, W.; Bunchasak, C., 2018: Effects of adding methionine in low-protein diet and subsequently fed low-energy diet on productive performance, blood chemical profile, and lipid metabolism-related gene expression of broiler chickens. Poultry Science pey034.
34. Jin, L. M.; Wang, M.; Meng, X. Y.; Zhao, Z. X.; Zhao, Q. P., 2005: Effect of Content of Dietary Methionine on the Value of Blood Sugar of

Broiler Chickens with E.tenella. Acta Ecologiae Animalis Domastici 26, 61-64.
35. Kalbande, V. H.; Ravikanth, K.; Maini, S.; Rekhe, D. S., 2009: Methionine supplementation options in poultry. International Journal of Poultry Science 8, 588-591.
36. Kalinowski, A.; Moran, E. T.; Wyatt, C. L., 2003: Methionine and cystine requirements of slow-and fast-feathering broiler males from three to six weeks of age. Poultry Science 82, 1428-1437.
37. Kim, W. K.; Froelich, C. A.; Patterson, P. H.; Ricke, S. C., 2006: The Potential to Reduce Poultry Nitrogen Emissions with Dietary Methionine or Methionine Analogues Supplementation. World's Poultry Science Journal 62, 338-353.
38. Li, P.; Yin, Y. L.; Li, D.; Kim, S. W.; Wu, G., 2007: Amino acids and immune function. British Journal of Nutrition 98, 237-252.
39. Liu, Y.; Song, G.; Yi, G.; Hou, Y.; Huang, J.; Vazquez-Anon, M.; Knight, C., 2006: Effect of supplementing 2-hydroxy-4-(methylthio) butanoic acid and DL-methionine in corn-soybean-cottonseed meal diets on growth performance and carcass quality of broilers. Asian Australasian Journal of Animal Sciences 19, 1197.
40. Lumpkins, B. S.; Batal, A. B.; Baker, D. H., 2007: Variations in the digestible sulfur amino acid requirement of broiler chickens due to sex, growth criteria, rearing environment, and processing yield characteristics. Poultry Science 86, 325-330.
41. McDevitt, R.; Mack, S.; Wallis, I., 2000: Can betaine partially replace or enhance the effect of methionine by improving broiler growth and carcase characteristics. British Poultry Science 41, 473-480.
42. Métayer-Coustard, S.; Mameri, H.; Seiliez, I.; Crochet, S.; Crépieux, P.; Mercier, Y.; Tesseraud, S., 2010: Methionine deprivation regulates the S6K1 pathway and protein synthesis in avian QM7 myoblasts without activating the GCN2/eIF2 alpha cascade. The Journal of Nutrition 140, 1539-1545.
43. Métayer, S.; Seiliez, I.; Collin, A.; Duchêne, S.; Mercier, Y.; Geraert, P. A.; Tesseraud, S., 2008: Mechanisms through which sulfur amino acids control protein metabolism and oxidative status. The Journal of nutritional biochemistry 19, 207-215.
44. Mirzaaghatabar, F.; Saki, A. A.; Zamani, P.; Aliarabi, H.; Hemati Matin, H. R., 2011: Effect of Different Levels of Diet Methionine and Metabolisable Energy on Broiler Performance and Immune System. Food and Agricultural Immunology 22, 93-103.
45. Nagao, K.; Oki, M.; Tsukada, A.; Kita, K., 2011: Alleviation of body weight loss by dietary methionine is independent of insulin-like growth factor-I in protein-starved young chickens. Animal Science J 82, 560–564.
46. Nierobisz, L.; Felts, V.; Mozdziak, P., 2007: The effect of early dietary amino acid levels on muscle satellite cell dynamics in turkeys. Comparative Biochemistry and Physiology Part B 148, 286-294.
47. Nukreaw, R.; Bunchasak, C.; Markvichitr, K.; Choothesa, A.; Prasanpanich, S.; Loongyai, W., 2011: Effects of methionine supplementation in low-protein diets and subsequent re-feeding on growth performance, liver and serum lipid profile, body composition and carcass quality of broiler chickens at 42 days of age. The Journal of Poultry Science 48, 229-238.
48. Pillai, P.; Fanatico, A.; Beers, K.; Blair, M.; Emmert, J., 2006: Homocysteine remethylation in young broilers fed varying levels of methionine, choline, and betaine. Poultry Science 85, 90-95.
49. Powell, D.; McFarland, D.; Cowieson, A.; Muir, W.; Velleman, S., 2013: The effect of nutritional status on myogenic satellite cell proliferation and differentiation. Poultry Science 92, 2163-2173.
50. Powell, D.; McFarland, D.; Cowieson, A.; Muir, W.; Velleman, S., 2014: The effect of nutritional status and muscle fiber type on myogenic satellite cell fate and apoptosis. Poultry Science 93, 163-173.
51. Powell, D.; Velleman, S.; Cowieson, A.; Muir, W., 2016: Methionine concentration in the pre-starter diet: its effect on broiler breast muscle development. Animal Production Science 57, 448-457.
52. Rao, S.; Raju, M.; Panda, A.; Saharia, P.; Sunder, G. S., 2011: Effect of supplementing betaine on performance, carcass traits and immune responses in broiler chicken fed diets containing different concentrations of methionine. Asian-Australasian Journal of Animal Sciences 24, 662-669.
53. Ruan, T.; Li, L. J.; Peng, X.; Wu, B. Y., 2017: Effects of Methionine on the Immune Function in Animals. Health 9, 857-869.
54. Sharma, M.; Singh, R.; Mandal, A. B., 2015: Effect of methionine supplementation in ameliorating aflatoxicosis in broiler chickens. Animal Nutrition and Feed Technology 15, 161-169.
55. Shen, Y. B.; Ferket, P.; Park, I.; Malheiros, R. D.; Kim, S. W., 2015: Effects of feed grade L-

methionine on intestinal redox status, intestinal development, and growth performance of young chickens compared with conventional DL-methionine. Journal of Animal Science 93, 2977-2986.

56. Si, J.; Fritts, C. A.; Waldroup, P. W.; Burnham, D. J., 2004: Effects of excess methionine from meeting needs for total sulfur amino acids on utilization of diets low in crude protein by broiler chicks. Journal of Applied Poultry Research 13, 579-587.
57. Stradiotti, A. C.; Bendassolli, J. A.; Ducatti, C.; Sartori, J. R.; Pelícia, V. C.; Araujo, P. C.; Pezzato, A. C., 2016: Incorporation of Labeled Methionine as a Tissue Tracer in Broiler Chickens. Revista Brasileira de Ciência Avícola 18, 719-724.
58. Tang, L.; Wang, G. X.; Jiang, J.; Feng, L.; Yang, L.; Li, S. H.; Kuang, S. Y.; Zhou, X. Q., 2009: Effect of Methionine on Intestinal Enzymes Activities, Microflora and Humoral Immune of Juvenile Jian Carp (Cyprinus carpio var. Jian). Aquaculture Nutrition 15, 477- 483.
59. Tang, Y.; Tan, B.; Xiong, X.; Li, F.; Ren, W.; Kong, X.; Qiu, W.; Hardwidge, P. R.; Yin, Y., 2015: Methionine deficiency reduces autophagy and accelerates death in intestinal epithelial cells infected with enterotoxigenic Escherichia coli. Amino acids 47, 2199-2204.
60. Tesseraud, S.; Coustard, S. M.; Collin, A.; Seiliez, I., 2009: Role of sulfur amino acids in controlling nutrient metabolism and cell functions: implications for nutrition. British Journal of Nutrition 101, 1132-1139.
61. Tesseraud, S.; Everaert, N.; Ezzine, S. B. O.; Collin, A.; Métayer-Coustard, S.; Berri, C., 2011: Manipulating tissue metabolism by amino acids. World Poultry Science J 67, 243-252.
62. Townley-Tilson, W. D.; Callis, T. E.; Wang, D., 2010: MicroRNAs 1, 133, and 206: Critical factors of skeletal and cardiac muscle development, function, and disease. The International Journal of Biochemistry & Cell Biology 42, 1252-1255.
63. Troen, A. M.; Lutgens, E.; Smith, D. E.; Rosenberg, I. H.; Selhub, J., 2003: The atherogenic effect of excess methionine intake. Proceedings of the National Academy of Sciences 100, 15089-15094.
64. Vieira, S. L.; Lemme, A.; Goldenberg, D. B.; Brugalli, I., 2004: Responses of growing broilers to diets with increased sulfur amino acids to lysine ratios at two dietary protein levels. Poultry Science 83, 1307-1313.
65. Wang, Q.; McPherron, A. C., 2012: Myostatin inhibition induces muscle fibre hypertrophy prior to satellite cell activation. The Journal of Physiology 590, 2151-2165.
66. Waterland, R. A., 2006: Assessing the effects of high methionine intake on DNA methylation. The Journal of Nutrition 136, 1706-1710.
67. Wen, C.; Chen, Y.; Wu, P.; Wang, T.; Zhou, Y., 2014a: MSTN, mTOR and FoxO4 are involved in the enhancement of breast muscle growth by methionine in broilers with lower hatching weight. PloS one 9, 114236.
68. Wen, C.; Chen, X.; Chen, G.; Wu, P.; Chen, Y.; Zhou, Y.; Wang, T., 2014b: Methionine improves breast muscle growth and alters myogenic gene expression in broilers. Journal of Animal Science 92, 1068-1073.
69. Wen, C.; Jiang, X.; Ding, L.; Wang, T.; Zhou, Y., 2016: Effects of dietary methionine on growth performance, meat quality and oxidative status of breast muscle in fast-and slow-growing broilers. Poultry Science 96, 1707-1714.
70. Wu, B.; Cui, H.; Xi, P.; Jing, F.; Wei, C.; Liu, X., 2012a: Effect of methionine deficiency on the thymus and the subsets and proliferation of peripheral blood T-cell, and serum IL-2 contents in broilers. Journal of Integrative Agriculture 11, 1009-1019.
71. Wu, B.; Cui, H.; Peng, X.; Fang, J.; Cui, W.; Liu, X. D., 2013: Pathology of Bursae of Fabricius in Methionine-Deficient Broiler Chickens. Nutrients 5, 877-886.
72. Yang, Z.; Wang, Z.; Yang, H.; Zhao, F.; Kong, L., 2016: Response of growing goslings to dietary supplementation with methionine and betaine. British Poultry Science 57, 833-841.
73. Zhai, W.; Araujo, L. F.; Burgess, S. C.; Cooksey, A. M.; Pendarvis, K.; Mercier, Y.; Corzo, A., 2012: Protein expression in pectoral skeletal muscle of chickens as influenced by dietary methionine. Poultry Science 91, 2548-2555.
74. Zhai, W.; Schilling, M. W.; Jackson, V.; Peebles, E. D.; Mercier, Y., 2016: Effects of dietary lysine and methionine supplementation on Ross 708 male broilers from 21 to 42 days of age (II): breast meat quality. Journal of Applied Poultry Research 25, 212-222.
75. Zhang, L. B.; Guo, Y. M., 2008: Effects of Liquid DL-Methionine Hydroxy Analogue on Growth Performance and Immune Responses in Broiler Chickens. Chinese. Journal of Animal Veterinary Science 9, 1204-1211.
76. Zhang, S.; Gilbert, E. R.; Noonan, K. J.; Saremi, B.; Wong, E. A., 2018: Gene expression and activity of methionine converting enzymes in broiler chickens fed methionine isomers or precursors. Poultry Science 0, 1-12.

77. Zhang, S.; Saremi, B.; Gilbert, E. R.; Wong, E. A., 2016: Physiological and biochemical aspects of methionine isomers and a methionine analogue in broilers. Poultry Science 96, 425-439.

78. Zhan, X.; Li, J.; Xu, Z.; Zhao, R., 2006: Effects of methionine and betaine supplementation on growth performance, carcase composition and metabolism of lipids in male broilers. British Poultry Science 47, 576-580.

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